P. J. PAPADAKOS · B. LACHMANN

MECHANICAL VENTILATION

Clinical Applications and Pathophysiology

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This book is dedicated to our many students, residents, fellows, doctoral students, research colleagues, and collaborators in our long journey in the understanding of the pathophysiology of respiratory failure and mechanical ventilation. We could not have begun our travels without the base of support provided by our loving spouses, children, and families.

We are enormously thankful to our administrative assistants Laraine Visser-Isles and Shari Champagne for the many hours spent editing manuscripts, managing our schedules and deadlines, and of course keeping us based in reality. This book could not have been produced without the hard work of the staff at Elsevier, with a special thanks to Lucia Gunzel, who kept us on course and provided us the framework to bring this project to press.

PREFACE

Mechanical ventilation has become the most commonly used mode of life support in medicine today. It is widely used in management of acutely ill surgical and ICU patients; it is also used in the chronic support of patients with a wide spectrum of chronic diseases that can cause respiratory failure. For many years the impact of this commonly preformed procedure was not fully understood, either in how it modulated lung function or how it affected other organ function. In recent years researchers have made great strides in understanding how respiratory failure and mechanical ventilation affect the complex interaction of gas exchange, cytokine release and cellular immunity. We have made a great effort to assemble the leaders of the field to review all aspects of mechanical ventilation. Our contributors span the globe and constitute a renowned group of experts who have contributed much to our basic knowledge and patient care. Through many years of researching, writing, lecturing and caring for patients they have created the framework for this book.

The primary aim of this text is to cover the breadth of the topic in a practical yet organized fashion. We hope its primary use will be as a practical everyday reference, but it will also be a useful foundation for further reading and research. We begin with chapters that review the myriad diseases and conditions that lead to respiratory failure, including common restrictive and obstructive diseases. We also review current knowledge on acute lung injury and ventilator-induced lung injury. All important aspects of the anatomy and ventilation mechanics are reviewed to allow the reader to better understand their importance patient care. New aspects of acid–base balance are discussed to give us the ability to better recognize derangements of cellular function due to failure to deliver oxygen and remove waste products. Various interactions between the pulmonary system and other organ systems are presented in such a way to reinforce the elegant concept of cell–cell interaction.

The many modalities of monitoring and diagnosing respiratory failure are necessary to rapidly observe changes in disease states and provide benchmarks and endpoints in the care of those patients. The book reviews all modes of ventilatory support currently used in all age groups, but it also introduces computer-guided therapies and other cutting-edge technologies. We took special care to review the many unique environments in which patients are supported, from prehospital sites to specialized units of the tertiary medical centers.

Information on adjunctive therapy, both pharmacologic and special device therapy, is integrated throughout to provide a complete information package that it intended to reduce complications and decrease time on ventilatory support. New aspects and guidelines for use of antibiotics are presented to educate clinicians on the latest in bacterial resistance that plagues the modern ICUs. The importance of sedation and neuromuscular blockade in titrating mechanical ventilation is emphasized to provide bedside clinicians with further cost- and time-effective tools to develop protocols and guidelines. Case reports and discussions are used to illustrate and reinforce the multiple topics covered. We hope that they will also serve as a basis for training in the care of common disease states.

Economic and ethical aspects of mechanical ventilation are important core topics. The high cost of ICU patient care greatly affects individual hospital budgets as well as broader health care budgets. The ability to provide cost-effective care is key to both the developed and developing world as the information highway leads to rapid sharing of techniques and care plans. The care provided at the end of life has become a cornerstone of ethical care.

The editors hope that their twenty-year collaboration between Rotterdam and Rochester will serve to illustrate how investigators and clinicians look for common ground to increase their understanding of pulmonary pathophysiology and apply this knowledge at the bedside. Researchers and bedside clinicians should work together to provide patient care supported by strong scientific evidence. All levels of readers can learn from this group of authors and their impressive knowledge of the many diverse aspects of this ever-growing field.

Peter J. Papadakos, MD, FCCM
Burkhard Lachmann, MD, PhD

CONTRIBUTORS

Michael J. Apostolakos, MD
Associate Professor of Medicine, Director, Adult Critical Care, University of Rochester Medical Center, Rochester, New York

Joan R. Badia, MD
Intensive Care Unit, Pulmonary Medicine Service, Clinical Institute for Pulmonary Medicine and Thoracic Surgery; Respiratory Care and Allergy Service, Hospital Clinic, Barcelona, Spain

Sean M. Bagshaw, MD, MSc, FRCPC
Division of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta Hospital, University of Alberta, Edmonton, Canada

David J. Baker, DM, FRCA
Staff Anesthesiologist, Department of Anesthesiology, Necker Hospital for Sick Children, Paris, France

Rinaldo Bellomo, MD, FRACP, FCCP, FJFICM
Professor, University of Melbourne; Honorary Professor of Medicine, Monash University; Director of Research, Department of Intensive Care, Austin Hospital, Melbourne, Australia

Sven Bercker, MD
Department of Anesthesiology and Intensive Care Medicine, University of Leipzig Medical Faculty, Leipzig, Germany

Zaida D. Bisbal, MD
Research Associate, Dorrington Medical Associates, Houston, Texas

Anthony F. T. Brown, MBChB, FRCP, FRCS, FACEM, FCEM
Senior Staff Specialist, Department of Emergency Medicine, Royal Brisbane and Women's Hospital, Brisbane; Associate Professor of Anesthesiology and Critical Care, School of Medicine, University of Queensland, Australia

Gustavo Buchele, MD
Department of Intensive Care Medicine, Erasme University Hospital, Brussels, Belgium

Thilo Busch, PhD
Department of Anesthesiology and Intensive Care Medicine, University of Leipzig Medical Faculty, Leipzig, Germany

Enrico Calzia, MD
Pathophysiology Section, Department of Anesthesiology, University of Ulm, Ulm, Germany

Annalisa Carlucci, MD
Respiratory Intensive Care Unit, Salvatore Maugeri Foundation, IRCCS, Scientific Institute of Pavia, Pavia, Italy

Jean Chastre, MD
Intensive Care Unit, Division of Cardiology, Pitié–Salpêtrière Hospital, Pierre and Marie Curie University, Paris, France

Sanjeev V. Chhangani, MBA, MD, FCCM
Medical Director, Surgical Intensive Care Unit, Rochester General Hospital; Associate Professor, Department of Anesthesiology and Critical Care, University of Rochester School of Medicine and Dentistry, Rochester, New York

Davide Chiumello, MD
Department of Anesthesia and Intensive Care Medicine, IRCCS Foundation, Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, University of Milan, Milan, Italy

Alain Combes, MD, PhD
Intensive Care Unit, Division of Cardiology, Pitié–Salpêtrière Hospital, Pierre and Marie Curie University, Paris, France

Edgardo D'Angelo, MD
Professor of Physiology, Institute of Human Physiology, University of Milan, Milan, Italy

Gary Dudek, MD
Assistant Professor of Medicine, Pulmonary and Critical Care Division, University of Rochester Medical Center, Rochester, New York

Michael Ebsen, MD
Director, Institute of Pathology, Städtisches Krankenhaus Kiel, Kiel, Germany

Brigitte Fauroux, MD, PhD
Pediatric Pulmonary Department and Research Unit, INSERM, Armand Trousseau Children's Hospital, Paris, France

Terence R. Flotte, MD
Dean and Deputy Executive Chancellor, University of Massachusetts Medical School, Worcester, Massachusetts

Saskia Gischler, MD
Pediatric Surgical Intensive Care Unit, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands

Diederik Gommers, MD
Department of Anesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands

Hérve Guénard, MD, PhD
Department of Physiology, University Hospital of Bordeaux, Victor Segalen University, Bordeaux, France

Claude Guérin, MD
Division of Intensive Care Medicine, Croix Rousse Hospital, University of Lyon, Lyon, France

Jack J. Haitsma, MD, PhD
Interpartmental Division of Critical Care, University of Toronto; Keenan Research Centre, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada

Robert-Jan Houmes, MD
Pediatric Surgical Intensive Care Unit, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands

Yuh-Chin T. Huang, MD, MHS, FCCP
Professor of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, Duke University Medical Center, Durham, North Carolina

Shazia M. Jamil, MD, FCCP
Division of Chest/Critical Care Medicine, Scripps Clinic and Scripps Green Hospital; Assistant Clinical Professor, Department of Medicine, University of California–San Diego School of Medicine, San Diego, California

Jens Ingemann Jensen, MD, PhD, DSc, FCCP
Associate Clinical Professor, Department of Anesthesiology, University of Rochester Medical Center, Rochester, New York

Keith E. Johnson, MD
Resident, Department of Anesthesiology, New York Methodist Hospital, Brooklyn, New York

Gavin M. Joynt, MBBCh, FFA, FHKCA(IC), FJFICM, FCCP
Professor, Department of Anesthesia and Intensive Care, The Chinese University of Hong Kong; Intensive Care Unit, Prince of Wales Hospital, Hong Kong, People's Republic of China

Udo Kaisers, MD, PhD
Department of Anesthesiology and Intensive Care Medicine, University of Leipzig Faculty of Medicine, Leipzig, Germany

