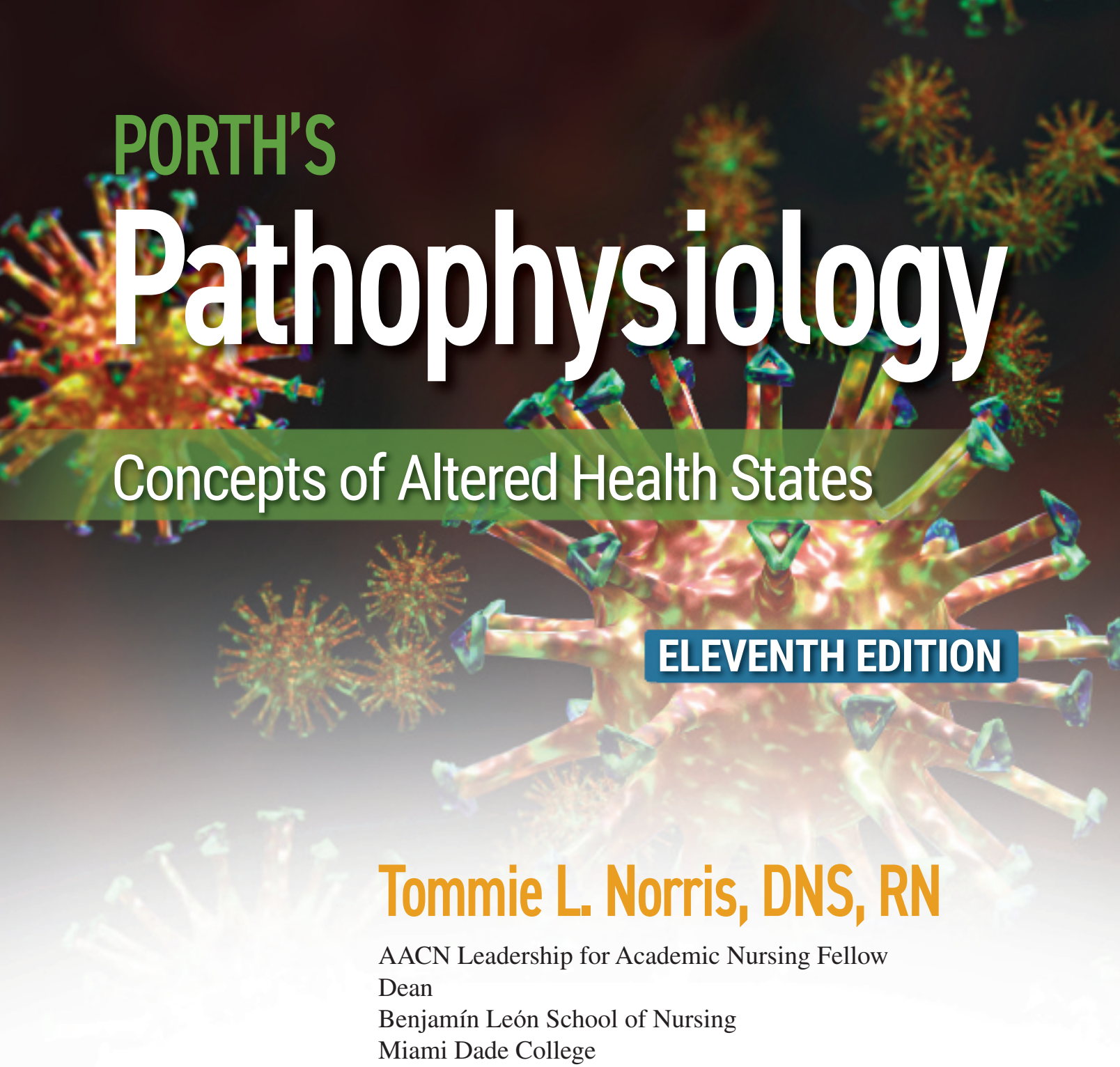
PORTH'S

Pathophysiology

Concepts of Altered Health States

ELEVENTH EDITION



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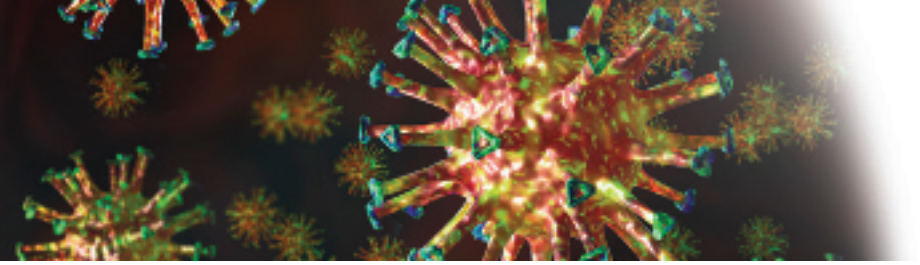