George E. Karras, Jr., MD, FCCM
Medical Director, Critical Care Unit and Respiratory Care Services, Mercy Medical Center, Springfield, Massachusetts

Hans-Ulrich Kauczor, MD
Director of Radiology, German Cancer Research Center, Heidelberg, Germany

John A. Kellum, MD, FCCP, FACP, FCCM
Departments of Critical Care Medicine, Anesthesiology and Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

Nick H. Kim, MD
Assistant Clinical Professor of Medicine, Department of Medicine, University of California–San Diego, San Diego, California

Younsuck Koh, MD, PhD, FCCM
Professor, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Asan Medical Center, Ulsan University College of Medicine, Seoul, Korea

Antonia Koutsoukou, MD
Assistant Professor, Department of Critical Care and Pulmonary Medicine, University of Athens Medical School, Evangelismos Hospital, Athens, Greece

Werner Kuckelt, MD
Director, Division of Surgical and General Intensive Care Medicine, Department of Anesthesiology, Central Hospital Links der Weser, Bremen, Germany

Burkhard Lachmann, MD, PhD
Professor of Experimental Anesthesiology, Department of Anesthesiology, Erasmus University, Rotterdam, The Netherlands

Chae-Man Lim, MD, PhD
Professor, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Asan Medical Center, Ulsan University College of Medicine, Seoul, Korea

Jeffrey Lipman, MBBCh, DA, FFA, FJFICM, MD
Professor and Head, Department of Anesthesiology and Critical Care, University of Queensland; Director, Intensive Care Unit, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia

Frédéric Lofaso, MD, PhD
Department of Physiology, Raymond Poincaré Hospital, Garches, France

Charles-Edouard Luyt, MD, PhD
Intensive Care Unit, Division of Cardiology, Pitié–Salpêtrière Hospital, Pierre and Marie Curie University, Paris, France

Paul E. Marik, MD, FCCP, FCCM
Chief of Pulmonary and Critical Care Medicine, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania

Klaus Markstaller, MD
Department of Anesthesiology, Inselspital, University of Bern, Bern, Switzerland

Jürgen P. Meinhardt, MD
Departments of Anesthesiology and Intensive Care Medicine and Radiology, University Hospital of Mannheim, Faculty of Clinical Medicine Mannheim, University of Heidelberg, Mannheim, Germany

Joseph Milic-Emili, MD
Professor Emeritus, Departments of Physiology and Medicine, McGill University, Montreal, Quebec, Canada

Konrad Morgenroth, MD
Professor, Department of Pathology, Ruhr University Bochum, Bochum, Germany

Iqbal Mustafa, MD, PhD (deceased)
Formerly, Professor and Founder of Critical Care Medicine, Harapan Kita National Cardiac Center, Jakarta, Indonesia

Claus-Martin Muth, MD
Pathophysiology Section, Department of Anesthesiology, University of Ulm, Ulm, Germany

Rahul Nanchal, MD
Assistant Professor of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin

Stefano Nava, MD
Respiratory Intensive Care Unit, Salvatore Maugeri Foundation, IRCCS, Scientific Institute of Pavia, Pavia, Italy

Michael S. Niederman, MD
Professor and Vice-Chairman, Department of Medicine, SUNY Stony Brook; Chairman, Department of Medicine, Winthrop University Hospital, Mineola, New York

Gustavo A. Ospina-Tascón, MD
Department of Intensive Care Medicine, Erasme University Hospital, Brussels, Belgium

Jaideep J. Pandit, DPhil, FRCA
Consultant Anaesthetist, Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford University, Oxford, United Kingdom

Peter J. Papadakos, MD, FCCM
Professor of Anesthesiology, Surgery and Neurosurgery, University of Rochester; Director, Division of Critical Care Medicine, Department of Medicine, University of Rochester Medical Center, Rochester, New York

Paolo Pelosi, MD, PhD
Department of Anesthesia and Intensive Care Medicine, University of Insubria, Varese-Circolo and Fondazione Macchi Hospital, Varese, Italy

Irene Perillo, MD
Department of Medicine, School of Medicine and Dentistry, University of Rochester, Rochester, New York

Michael R. Pinsky, MD, CM, Dr hc, FCCP, FCCM
Professor of Critical Care Medicine, Bioengineering and Anesthesiology, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Christian Putensen, MD
Professor and Director, Division of Intensive Care Medicine, Department of Anesthesiology and Intensive Care Medicine, University of Bonn, Bonn, Germany

Michael Quintel, MD
Department of Anesthesiology and Intensive Care Medicine, Georg-August University Hospital, Göttingen, Germany

Milena Racagni, MD
Department of Anesthesia and Intensive Care Medicine, IRCCS Foundation, Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, University of Milan, Milan, Italy

Peter Radermacher, MD
Pathophysiology Section, Department of Anesthesiology, University of Ulm, Ulm, Germany

Jayashree Raikhelkar, MD
Assistant Professor, Department of Anesthesiology, Mount Sinai School of Medicine, New York, New York

Miranda D. Reis, MD
Department of Anesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands

Irwin Reiss, MD
Pediatric Surgical Intensive Care Unit, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands

Andreas Reske, MD
Department of Anesthesiology and Intensive Care Medicine, University Hospital Leipzig, Leipzig, Germany

Hans Ulrich Rothen, MD, PhD
Division of Intensive Care Medicine, Departments of Anesthesiology and Emergency Medicine, University Hospital Bern, Bern, Switzerland

Charis Roussos, MD, MSc, PhD, MRS, FRCP(C)
Department of Critical Care and Pulmonary Services, University of Athens Medical School, Evangelismos Hospital, Athens, Greece

Dierk Schreiter, MD
Surgical Intensive Care Unit and Division of Traumatology, Department of Surgery, University of Leipzig, Leipzig, Germany

Marcus J. Schultz, MD, PhD
Department of Intensive Care, Laboratory of Experimental Intensive Care and Anesthesiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; The Interdepartmental Division of Critical Care, St. Michael's Hospital, Toronto, Ontario, Canada

Thomas P. Shanley, MD
Janette Ferrantino Professor of Pediatrics and Communicable Diseases; Director, Pediatric Critical Care Medicine, C.S. Mott Children's Hospital, The University of Michigan Medical School, Ann Arbor, Michigan

Ioanna Sigala, MD
Department of Critical Care and Pulmonary Services, University of Athens Medical School, Evangelismos Hospital, Athens, Greece

Indra Singh, MD
Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Jaspal Singh, MD, MHS
Assistant Professor of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, Duke University Medical Center, Durham, North Carolina

Arthur S. Slutsky, MD
Professor of Medicine, Surgery and Biomedical Engineering, Interdepartmental Division of Critical Care, University of Toronto; Vice President for Research, St. Michael's Hospital, Toronto; Keenan Research Centre, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada

Pejman Soheili, MD
Pulmonary and Critical Care Division, Department of Medicine, University of Rochester Medical Center, Rochester, New York

Roger G. Spragg, MD
Professor of Medicine Emeritus, Department of Medicine, University of California–San Diego, San Diego, California

Robert W. Taylor, MD, FCCM, FCCP
ICU-USA, St. Louis, Missouri

Per A.J. Thorborg, MD, PhD
Department of Anesthesiology and Perioperative Medicine, Oregon Health Sciences University, Portland, Oregon

Dick Tibboel, MD
Pediatric Surgical Intensive Care Unit, Erasmus Medical Center and Sophia Children's Hospital, Rotterdam, The Netherlands

Antonio Torres, MD, PhD, FACS
Pulmonary Medicine and Respiratory Care Service, Hospital Clinic of Barcelona, Barcelona, Spain

Mark J. Utell, MD
Professor of Medicine and Environmental Medicine, University of Rochester Medical Center; Pulmonary and Critical Care Division, Department of Medicine, Rochester, New York

Robert A. van Hulst, MD, PhD
Department of Anesthesiology, Erasmus Medical Center; Diving Medical Center, Royal Netherlands Navy, Rotterdam, The Netherlands

A.H.L.C. van Kaam, MD, PhD
Department of Neonatology, Emma Children's Hospital, Amsterdam, The Netherlands

Joseph Varon, MD, FACP, FCCP, FCCM
Professor, The University of Texas Health Science Center, St. Luke's Episcopal Hospital, Houston, Texas

Theodoros Vassilakopoulos, MD
Department of Critical Care and Pulmonary Services, University of Athens Medical School, Evangelismos Hospital, Athens, Greece

Bala Venkatesh, MBBS, MD (Int. Med), FRCA, FFARCSI, MD (UK), EDICM, FJFICM
Senior Specialist in Intensive Care, Princess Alexandra Hospital; Deputy Director of Intensive Care, Wesley Hospital; Professor, Division of Anesthesiology and Critical Care, University of Queensland, Queensland, Australia

Jean-Louis Vincent, MD
Professor of Intensive Care Medicine, University of Brussels; Department of Intensive Care Medicine, Erasme University Hospital, Brussels, Belgium

Denham S. Ward, MD, PhD
Professor of Anesthesiology and Biomedical Engineering, Associate Dean for Faculty Development, Department of Medical Education, University of Rochester, Rochester, New York

Helmar Wauer, MD
Department of Anesthesiology and Critical Care, Charite University Hospital, Humboldt University of Berlin, Berlin, Germany

Steffen Wolf, MD
Department of Anesthesiology and Critical Care, Charite University Hospital, Humboldt University of Berlin, Berlin, Germany

Hector R. Wong, MD
Department of Pediatrics, University of Cincinnati College of Medicine, Division of Critical Care Medicine, Cincinnati Children's Hospital Medical Center and the Children's Hospital Research Foundation, Cincinnati, Ohio

CHAPTER 1

Restrictive Diseases

Joseph Varon, Paul E. Marik, and Zaida D. Bisbal

The restrictive lung diseases (RLDs) are a group of pulmonary disorders with parenchymal "infiltrates" that result in disruption of the distal lung parenchyma. RLDs can be classified as fibrotic, traumatic, or infectious diseases that cause parenchymal disruption. The common features of RLDs include the reduction of lung volumes secondary to an alteration in lung parenchyma or a disease of the pleura, chest wall, or neuromuscular apparatus.[1] In most RLDs, the total lung capacity, vital capacity, and the resting lung volume are significantly compromised.[2] Mechanical ventilation for patients with RLDs may be a difficult challenge. This chapter presents some of the common RLDs as well as some ventilatory strategies for these patients.

PATHOPHYSIOLOGY AND BASIC EPIDEMIOLOGIC FEATURES

The lung interstitium corresponds to an anatomic space interposed between alveolar membranes of the alveolar epithelial lining cells and the endothelial cells of the interstitial capillaries. Most patients with RLDs have alterations of this anatomic space. In the United States, the prevalence of RLDs has been estimated at five cases per 100,000 people. The prevalence in persons between the ages of 35 and 44 years is 2.7 cases per 100,000 persons. In people more than 75 years of age, the prevalence is higher than 175 cases per 100,000 persons.

Most RLDs are diseases of the lung interstitium.[3] Of the common interstitial lung diseases (ILDs) that cause RLDs, the most common include idiopathic pulmonary fibrosis, sarcoidosis, and some of the pneumoconioses.[4] Occupational and environmental exposures to organic and inorganic dusts are important causes of ILDs.[5]

MANAGEMENT OF ACUTE RESPIRATORY FAILURE IN PATIENTS WITH RESTRICTIVE LUNG DISEASES

The precipitating events leading to progressive respiratory failure in patients with ILD include upper and lower respiratory tract infections (bacterial or viral), pulmonary embolism, arrhythmias, myocardial ischemia, and biventricular cardiac failure. All attempts should be made to avoid endotracheal intubation and mechanical ventilation with aggressive medical treatment. The limited potential benefit of mechanical ventilation in a patient with end-stage ILD should be discussed with both the patient and his or her family. These discussions are best held with the patient and his or her primary care physician or pulmonologist before an acute crisis occurs, to determine the patient's preferences for end-of-life medical care and limitations of therapy. Mechanical ventilation is not curative and may serve only to prolong the dying process. The increased right ventricular afterload consequent to positive pressure ventilation (PPV) may precipitate acute or chronic cor pulmonale with hemodynamic embarrassment. Although available data on the role of noninvasive PPV (NIPPV) in patients with ILD are limited, this ventilatory modality may relieve dyspnea and improve patient comfort. NIPPV should therefore be considered in alert and cooperative patients. Mechanical ventilation should be considered in patients with a treatable precipitating cause who are likely to survive their hospital stay.

The ventilatory management of these patients is, however, quite challenging. The goal of mechanical ventilation is to improve dyspnea without aiming to normalize the blood gas profile. The ventilatory strategy should include measures to minimize the risk of barotrauma, principally by using reduced tidal volumes to maintain the plateau inspiratory pressures at less than 35 cm H_2O.[6] Anzueto and colleagues reported a 10% incidence of barotrauma in patients with chronic ILD who required mechanical ventilation.[7] "Physiologic positive end-expiratory pressure (PEEP)" of 5 cm H_2O is suggested to minimize the risk of atelectasis, although evidence to support this practice is lacking. A trial of higher PEEP should be considered in patients with refractory hypoxemia. Once the patient has been intubated and stabilized, an early trial of pressure support ventilation may be warranted. Early extubation may minimize the morbidity associated with mechanical ventilation. To facilitate this goal, the use of sedative agents should be minimized, and invasive forms of ventilation should be avoided (controlled mechanical ventilation/pressure controlled ventilation).

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF), also known as cryptogenic fibrosing alveolitis, is a chronic, progressive inflammatory disorder of the lower respiratory tract of unknown origin. It is characterized by an atypical proliferation of mesenchymal cells, overproduction and disorganized deposition of collagen, and impaired gas exchange.[8,9] These pathologic processes, in turn, lead to decreased lung compliance, with a progressive increase in the work of breathing.[10]

The exact incidence and prevalence of IPF are unknown; however, the prevalence in the United States has been estimated to be between three and six cases per 100,000 of the population.[5,11] The usual age at diagnosis is between the fourth and sixth decade. This disorder does not have predilection for race or ethnicity. Approximately two thirds of patients with IPF are more than 60 years old at the time of presentation, with a mean age at diagnosis of 66 years.[5,12] The prognosis of IPF is poor; almost all patients die of respiratory failure. The survival range is approximately 4 to 5 years.[10,13]

From a pathophysiologic standpoint, IPF is initiated by an alveolar epithelial microinjury, followed by the production of fibroblastic foci leading to an excessive deposition of extracellular matrix and destruction of the lung parenchymal architecture.[14,15] The initial mechanism includes interactions of cytokines and other mediators with cells resident in the lung.[16]

Polypeptide mediators, including proinflammatory cytokines and chemokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and monocyte chemoattractant protein-1 (MCP-1) are released by inflammatory cells, most notably alveolar macrophages. The resident epithelial cells, fibroblasts, and endothelial cells within the lungs also produce a multitude of cytokines and growth factors that activate fibroblast proliferation and matrix synthesis. Tissue injury with fibrosis is believed to result from an imbalance between proinflammatory and anti-inflammatory cytokines, fibrogenic and antifibrogenic polypeptides, and angiogenic and angiostatic molecules.[17,18]

The most common clinical presentation of IPF is that of insidious progressive shortness of breath, dyspnea on exertion, and a nonproductive cough. Almost 50% of patients have constitutional symptoms such as fatigue and weight loss.[10,19] On auscultation, there are fine inspiratory crackles, heard best in midinspiration to end inspiration. With more severe disease, increased right-sided heart pressures and right ventricular failure may be evident, with signs of cor pulmonale, digital clubbing, and cyanosis. In fewer than 10% of patients with severe IPF, left ventricular dysfunction is present, the result of coexisting right-sided heart failure with ventricular interdependence.

In the diagnostic workup of patients with suspected IPF, a detailed medical history is required that should include a review of symptoms associated with systemic disorders, exposure to occupational and environmental agents, and the use of medications and drugs. Almost all patients with IPF have an abnormal chest radiograph.[20] Retrospectively, basal reticular opacities are often evident on previous chest radiographs for several years before the development of symptoms. A normal chest radiograph cannot be used to exclude IPF. High-resolution computed tomographic (HRCT) scans are likely to show evidence of interstitial disease in most patient with a normal chest radiograph or ill-defined opacities.[21–23] Pulmonary function tests demonstrate a restrictive pattern (reduced vital capacity often with an increased ration of forced expiratory volume in 1 second to forced vital capacity) which becomes more severe with time. The diffusing capacity is decreased with evidence of impaired gas exchange (decreased partial pressure of arterial oxygen and increased alveolar-arterial pressure of oxygen) initially with exercise and then at rest.

Sarcoidosis

Sarcoidosis is a common ILD that leads to RLD. This disorder is a multisystem inflammatory disorder of unknown origin that primarily affects the lung and lymphatic systems. It is distinguished by the presence of discrete, compact, noncaseating epithelioid granulomas in any organ system. The noncaseating epithelioid granulomas are characterized by highly differentiated mononuclear phagocytes and lymphocytes. These granulomas are responsible for the development of fibrotic changes that commonly begin at the periphery of the

granuloma and extend centrally, resulting in complete fibrosis and hyalinization.[24]

The incidence rates of sarcoidosis in one population-based study in the United States were 5.9 per 100,000 person-years for men and 6.3 per 100,000 person-years for woman.[25] This disorder affects people of all races and all ages, but African Americans have a higher risk for sarcoidosis than any other race. Sarcoidosis normally affects young adults between 25 and 35 years of age and has a worldwide distribution. The illness can be self-limited or chronic, with episodic recrudescence and remissions.