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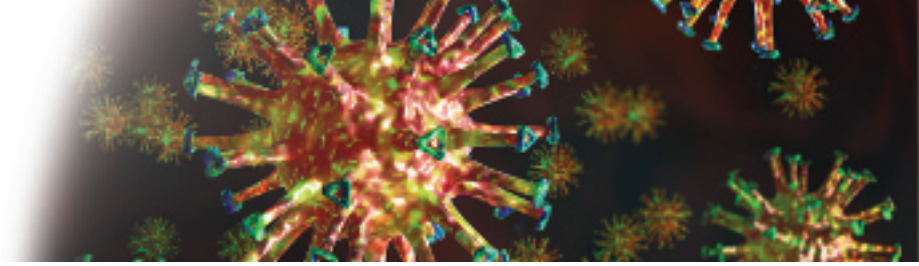

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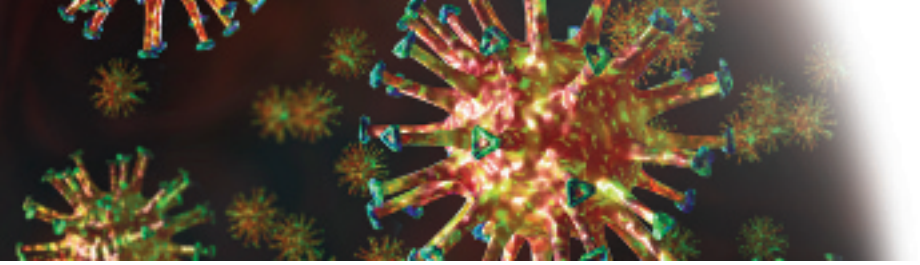


Preface

Since its first edition in 1982, *Porth's Pathophysiology* has grown to become a trusted and definitive resource for students, instructors, and healthcare professionals. The goal for each edition has been to develop a text that is current, accurate, and comprehensive, and presented in a logical manner. This book was written with the intent of making the subject of pathophysiology an exciting exploration that relates normal body functioning to the physiologic changes that occur as a result of disease, as well as the body's remarkable ability to compensate for these changes. Indeed, it is these changes that represent the signs and symptoms of disease.

Although this book's vision and objectives have remained consistent, this edition considers the many technological advances allowing healthcare providers to diagnose earlier and with more accuracy. As the world faced new diseases such as COVID-19, the text incorporated up-to-date information with the understanding that advances will undoubtedly be forthcoming. Contributors from around the world and from diverse disciplines provided the expertise to make the information applicable to a broad audience. A strong foundation in pathophysiology is essential to give healthcare providers the clinical reasoning tools to critically analyze complex patient situations—both those that are common and those that are rare.

This text focuses on the scientific basis upon which the practice components of the health professions are based. The evidence-based information garnered from the text provides practitioners with the knowledge for effective clinical decision making within a dynamic profession. For the 11th edition, the style of the *Publication Manual of the American Psychological Association*, 7th Edition, was used in each chapter for the References list and for the in-text citations; this format allows readers to more easily see references at a glance in the text and facilitates locating references listed alphabetically at the ends of the chapters.

A holistic conceptual framework uses body systems as an organizing structure and demonstrates how the systems are interrelated. Selection of content was based on common causes of morbidity and mortality across the life span, and recent advances in the fields of genetics, epigenetics, immunology, microbiology, and molecular biology are included. Concepts are presented in a manner that is logical and understandable for students. One goal of the new edition is to provide critical information needed to understand complex health alterations by expanding on the number of definitions for key terms. Many students are challenged with what seems to be "another language"—that of health and healthcare. As the diversity of nurses and other healthcare providers increases, it is imperative to provide support to clarify the meaning of key concepts. The chapters are arranged so that fundamental concepts such as cellular adaptation, inflammation and repair, genetic control of cell function and inheritance, and immunologic processes appear in the early chapters before the specific discussions of particular disease states. In addition, nursing concepts are included in this edition to focus on major ideas and to group and categorize content.

Proven strengths of the text continue to be the expanded chapters on health and disease; nutrition; sleep and sleep disorders; and thought, emotion, and mood disorders. Advances in healthcare are presented through the inclusion of international studies, World Health Organization guidelines, updated standards, and the health variants of diverse populations.