Sarcoidosis almost always affects the lungs and thoracic lymph nodes. Patients usually present with acute or insidious respiratory problems with bilateral hilar lymphadenopathy or pulmonary infiltrates and variable symptoms associated with involvement of the skin, muscle, eyes, liver, heart, or central nervous system.[26–28]

T cells are considered to play a central role in the pathogenesis of sarcoidosis, which is associated with an exaggerated cellular immune reaction to unknown antigens (exogenous or autoantigens).[29] The inflammatory response is distinguished by a large number of activated macrophages and CD4 helper T (Th) lymphocytes. Sarcoidosis is characterized by a Th1-type immune response with IL-2 release, accumulation of CD4 cells, an inverted CD4/CD8 ratio, and the release of Th1 cytokines including interferon and TNF.[30–32] Finally, there is significant immunoglobulin production secondary to B-cell hyperreactivity.[33]

In some patients, sarcoidosis can be asymptomatic or have mild nonspecific symptoms. However, most patients present with systemic complaints including fever, anorexia, and arthralgias. Almost 50% of patients present with dyspnea and dry cough, one third present with chest pain; clubbing and crackles rarely occur.[34–36] Hemoptysis is rare. Löfgren's syndrome is characterized by fever, bilateral hilar lymphadenopathy, and polyarthralgias. Because pulmonary sarcoidosis affects the alveoli, blood vessels, and bronchioles, pulmonary function abnormalities include a restricted lung pattern and abnormalities in gas exchange. Given that the conducting airways are usually involved, limitation of air flow is a common finding.

The diagnosis of sarcoidosis can be difficult and usually requires histologic confirmation of granulomatous inflammation, exclusion of other noncaseating granulomatous diseases, and clinical evidence of involvement in more than one organ. An extensive history and physical examination are imperative and should include historical information regarding occupational and environmental exposure to potential pulmonary pathogens.[37] The diagnosis of sarcoidosis is best established by histology, to exclude infectious or malignant conditions. Biopsy specimens should be collected from the most accessible organ and by the least invasive method. The diagnosis of pulmonary sarcoidosis depends on three findings: the presence of granulomas and a rim of lymphocytes and fibroblasts in the outer margin of granulomas, perilymphatic interstitial distribution of granulomas, and the exclusion of another cause.[38,39]

Three stages of pulmonary sarcoidosis have been described. The first stage is characterized by bilateral hilar adenopathy without parenchymal infiltrates on chest radiograph. The second stage is characterized by bilateral hilar adenopathy with pulmonary infiltration. The third stage is pulmonary infiltration or fibrosis. The final stage is characterized for infiltrates without adenopathy and shows evidence of bullae, cysts, and emphysematous changes.[40]

The treatment of sarcoidosis remains problematic, with no known curative therapy. Multiple therapeutic modalities have been investigated.[41] Treatment depends on the patient's symptoms, stage of disease, and degree of organ involvement.

Asbestosis

Asbestosis is an important occupational lung disease and a common cause of pulmonary fibrosis. Asbestos is a group of naturally occurring, heat-resistant fibrous silicates.[42,43] The most common type of asbestos is chrysotile fiber.[44] In the United States, millions of workers have had occupational exposure to asbestos throughout the last century; asbestos has been used in industrial and nonindustrial environments. Asbestos has been used in textiles, cement, insulation and construction material, and friction materials.

Asbestosis is characterized by slowly progressive diffuse interstitial fibrosis of the lung parenchyma caused by inhalation of asbestos fibers. The condition has been recognized for more than a century. It occurs when there is exposure to high levels of asbestos, as was common among asbestos workers of last century. In addition, asbestos exposure can produce non–small cell and small cell carcinoma of the lung and mesothelioma of the pleura and peritoneum.[45–47]

People who smoke have an increased risk for the development of bronchogenic carcinoma because tobacco smoke and asbestos have synergistic carcinogenicity.[48] People who smoke and have been exposed to asbestos are 90 times more susceptible to developing lung carcinoma than people who either smoke or have been exposed to asbestos.[49]

In asbestosis, the alveolar bifurcation is the predominant site of inflammation and is related to the influx of alveolar macrophages. Asbestos-activated macrophages generate growth factors including fibronectin, platelet-derived growth factor, insulin-like growth factor, and fibroblast growth factor, which interact to induce fibroblast proliferation. Oxygen-free radicals that are released by macrophages damage proteins and lipid membranes, thereby maintaining the inflammatory process. A plasminogen

activator causes further damage of the interstitium of the lung by degrading matrix glycoproteins.[50–52]

Asbestosis is usually asymptomatic for at least 20 to 30 years after the initial exposure. The time can be shorter with intense exposure.[53] The most common symptom is dyspnea on exertion; a productive cough denotes concomitant bronchitis or a respiratory infection. Chest discomfort is present particularly in advanced cases. Persistent rales are a common clinical finding. They are best auscultated at the base of the lungs posteriorly and in the lower lateral areas. Rales can be heard in the end-inspiratory phase at the beginning of the disease, but in advanced disease, rales may be heard during the whole inspiratory phase. Finger clubbing is present in 25% to 50% of cases. In advanced stages, patients may develop cor pulmonale with peripheral edema, jugular venous distention, hepatojugular reflux, and right ventricular gallop.[54]

A history of remote exposure to asbestos is required to make the diagnosis. The presence of pleural plaques is practically pathognomonic of previous exposure. Common findings on chest radiographs include small bilateral parenchymal opacities with diffuse reticulonodular pattern, notably at the lung bases. In addition, bilateral midlung zone plaques on the parietal pleura can be seen.[55–57] The diffuse lung infiltrates cause the appearance of shaggy heart borders and bilateral pleural thickening. Pleural involvement is the most characteristic finding of asbestos exposure. Almost 50% of patients exposed to asbestos develop pleural plaques. CT scanning has good sensitivity and is very useful in the assessment of pleural abnormalities and in the delineation of a parenchymal density that could be related to bronchogenic carcinoma. An HRCT scan allows better definition of interstitial infiltrates and may be helpful in diagnosing early stages of asbestosis.[58] The early physiologic manifestations include air trapping, as demonstrated by an increased ratio of residual volume to total lung capacity, and small airway obstruction.[59] With disease progression, there is a reduction of lung volumes.

Silicosis

Silicosis is a debilitating and often fatal coal worker's occupational lung disease caused by the prolonged exposure and inhalation of free crystalline silica dust (quartz, tridyrnite, and cristobalite).[60,61] Silica is the most abundant mineral on the earth. Silicosis presents as varying degrees of fibronodular lung disease, depending on dose and period since onset of exposure. Patients with a history of silicosis are at a high risk of developing tuberculosis. In the United States, more than one million people have been exposed to crystalline silica and are at risk of developing silicosis.[62–64]

There are three clinical types of silicosis. The first is chronic silicosis, which is the most common form of the disease. It appears after contact with low concentrations of silica and with a period of at least 10 years of exposure; the disease can be either simple silicosis or complicated silicosis, known as progressive massive fibrosis. The difference between simple and complicated silicosis is based in the chest radiographic findings. The second type of silicosis is called accelerated silicosis, which develops after 5 to 10 years of exposure to high concentrations of silica. In these cases, the lesions appear earlier, and progression is faster. In acute silicosis, symptoms develop within the first weeks to 5 years after exposure to very high concentrations of silica.[65]

Large silica particles are deposited in the upper airways and are cleared by local defense mechanisms. Smaller particles are deposited distally in the alveoli, where they lead to pulmonary fibrosis. These particles activate silicon-based radicals, which, in turn generate hydroxyl, hydrogen peroxide, and other radicals.[66] These radicals produce an injury to the cell membranes by lipid peroxidation and inactivate essential cell proteins. Alveolar macrophages phagocytose the silica particles and become activated, releasing cytokines and chemokines such as TNF, IL-1, IL-8, and leukotriene B_4, which enlist other inflammatory cells. Transforming growth factor-α induces proliferation of type 2 pneumocytes, and several cytokines stimulate fibroblasts to generate collagen with resulting fibrosis. Silica particles survive attempts of digestion by the alveolar macrophages, thus perpetuating the cycle of injury.

Patients in early stages of silicosis present with shortness of breath and a nonproductive cough. Patients with advanced silicosis may have chest pain. Patients with silicosis are at high risk for developing tuberculosis. In general, tachypnea, expiratory prolongation, rhonchi, and rales may be present. Digital clubbing is uncommon. Advanced stages of complicated silicosis results in cor pulmonale. The progression of silicosis in complicated cases leads to respiratory failure, which may cause death.[67] Symptoms in acute silicosis include severe dyspnea, fever, cough, and weight loss.

An occupational history and chest radiographs are usually sufficient for the diagnosis of uncomplicated silicosis. Radiographically, silicosis is characterized by small, nodular pulmonary opacifications and by eggshell calcification of hilar nodes.[68] In simple chronic silicosis, the opacities are less than 1 cm in diameter, mostly in the upper lung fields, whereas in complicated silicosis, the opacities are greater than 1 cm in diameter. Initial changes in acute silicosis include a diffuse haze in the lower lung fields; subsequently, ground-glass opacities and coarse linear or rounded opacities occur. A miliary picture with very small, round opacities may also occur in the lower lung fields.[69]

Traumatic Diseases

Trauma is the leading cause of death in persons less than 44 years of age and is the fourth leading cause of

death overall.[70] Approximately 140,000 traumatic deaths occur in the United States annually. Chest trauma is the cause of death in up to one fourth of patients with multiple system trauma. Injury may occur to the chest wall, lung, great vessels, and mediastinal viscera. Traumatic injuries to the chest may result in restrictive pulmonary complications including tension pneumothorax, open pneumothorax, and flail chest with pulmonary contusion. Each of these conditions requires different management and ventilatory strategies. However, most injuries are initially managed with supplementary oxygen, chest tube insertion, and volume resuscitation. The indications for thoracotomy in a chest trauma victim include cardiac tamponade, massive hemothorax; pulmonary air leak larger than 15 to 20 L/minute, and aortic arch, esophageal, tracheal, or major bronchial disruption.