ORGANIZATION

The units in this book identify broad areas of content, such as alterations in the circulatory system. Many of the units have an introductory chapter that contains essential information about the structure and function of the body systems that are being discussed in the unit. Each such chapter provides the foundation for understanding the pathophysiology content presented in the subsequent chapters. The chapter outline that appears at the beginning of each chapter provides an overall view of the chapter content and organization.

BUILDING CLINICAL JUDGMENT SKILLS

Nursing students are required to obtain nursing knowledge and to apply foundational nursing processes to practice effective clinical judgment. Being able to apply clinical judgment in practice is critical for patient safety and optimizing outcomes. This text includes unfolding case studies that provide an opportunity to apply pathophysiology concepts to clinical decision making. These features challenge readers to think critically and to assess clinical judgment. Healthcare providers are constantly required to make complex decisions in a dynamic care environment as more diagnostic tests, assessments, and history and physical are incorporated into plan of care; readers learn normal versus abnormal findings to enable understanding of more advanced concepts. The questions, and the rationales provided on the book's companion website, allow readers to validate their knowledge or recognize their need for further review for a better understanding. Additionally, accompanying products CoursePoint+ and Lippincott NCLEX-RN PassPoint provide an adaptive experience that allows students to build confidence by answering questions like those found on the Next Generation NCLEX (NGN) examination.

INCLUSIVE LANGUAGE

A note about the language used in this book. Wolters Kluwer recognizes that people have a diverse range of identities, and we are committed to using inclusive and nonbiased language in our content. Please note that whenever "male" is used in this book, it refers to a person assigned male at birth, and whenever "female" is used, it refers to a person assigned female at birth. In line with the principles of nursing, we strive not to define people by their diagnoses, but to recognize their personhood first and foremost, using as much as possible the language diverse groups use to define themselves, and including only information that is relevant to nursing care. Data that allow students to understand differences and similarities of ethnic and racial makeup of patients contribute to a better ability to evaluate findings.

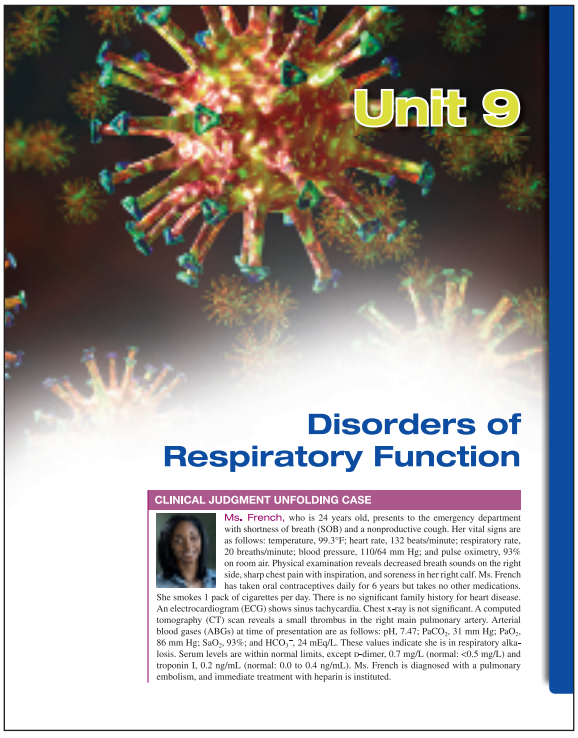
We strive to better address the unique perspectives, complex challenges, and lived experiences of diverse populations traditionally underrepresented in health literature. When describing or referencing populations discussed in research studies, we will adhere to the identities presented in those studies to maintain fidelity to the evidence presented by the study investigators. We follow best practices of language set forth by the *Publication Manual of the American Psychological Association,* 7th Edition, but acknowledge that language evolves rapidly, and we will update the language used in future editions of this book as necessary.

FEATURES OF THIS BOOK

This book includes the following special features to help you master the essential content.

Clinical Judgment Unfolding Cases

Each unit opens with a case study that introduces a patient's case history and symptoms.



Throughout some of the chapters in that unit, more information is added to the case as it relates to the information being presented, and the student is presented with questions to develop their clinical judgment. (Answers are available for instructors at http://thepoint.lww.com/Porth11e.)