Chest Wall Trauma

Rib fractures are the most common chest wall injury. Rib fractures are an important indicator of underlying injury. Fractures of the first to third ribs are associated with injury to the great vessel and with bronchial injury, whereas lower rib fractures are associated with kidney, liver, and splenic lacerations. Flail chest occurs when three or more ribs are fractured in two places or in multiple fractures associated with sternal fracture. The clinical significance of flail chest varies, depending on the size and location of the flail segment and the extent of the underlying pulmonary contusion. Patients with severe hypoxemia require endotracheal intubation and PPV.[71,72] Indeed, correction of flail chest occurs with the application of PPV. However, the clinician must observe for late development of pneumothorax, especially tension pneumothorax, in the mechanically ventilated patient.[73]

Sternal fractures can occur in the trauma patient and are associated with myocardial contusion, cardiac rupture and tamponade, and pulmonary contusion.[74] Early surgical fixation is often necessary; urgent surgery may be indicated when costosternal dislocations compromise the trachea or the neurovascular structures at the thoracic inlet.

Pneumothorax

Pneumothoraces result from penetrating trauma or blunt trauma with rib fractures. Pneumothorax may be caused by PPV (barotrauma). The presence of pneumothorax in a mechanically ventilated patient requires chest tube insertion.[75]

Open pneumothorax requires covering of chest wall injury with an airtight dressing and insertion of a chest tube. Tension pneumothorax requires immediate needle decompression and chest tube insertion.[76] Clinical findings include unilateral absence of breath sounds, severe dyspnea, tracheal shift, jugular venous distention, and cyanosis.

Hemothorax

Initial treatment of hemothorax requires insertion of chest tube to evacuate the hemothorax, reexpand the lung, and monitor the rate of bleeding. Indications for thoracotomy include initial chest tube drainage of greater than 1500 mL or continued bleeding of more than 300 mL/hour for more than 2 to 3 hours.[77]

Major Vessel Injury and Cardiac Tamponade

Major vessel injury and cardiac tamponade are common causes of death in major trauma. Major vascular bleeding or cardiac injury can compress the heart and lungs and physiologically can behave like an RLD. Radiographic evidence includes a widened mediastinum, aortic knob obliteration, and tracheal or nasogastric tube deviation. Arteriography or CT scanning is required for the diagnosis. Cardiac tamponade requires thoracotomy and pericardial decompression. Pericardiocentesis may be performed if the diagnosis is uncertain or as a temporizing measure during preparation for thoracotomy.[78,79]

Pulmonary Contusion

Pulmonary contusion is a common complication of chest trauma. Ventilatory management consists of supplemental oxygen administration and mechanical ventilation with the addition of PEEP, if indicated in patients with worsening hypoxemia.

Infectious Diseases

Numerous infectious processes can compromise the elastic properties of the lungs. Common restrictive situations arise from infections that lead to the acute respiratory distress syndrome (ARDS) and thoracic empyema.

Pulmonary Infections and Acute Respiratory Distress Syndrome

The basic abnormality in ARDS is the disruption of the normal alveolar-capillary barrier. Moreover, it is now evident that ARDS is not simply a form of pulmonary edema caused by increased microvascular permeability, but rather is a manifestation of a more generalized permeability defect.[80] Research in recent years has been focused on possible mediators of lung injury in ARDS such as free radicals, proteinases, and soluble agents including cytokines, arachidonic acid metabolites, and charged proteins.[81]

The pathophysiologic consequences of lung edema in ARDS include decreases in lung volumes and compliance and large intrapulmonary shunts (blood perfusing unventilated segments of the lung). A fall in the residual volume is uniformly present and contributes to ventilation-perfusion inequality. It has been hypothesized that a defective surfactant may be partially responsible for the

small lung volumes and that it may worsen edema accumulation in ARDS (because increases in alveolar surface tension have been shown to increase lung water content by lowering interstitial hydrostatic pressure).[82,83] The decrease in lung compliance is secondary to the increased lung recoil pressure of the edematous lung, which clinically increases the work of breathing and leads to respiratory muscle fatigue.

The pulmonary vasculature is prominently affected in ARDS. Pulmonary hypertension not related to hypoxemia is a very common finding in patients with ARDS. Indeed, this condition is caused by a three- to five-fold increase in pulmonary vascular resistance and is associated with an increase in right ventricular work.[84] Pulmonary angiography studies performed within 48 hours of the onset of ARDS have shown that 48% of patients have demonstrable filling defects (intravascular thrombi) in vessels larger than 1 mm in diameter.[85] Patients who die of respiratory failure usually show a progressive decrease in lung compliance, worsening hypoxemia, and a progressive increase in dead space with hypercapnia. Pathologic examination of the lungs in these patients reveals extensive interstitial and alveolar fibrosis.[86]

To date, there are no specific pharmacologic interventions of proven value for the treatment of ARDS. Although corticosteroids and prostaglandin E_1 have been widely used clinically, studies have failed to show any benefit in outcome, lung compliance, pulmonary shunts, chest radiograph, severity score, or survival.[87–90]

The mainstay therapy of ARDS is the management of the underlying disorder. Unfortunately, this is not always possible (as is the case in aspiration of gastric contents, smoke inhalation, or trauma). Treatable causes of ARDS include sepsis, respiratory infections, and shock. The ventilatory management of patients with ARDS is extensively reviewed elsewhere (see Chapter 4).

Empyema

Any respiratory tract infection that leads to complicated pleural effusion and empyema has the potential to cause RLD. This restrictive process may be transitory or permanent, depending on how soon the clinician can achieve drainage of the infectious process.

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CHAPTER 2

Chronic Obstructive Pulmonary Disease

Keith E. Johnson

Chronic obstructive pulmonary disease (COPD) is one of the most common pulmonary disorders seen by physicians in the world. In the United States, it is estimated that more than 16 million Americans are affected by this disease. COPD is a term that describes a collection of diseases that result in chronic obstruction of airflow within the lungs and to the external environment and are generally not fully reversible. COPD is a disease that is strongly associated with smoking, typically is more common in men, and often is either asymptomatic or only mildly symptomatic. Traditionally, it has been subdivided into several entities, including chronic bronchitis and emphysema. Additionally, asthma is also included in the group of obstructive diseases in many paradigms.

CHRONIC BRONCHITIS

Chronic bronchitis is a medical condition describing excessive tracheobronchial mucus production that results in obstruction of the small airways. This mucus production is sufficient to cause a cough with expectoration for at least 3 months out of every year for a period of 2 successive years. It is important to delineate this condition from acute bronchitis, a self-limited condition of the bronchi most often caused by viral infections in association with an upper respiratory infection.

Pathology

Chronic bronchitis results from hypertrophy of the submucosal glands that line the large cartilaginous airways. This hypertrophy leads to airflow obstruction in the small airways. This condition is characterized by hyperplasia of the goblet cells and proliferation of the inflammatory cells of the mucosa and submucosa that lead to edema, peribronchial fibrosis, and mucus plugging of these airways, as well as hypertrophy of the surrounding smooth muscles.

The pathogenesis of this disorder is based in the alveolar epithelial layer. The inflammation associated with bronchitis is neutrophilic. It results from the actions of interleukin-8 and other chemotactic and proinflammatory cytokines, as well as colony-stimulating factors, that are released by these airway epithelial cells in response to stimuli.

Epidemiology

The pathogenesis of bronchitis and emphysema has several contributors, perhaps the largest of which is smoking. In addition, air pollution, occupation, and genetic factors all play a role in the formation of this disease.

Smoking has been shown in repeated studies to inhibit the ciliary motion responsible for "sweeping" the airways clean. This inhibits the function of alveolar macrophages and directly leads to mucosal cell hypertrophy. Inhaled cigarette smoke produces an increase in pulmonary resistance secondary to smooth muscle contraction. The risk of death from emphysema or chronic bronchitis is more than 30 times higher for smokers consuming at least 30 cigarettes/day.

Air pollution has been shown to be another factor in the development of emphysema and bronchitis. Heavy pollution with sulfur dioxide has been shown to exacerbate bronchitis. In industrialized areas, emphysema and bronchitis exacerbations are shown to increase in times of

high sulfur dioxide levels, such as happens with warm weather inversions over the cities of southern California.

An individual's occupation can also encourage the formation of bronchitis. Chronic bronchitis is more common among workers whose employment exposes them to dusts or noxious gases. Reviewing epidemiologic studies, one can see an accelerated decline in lung function in plastic plant workers and cotton carding mill workers.

In reviewing bronchitis, there is evidence of a familial tendency to the disease. Children of parents who smoke are more likely to experience severe respiratory illnesses and have a higher incidence of chronic respiratory symptoms.

A predominant feature of the progression of COPD is progressive airflow obstruction, leading to decreased forced expiratory volume in 1 second (FEV_1). Respiratory infections have not been found to influence the overall course of the disease. By the time chronic airflow obstruction is present, the FEV_1 has decreased well below the normal range. Smoking cessation will not reverse the changes to this point, but it will slow the rate of the progressive loss of lung function.

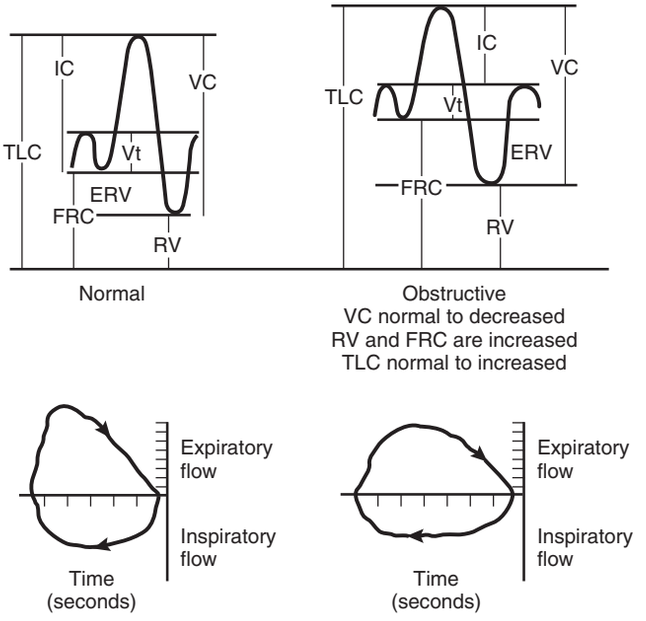

Figure 2.1 Top: Lung Volumes and Capacities: Normal (left) vs. Obstructive (right) diseases. Bottom: Flow Volume Loops: Normal (left) vs. Obstructive (right) diseases.

Clinical Features

The primary symptom of this disease is sputum production. Dyspnea does not usually appear until bronchitis is fairly advanced. Patients generally have a long history of sputum production and cough, lasting many years, with a modest history of smoking. Generally, the cough begins in the winter months, and it progresses through the rest of the year. Often, the patient is overweight and cyanotic. There is usually no respiratory distress at rest.

These patients are often described as "blue bloaters," secondary to chronically elevated partial arterial pressure of carbon dioxide ($PaCO_2$) and lowered partial arterial pressure of oxygen (PaO_2). The cough and sputum production are usually accompanied by frequent respiratory tract infections and recurrent episodes of cor pulmonale.

The total lung capacity (TLC) is often normal, and there is a moderate elevation in residual volume (RV) (Fig. 2.1). The increase in RV is secondary to the slowing of expiratory airflow, in combination with the resulting gas trapping behind the prematurely closed airways. The advantages of the increase in the RV and functional residual capacity (FRC) for the patient are an enlarged airway diameter and an increase in elastic recoil on expiration. The disadvantage is that the work of breathing dramatically increases at the higher lung volumes. The vital capacity (VC) is diminished, and the maximal expiratory flow rates are low, because a decreased ratio of FEV_1 to forced VC (FVC) is noted. The best tests to determine these values are the forced expiratory flow between 25% and 75% VC (FEF_{25-75}) and the maximal midexpiratory flow (MMEF). Normally, FEV_1/ FVC is 80%. In the presence of mild COPD, this ratio decreases to 60% to 50%. In moderate COPD, the ratio is 40% to 60%, and less than 40% is considered severe COPD.

On chest radiography, chronic bronchitis is rarely identified. The two most commonly encountered findings associated with chronic bronchitis are thickened bronchial walls identified by tubular shadows and a generalized increase in bronchovascular markings. These patients are commonly described as "blue bloaters" because they have more severe hypoxia, with an elevated $PaCO_2$. Arterial blood gas determinations show a PaO_2 generally less than 65 mm Hg and a $PaCO_2$ chronically increased to greater than 45 mm Hg. As a result of the chronic retention of carbon dioxide, these patients develop a compensatory metabolic alkalosis as seen in their arterial blood gas values. The hypoxic and hypercarbic combination of the blood gas leads to pulmonary hypertension (arterial hypoxemia and the ensuing respiratory acidosis result in pulmonary vasoconstriction) and to indirect erythrocytosis caused by the chronic arterial hypoxemia. The chronic pulmonary hypertension leads to cor pulmonale and right ventricular hypertrophy, evidenced by right axis deviation on the electrocardiogram (ECG). Right ventricular failure often results, leading to systemic hypertension of the venous circulation, distended jugular veins, peripheral edema, hepatomegaly secondary to passive venous congestion, and, occasionally, ascites. Pleural effusions also can develop if left ventricular failure occurs.

EMPHYSEMA

Emphysema is a medical condition that results from the permanent, abnormal distention of the distal air spaces of the terminal bronchioles, with destruction of the alveolar septa. It is estimated that of the 16 million Americans with COPD, 3 million of them have emphysema. Emphysema is characterized by a loss of elasticity in the walls of the alveolar pathways that results in an increase in lung compliance. Eventually, the smaller alveoli stretch and break, thus creating larger air spaces that are less efficient in handling the O_2 and CO_2 exchange. As a result, there is airway collapse on exhalation that leads to an increase in airway resistance. This obstruction also can cause bullae formation, with compression of adjacent lung tissue.

Although smoking is the major predisposing factor in emphysema, an imbalance between antiprotease and protease enzymes results in degradation of pulmonary interstitial fibers. This degradation is caused by the elastase enzyme, as well as by the absence of α_1-antitrypsin. The absence of the α_1-antitrypsin gene is found in about 0.1% of the population, but 80% of these individuals develop emphysema. The tendency to develop emphysema is variable, but smokers develop disabling emphysema 15 to 20 years before those who do not smoke. In addition, 5% to 10% of persons with this deficiency develop liver disease, most often cirrhosis. Those who are heterozygotes for α_1-antitrypsin and who have 50% or more of the enzymatic activity seem to be protected against the development of emphysema. Although most smokers have normal levels of α_1-antitrypsin, long-term inhalation of cigarette smoke increases elastase activity and inactivates α_1-antitrypsin in the lungs.

Clinical Features

The major symptom of emphysema is severe dyspnea, often exertional. Patients describe a minimal cough that is frequently nonproductive. As the FEV_1 decreases to less than 40% of normal, the patient will begin to experience dyspnea during activities of daily living. The patient's body build shows evidence of weight loss secondary to increased energy expenditure for breathing, with less caloric intake. The patient is generally distressed, with obvious use of accessory muscles to lift the sternum with each inspiration. These patients are often described as "pink puffers" because they have mild hypoxia with normal $PaCO_2$. They are also free of signs of right-sided heart failure.

Chest radiography demonstrates overinflation of the lungs, with flattened low diaphragms. Often, the lung fields are hyperlucent secondary to the arterial vascular deficiency in the lung periphery. If bullae are noted as well, then the diagnosis of emphysema is almost a certainty. However, only a few patients with emphysema have bullae. Another finding associated with emphysema is the loss of the normal, domed appearance of the cardiac silhouette; instead, it shifts to a vertically oriented appearance. If the FEV_1/FVC is less than or equal to 50% or the $PaCO_2$ is greater than or equal to 50 to 55, the risk of respiratory failure following surgery is increased and post-operative mechanical ventilation should be expected.

Diagnosis

Pulmonary function tests are relatively insensitive to obstruction of small, peripheral airways. These tests show increased TLC with decreased VC and a decrease in maximal expiratory flow rates, such as FEV_1/FVC. RV is also increased, reflecting the larger TLC with decreased VC. The decrease in the FEF_{25-75} is even greater. The best tests to determine this are the FEF_{25-75} and the MMEF. Normally, FEV_1/FVC is 80%. In the presence of mild COPD, this ratio decreases to 60% to 50%. In moderate COPD, the ratio is 40% to 60%, and less than 40% is considered severe COPD.

Patients with emphysema are often described as "pink puffers." This description is secondary to the increase in PaO_2, which is found on an arterial blood gas determination to be greater than 65 mm Hg, and the normal (40 mm Hg) or slightly decreased $PaCO_2$. Emphysematous lung destruction leads to a loss of pulmonary capillaries as a result of destruction of the alveoli walls. The ensuing loss of pulmonary capillary bed area causes the loss of diffusion capacity, although PaO_2 is found to be only mildly depressed, resulting in minimal pulmonary vasoconstriction. Unlike in chronic bronchitis, erythrocytosis does not occur, nor does one see cor pulmonale.

TREATMENT OF CHRONIC BRONCHITIS AND EMPHYSEMA

The goals of treatment of COPD are relatively simple. The treatment plan is designed to relieve the existing symptoms of COPD while slowing the progressive decline in pulmonary function that is associated with this disease. There are two types of therapies attempted in COPD. The first revolves around the cessation of smoking and the addition of supplemental O_2 for the patient with COPD. These are the only two therapeutic interventions that have been proven to alter the natural progression of COPD favorably. In addition, drug therapies are available to assist in reducing the symptoms of COPD.

First, cessation of smoking is critical. Smoking cessation diminishes the symptoms of chronic bronchitis. It also eliminates the accelerated loss of lung function observed in persons who continue to smoke. In addition, long-term O_2 administration, also known as home O_2, is usually

recommended to patients whose Pa_{O_2} is less than 55 mm Hg or whose hematocrit is greater than 55%. In addition, if there is evidence of cor pulmonale, the addition of home O_2 is often implemented. Supplemental O_2 administration should allow the Pa_{O_2} to increase to between 55 and 80 mm Hg. This is often accomplished through the use of a nasal cannula, flowing at 2 L/minute. However, the flow rate often must be titrated to each individual patient, based on the arterial blood gas measurements. Relief of arterial hypoxemia has been proven to be more effective than any current drug therapy in reducing pulmonary vascular resistance and in reducing excessive erythrocytosis with corresponding increases in blood viscosity (Table 2.1).