CLINICAL JUDGMENT UNFOLDING CASE

Remember Ms. French, the person with pulmonary embolism you met at the beginning of the unit? In pulmonary embolism, an area of the pulmonary vasculature becomes obstructed by an embolus, impairing blood flow to the alveoli and interfering with gas exchange.

1. Why would a pulmonary embolism interfere with blood flow to the alveoli?
2. Describe the difference between an embolus and an embolism.

Learning Objectives

Learning Objectives appear at the beginning of each major section of content to provide a focus for your study. After you have finished reading the chapter, you may want to go back and make sure that you have met each of the objectives.

LEARNING OBJECTIVES

After completing this chapter, the learner will be able to meet the following objectives:

1. Cite the general purpose of changes in cell structure and function that occur as the result of normal adaptive processes.
2. Describe cell changes that occur with atrophy, hypertrophy, hyperplasia, metaplasia, and dysplasia, and state general conditions under which the changes occur.
3. Compare the pathogenesis and effects of dystrophic and metastatic calcifications.
4. Describe the mechanisms whereby physical agents such as blunt trauma, electrical forces, and extremes of temperature produce cell injury.
5. Differentiate between the effects of ionizing and nonionizing radiation in terms of their ability to cause cell injury.
6. State the mechanisms and manifestations of cell injury associated with lead poisoning.
7. Relate free radical formation and oxidative stress to cell injury and death.

Nursing Concepts

Nursing Concepts listed at the beginning of each chapter make clear how content applies to concepts-based curricula.

NURSING CONCEPTS

Acid–Base
Oxygenation
Perfusion

Key Terms and Glossary

It is essential for any professional to use and understand the vocabulary of their profession. Throughout the text, you will encounter key terms in bold purple. This is a signal that a word and the ideas associated with it are important to learn. In addition, a glossary is provided to help you expand your vocabulary and improve your comprehension of what you are reading. The glossary contains concise definitions of frequently encountered terms. If you are unsure of the meaning of a term you encounter in your reading, check the glossary in the back of the book before proceeding. This edition provides even more key terms to improve reading comprehension.

Melatonin, a hormone produced by the pineal gland, is thought to help regulate the sleep–wake cycle and, possibly, circadian rhythm (Barrett et al., 2019). The **pineal gland** synthesizes and releases melatonin at night, a rhythm that is under direct control of the SCN (see Fig. 17.1). Large numbers of melatonin receptors are present in the SCN, suggesting a feedback loop between the SCN and the pineal gland.

Boxes

Boxes are used throughout the text to summarize and highlight key information.

"Key Points" Boxes

One of the ways to approach learning is to focus on the major ideas or concepts rather than trying to memorize a list of related and unrelated bits of information. Healthcare providers must apply these concepts in the clinical setting, which requires an understanding of the underlying etiology, histology, symptoms, risk factors, and hallmark features of a particular disease. As you have probably already discovered, it is impossible to memorize everything that is in a particular section or chapter of the book. Not only does your brain have a difficult time trying to figure out where to store all the different bits of information, your brain does not know how to retrieve the information when you need it. Most important of all, memorized lists of content can seldom, if ever, be applied directly to an actual clinical situation. The "Key Points" boxes guide you in identifying the major ideas or concepts that form the foundation for truly understanding the major areas of content. When you understand the concepts in the "Key Points" boxes, you will have a framework for remembering and using the facts presented in the text.

KEY POINTS

FUNCTIONS OF THE SKIN

- The skin prevents body fluids from leaving the body, protects the body from potentially damaging environmental agents, and serves as an area for heat exchange. In addition, cells of the skin immune system provide protection against invading microorganisms.
- Receptors in the skin relay touch, pressure, temperature, and pain sensation to the central nervous system for localization and discrimination.

"In Summary" Boxes

The "In Summary" boxes at the end of each main section provide a review and a reinforcement of the important content that has been covered. Use the summaries to ensure that you have understood what you have read.

IN SUMMARY

COVID-19 is caused by a coronavirus called SARS-CoV-2. COVID-19 is highly infectious and is transmitted via droplet or aerosol. The virus gains entry by the ACE-2 receptors found on the epithelium of the nasopharynx and the upper respiratory tract. Known risk factors include compromised immunity, respiratory disease, developmental delay, congenital heart disease, and sickle cell disease. The hallmark signs are fever and respiratory symptoms, which can vary from mild to severe. The rapid antigen (or rapid diagnostic) test has allowed people to test at home and take measures to decrease the spread. Vaccines based on mutations continue to become widely available.