In addition, drug therapy is often prescribed to patients with COPD. Bronchodilators are the main agents for treatment of these diseases. These drugs cause only a limited increase in the FEV_1 in these patients, but more importantly, they eliminate symptoms by decreasing hyperinflation of the lungs and reducing the dyspneic feeling, and they often improve exercise tolerance. Surprisingly, with the subjective improvement in the patient's symptoms, one finds little improvement in the spirometric measurements.

β_2-Agonists also have been suggested to provide a decrease in lung infections. This benefit is postulated to be a result of the decrease in the adhesion of bacteria such as *Haemophilus influenzae* to the airway epithelial cells.

Table 2-1 Chronic Obstructive Pulmonary Disease: Differentiating Emphysema and Bronchitis

Characteristic	Emphysema	Bronchitis
Age at time of diagnosis (yr)	60+/–	50+/–
Dyspnea	Severe	Mild
Cough	After dyspnea begins	Before dyspnea
Sputum	Scant, mucoid	Copious, purulent
Chest film	Hyperinflated, bullous changes, reduced cardiac size	Increased bronchovascular markings in the lung fields, cardiomegaly
Chronic Pa_{CO_2} (mm Hg)	35–40	50–60
Chronic Pa_{O_2} (mm Hg)	65–75	45–60
Hematocrit (%)	35–45	50–55
Pulmonary hypertension: Rest Exercise	 None to mild Moderate	 Moderate to severe Worsens
Cor pulmonale	Rare, except in terminal disease	Common
Elastic recoil	Severely decreased	Normal
Resistance	Normal to slightly increased	High
Diffusing capacity	Decreased	Normal to slightly decreased

Pa_{CO_2}, partial arterial pressure of carbon dioxide; Pa_{O_2}, partial arterial pressure of oxygen.

However, COPD is more effectively treated by anticholinergics than by β_2-agonists, unlike in asthma. Inhaled corticosteroids are an important part of the drug arsenal as well. In addition, broad-spectrum antibiotics, such as ampicillin or erythromycin, are prescribed for acute episodes of worsening clinical symptoms, associated with increased sputum production, increased dyspnea, or purulence of sputum. Annual vaccinations against pneumococcal infection and influenza are also likely to be of help.

In patients with cor pulmonale secondary to bronchitis, drug-induced diuresis may be necessary. This approach is considered in patients with cor pulmonale and signs of right ventricular failure. A common sign of these conditions is increasing peripheral edema. However, side effects, such as diuretic-induced chloride depletion, can result in metabolic alkalosis, especially important in these patients because it decreases the respiratory drive and can result in chronic retention of CO_2. A newer surgical modality to ameliorate the respiratory dysfunction caused by severe emphysema is lung volume reduction surgery. Generally, surgical excision of the most diseased portion of the lung results in a greater amount of functional lung tissue afterwards. It is only found to be effective in those patients having emphysema in the upper lobes of the lung. It is not effective for emphysema confined to the lower lobes of the lung, or those who have emphysema throughout the lungs. Surgical excision of 20-30% of the most diseased portion of the lung results in an approximately 50% reduction in the work of breathing within 24 hours after surgery. Secondly, dynamic compliance is found to be abnormally low in patients with severe emphysema. This compliance value dramatically normalizes with surgical excision. Thirdly, severe emphysema is characterized by intrinsic PEEP (positive end-expiratory pressure) due to air trapping distal to those airways which collapse upon exhalation. After excision of 20-30% of the most diseased portion of the lung, intrinsic peer is reduced by 80% immediately after surgery, and this reduction is seen months after surgery. Lastly residual volume, generally seen as increased secondary to this air trapping, also is found to decrease with lung reduction surgery.

ASTHMA

Asthma is another common obstructive disease seen by physicians. It is estimated that 17 million Americans, nearly 5% of the population and including 5 million children, have asthma. Recently, the number of asthmatic patients, and the mortality rate associated with this disease have both been increasing. Risk factors associated with increased mortality include: black race, adolescence, history of any previous life-threatening epidoses, hospitalization within the last year, poor long-term medical care, medication non-compliance, and psychological or social problems. Asthma is a disease characterized by reversible expiratory airway obstruction secondary to airway narrowing in response to stimuli, airway hyperresponsiveness, and airway inflammation. In contrast to bronchitis and emphysema, in asthma the airway obstruction is not fixed, but rather it can vary widely over time and change in a period of minutes or in days to weeks. Although reversibility of expiratory airflow is an important characteristic of asthma, irreversible airflow obstruction can develop in some patients.

Epidemiology

The features of asthma have several possible explanations. These include an allergen-induced immunologic response and an abnormality in the parasympathetic-sympathetic regulation of the autonomic nervous system.

One of the most accepted explanations for asthma is that it is immunologic. In atopic persons, repeated exposure to antigens leads to a synthesis of specific immunoglobulin E (IgE) antibodies. Patients are frequently found to have increased levels of IgE in the serum. When an antigen attaches to this IgE, they form a cross-link, attach to a mast cell, and cause the mast cell to release histamine, eosinophilic chemotactic factor, interleukin, tumor necrosis factor, leukotrienes, prostaglandins, platelet-aggregating factor, and bradykinin. The substances cause a decrease of cyclic adenosine monophosphate (cAMP) in the bronchial smooth muscle cells that leads to bronchospasm and edema secondary to increased capillary permeability. In addition, these substances cause the eosinophilic infiltration of the airways in the hours following the allergen exposure.

Another theory related to the features characteristic of asthma is associated with central nervous system autoregulation. This hypothesis is supported by the observation that nonselective β-agonists, such as propranolol, result in increased airway obstruction. The hypothesis suggests a neural imbalance between the parasympathetic bronchoconstricting system and the inhibitory, bronchodilatory sympathetic system. It is postulated that chemical mediators released from mast cell degranulation interact with the autonomic nervous system. For example, chemical mediators can stimulate receptors in the airway to trigger reflex bronchoconstriction. In contrast, other mediators can sensitize smooth muscle bronchial cells to the effects of acetylcholine. In addition, stimulation of muscarinic receptors encourages mast cell release, thus providing a reinforcement of inflammation and bronchoconstriction.

Clinical Features

Typically, there is a family history of asthma. Asthma is associated with numerous predisposing factors. These include airborne allergens, aspirin, environmental and occupational factors, exercise, stress, and infection.

Asthma usually results in an attack, leading to an episode of wheezing, cough, and dyspnea. During the time before the attack, patients have periods of normal or near-normal pulmonary function, and no physical finding suggests asthma. As obstruction severity increases, wheezing becomes more audible and progresses earlier in the expiration phase. The absence of wheezing often suggests full airway obstruction. The cough of asthma is characteristic and can be associated with the production of copious sputum, typically mucoid and tenacious. Eosinophils often cause a yellowish tint to the sputum. Occasionally, cough is the only manifestation of asthma. The degree of dyspnea tends to vary greatly with time and is directly related to the severity of obstruction. In severe obstruction, the patient may experience "air hunger" as the foremost symptom. Patients often insist on sitting up to ease their breathing. In addition, patients often report chest tightness and discomfort relating to a sensation of not being able to inhale fully.

In mild asthma, Pa_{O_2} and Pa_{CO_2} are generally normal. The tachypnea and hyperventilation observed often result from pulmonary neural reflexes rather than from arterial hypoxia. The most common finding on the arterial blood gas determination during a severe asthmatic attack is hypoxemia. Hypercarbia or CO_2 retention is relatively uncommon because the diffusing capacity of CO_2 is 20 times greater than with O_2. CO_2 retention is found only late and only in severely affected patients. These patients typically hyperventilate, resulting in respiratory alkalosis.

In addition, during this attack, the FEV_1/FVC ratio is markedly reduced, as are the MMEF and the maximum breathing capacity. These measurements directly relate to the severity of expiratory airflow obstruction. They provide the ability to assess and monitor the severity of an asthmatic exacerbation. Typically, a patient presenting for hospitalization for treatment of an asthma attack has an FEV_1 of less than 35% of normal and an MMEF that is 20% of normal or lower. In addition, in moderate to severe attacks, the FRC increases by 1 to 2 L, whereas TLC remains normal. There is no change in the diffusing capacity of carbon monoxide. Flow volume looping shows a characteristic downward "scoop" of the expiratory limb (Fig. 2.2), reflecting the decreased expiratory volume overtime.

Status asthmaticus, an unrelenting asthma attack is the most severe episode of asthma and can be life-threatening. Most episodes of status asthmaticus respond to emergency management with oxygen, nebulized or inhaled β-agonists, anticholinergics, and IV steroids. Occasionally, however, a few patients fail to respond to this treatment.

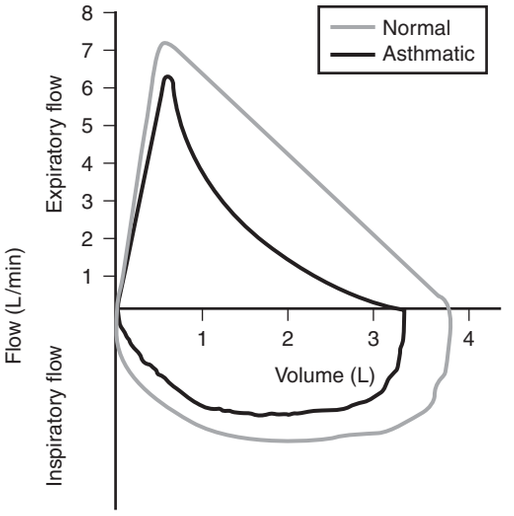

Figure 2.2 Flow Volume Loop of Normal vs. Asthmatic patients.

They develop signs of impending respiratory failure, which include tachypnea, tachycardia, marked sternal retractions reflecting accessory muscle usage, nasal flaring, anxiety, or alteration of mental. There is moderate to severe hypoxemia, and Pa_{CO_2} can either remain normal or elevated. Along with conservative therapy already in place, an IV terbutaline infusion is the drug of choice, titrating to a clinical endpoint of respiratory improvement, or tachycardia, with heart rate exceeding 180 beats/minute. Intubation of the trachea, with mechanical ventilation are done as a last resort, and is avoided because the endotracheal tube can itself serve as an airway irritant, thereby worsening the ongoing bronchoconstriction.

Chest radiography is not specific for asthma. One may see hyperinflation of the lungs. Generally, the use of chest radiography is better to rule out pneumonia or congestive heart failure, diagnoses often confused with asthma.

No single laboratory test can serve to confirm the diagnosis of asthma. However, a test for the response to bronchodilators often provides supportive evidence for clinical suspicions of asthma. The ECG can also be helpful by demonstrating evidence of acute right-sided heart failure and ventricular irritability during an acute asthma attack.

Other disorders with various causes are also classified as asthma. These include allergen-induced immunologic, exercise-induced, nocturnal, aspirin-induced, occupational, and infectious asthma. The first variant, allergen-induced asthma, is IgE mediated, and it is the most common form of reversible expiratory obstruction. Patients with this form commonly manifest other atopic manifestations, such as allergic rhinitis or dermatitis. A genetic predisposition is often identified by a presence of a family history. Peripheral blood eosinophilia and increased plasma IgE suggest this variant.

Exercise-induced asthma describes a patient in whom vigorous physical activity triggers acute airway narrowing and expiratory obstruction. This disorder is generally viewed as thermally induced asthma, thus identifying the association with fluctuation of heat and water that develops in the tracheal bronchial tree with warming and humidifying large air volumes during exercise.

Nocturnal asthma, a third variant, is said to reflect changes in airway tone, circadian variation in circulating catecholamine concentration, and gastroesophageal reflux related to the supine position associated with sleep. The incidence of asthma-related deaths has been shown to increase between midnight and morning.

Aspirin-induced asthma is a variant in which asthma and most nonsteroidal anti-inflammatory drugs cause acute bronchospasm. This condition occurs in approximately 10% to 15% of adult patients with asthma. It occurs anywhere from 15 minutes to 4 hours after drug ingestion. Although nasal polyps are associated with aspirin sensitivity, they are often present in the absence of this condition. It is thought that aspirin triggers bronchoconstriction in susceptible patients with asthma by blocking the cyclooxygenase mediation of arachidonic acid to prostaglandins. This would shunt the arachidonic acid toward the production of leukotrienes, a potent bronchoconstrictor.

Occupational asthma is the most common occupational lung disease. It is estimated to affect 5% to 10% of the world's population. Treatment for this disorder involves removing the individual from the work environment. More than 250 identified agents can cause occupational asthma; isocyanates are the leader and are responsible for 10% of cases. Chlorine and ammonia are two other common causes of occupational asthma.

Finally, the infectious asthma variant is one associated with an acute inflammatory disease of the bronchi. These cases may be caused by bacteria, viruses, or *Mycoplasma*. The treatment for this variant is eradication of the infection.

Treatment

The treatment of asthma is accomplished through a multimodal medical approach. Anti-inflammatory agents interrupt the development of inflammation, a central feature of asthma. These agents include oral corticosteroid drugs, inhaled corticosteroid therapy, and cromolyn sodium.

Corticosteroids have been found to be the most effective pharmacologic treatment for the control of chronic symptoms of asthma, as well as for preventing exacerbations, in patients with mild or severe asthma. These agents are generally given as inhaled drugs because the systemic side effects are less than with oral administration. Because the inhaled corticosteroids are highly lipophilic, they quickly access the airway cells and inhibit the genetic transcription of cytokine synthesizing genes. By reducing cytokine transcription, the corticosteroids serve to decrease airway inflammation and reduce airway hyperresponsiveness.

Cromolyn sodium, another anti-inflammatory agent, acts directly on the mast cell by stabilizing the cell membrane. It thereby limits the release of mast cell inflammatory mediators. Like the corticosteroids, this drug is administered as a metered dose inhalation. Although cromolyn sodium is an anti-inflammatory agent, it will not relieve bronchospasm once the condition is present.

A second modality is the use of bronchodilators that serve to relax the bronchiole smooth muscle. They include the β_2-agonist family, which serve as the optimal treatment for acute exacerbations. The β_2-agonists stimulate β_2-receptors on the bronchial smooth muscle, thereby activating adenylate cyclase and increasing intracellular cAMP concentrations. In addition, the methylxanthines are used, an example of which is theophylline, which results in mild bronchodilation with a long period of activity. Although theophylline reduces respiratory muscle fatigue and has a long duration of action, it is considered a third-line treatment because of its numerous significant side effects, such as nausea, vomiting, seizures, and tachyarrhythmia.

A third medical modality is the use of anticholinergic medications. These medications produce bronchodilation by decreasing the vagal tone through blocking the muscarinic receptors. Ipratropium, a derivative of atropine, has revived interest in this approach to treating asthma. Administered by metered dose inhaler, it is slower and less effective than the β-agonists such as albuterol. It causes bronchodilation by the blocking of cyclic guanosine monophosphate, and it has the advantage of not changing heart rate or intraocular pressure.

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CHAPTER 3

Acute Lung Injury: Injury from Drugs

Nick H. Kim and Roger G. Spragg

The clinical presentation of drug-induced lung disease (DILD) can vary from acute to delayed, mild to severe, and reversible to permanent injury. For some drugs, the incidence of DILD is relatively high, whereas with the majority of drugs, the incidence remains rare and unpredictable. The drugs implicated in DILD can be found in all major therapeutic classes, and the number of drugs associated with pulmonary toxicity is likely to rise as new agents are introduced and as additional experience is gained with current agents. The evidence linking individual drugs to lung injury is largely based on case reports. These reports provide evidence that many drugs are capable of producing a range of host responses and types of lung injury. Such pathologic and clinical heterogeneity underscores the importance of maintaining DILD in the differential diagnosis in patients presenting with acute lung injury (ALI). The diagnosis remains one of exclusion. Early recognition and cessation of the offending drug are critical to provide the best chance for a favorable outcome.

PATHOPHYSIOLOGY

The lung has limited ways of responding to injury. The histopathologic features of DILD are nonspecific and can be seen with other lung diseases. The clinical manifestations of DILD fall under a spectrum of pulmonary syndromes, including, but not limited to, the following: interstitial pneumonitis with or without pulmonary fibrosis, ALI (including acute respiratory distress syndrome [ARDS]), hypersensitivity pneumonitis, bronchiolitis obliterans with organizing pneumonia (BOOP), noncardiogenic pulmonary edema, and diffuse alveolar hemorrhage. Although a drug may usually be associated with a particular syndrome, many of these drugs have the potential for causing a variety of syndromes.

Most of the implicated drugs appear to cause an idiosyncratic reaction, although several drugs have recognized dose-related toxicities. Certain drugs also have known risk factors for the development of DILD. The pathogenesis of DILD, however, remains largely speculative or extrapolated from animal models. The proposed mechanisms of lung injury from drugs can be broadly divided into two categories: direct and indirect (Table 3.1). Direct mechanisms include enhanced production of reactive oxygen species and direct toxicity from drug or drug metabolites. Indirect mechanisms include immune or inflammatory responses and coagulation- or fibrin-mediated injury. These indirect mechanisms, however, are not unique to DILD and have been proposed as causes of other acute and chronic lung injuries.[1,2]

Lung injury mediated by reactive oxygen species has been implicated in DILD as well as in other causes of ALI.[3] Bleomycin, nitrofurantoin, oxygen, and paraquat are examples of agents believed to cause lung injury mediated by reactive oxygen species.[4] Reactive oxygen and nitrogen species are generated principally from phagocytic leukocytes, but they can also be produced by fibroblasts, smooth muscle cells, endothelium, and epithelium.[5] These reactive species are normally neutralized by glutathione, catalase, superoxide dismutase, and other naturally present antioxidants. Bronchoalveolar lavage analyses from patients with ARDS have shown an imbalance, with evidence of excess production of reactive oxygen species and diminished levels of glutathione.[3,5] Excess production of reactive oxygen species can induce cellular damage through several pathways, including