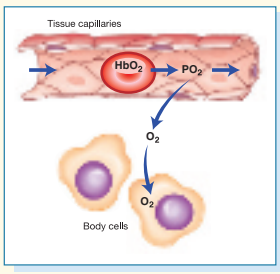
"Understanding" Boxes

"Understanding" boxes focus on the physiologic processes and phenomena that form the basis for understanding disorders presented in the text. This feature breaks a process or phenomenon down into its component parts and presents it in a sequential manner, providing an insight into the many opportunities for disease processes to disrupt the sequence.

Understanding **Oxygen Transport** *(Continued)*

Oxygen Dissociation in the Tissues

The dissociation or release of O_2 from hemoglobin occurs in the tissue capillaries where the PO_2 is less than that of the arterial blood. As oxygen dissociates from hemoglobin, it dissolves in the plasma and then moves into the tissues where the PO_2 is less than that in the capillaries. The affinity of hemoglobin for O_2 is influenced by the carbon dioxide (PCO_2) content of the blood and its pH temperature and 2,3-BPG, a byproduct of glycolysis in red blood cells. Under conditions of high metabolic demand, in which the PCO_2 is increased and the pH is decreased, the binding affinity of hemoglobin is decreased. During decreased metabolic demand, when the PCO_2 is decreased and the pH is increased, the affinity is increased.



"Geriatric Considerations" and "Pediatric Considerations" Boxes

"Geriatric Considerations" and "Pediatric Considerations" boxes at the end of each chapter provide insight on how the content of the chapter is reflected in these two populations. These life span considerations highlight variations that can be attributed to age—for example, the immaturity of the immune system of newborns and the decreased phagocytic action in older adults, both of which increase the risk for disease.

GERIATRIC Considerations

- The heart's very limited ability to regenerate is due to a very slow rate of replacement of the cardiac stem cells and myocytes (Levi, 2020).
- The ventricles become stiffer with age resulting in increased filling (diastolic) pressure leading to greater risk for diastolic heart failure (Levi, 2020).
- Thirty-five percent of older adults have obesity, which is a risk factor for coronary heart disease and atherosclerosis; Black people assigned female at birth aged 65 years and older are at the greatest risk (Leung, 2021).
- Symptoms associated with peptic ulcer disease in older adults are more severe than in younger adults, leading to dehydration, hemorrhage, infection, and risk of shock (Al-Khafaji, 2020).
- The decreased ability of the older adult to quickly respond to shock makes it imperative to observe for symptoms such as restlessness, which is the primary symptom of hypoxia; administer prophylactic oxygen; and carefully monitor intake and output (Al-Khafaji, 2020).

PEDIATRIC Considerations

- Levels of brain (b-type) natriuretic protein (BNP) are a biomarker to indicate severity of heart failure in infants (Levi, 2020).
- Cardiac hypertrophy in infants rereleases atrial natriuretic factor usually restricted to the atrium after birth along with contractile proteins to compensate for decreased cardiac output (Levi, 2020).
- Evidence of maternal rubella infection during the first 4 weeks of gestation is the greatest risk for congenital cardiac defects. Persistent patent ductus arteriosus is the most common congenital cardiac defect in infants of pregnant people infected with rubella during the early weeks of gestation (Levi, 2020).
- Acute renal failure in children is most often the result of hypovolemic or septic shock (Neviere, 2021).
- A line of demarcation of skin temperature is a sign that the child may be developing shock with accompanying cardiovascular compromise (Neviere, 2021).
- Neonates exhibit a paradoxical phenomenon of exhibiting bradycardia rather than tachycardia seen in infants and children in shock (Neviere, 2021).

Tables and Charts

Tables and charts are designed to present complex information in a format that makes it more meaningful and facilitates recall of the information. Tables, which have two or more columns, are often used for the purpose of comparing or contrasting information. Charts, which have one column, are used to summarize information.

TABLE 20.1 COMMON DISORDERS AFFECTING THE VESTIBULAR SYSTEM

TYPE OF DISORDER	PATHOLOGY
Acoustic neuroma	A noncancerous growth or tumor on the vestibulocochlear nerve
Benign paroxysmal positional vertigo (BPPV)	Disorder of otoliths
Ménière disease	Dislodgement of otoliths that participate in the receptor function of the vestibular system
Motion sickness	Repeated stimulation of the vestibular system such as during car, air, and boat travel
Labyrinthitis	Acute viral or bacterial infection of the vestibular pathways
Vestibular migraine	Dizziness or vertigo occurs with or without headache; related to the neurotransmitter serotonin

CHART 17.2 SIGNS AND SYMPTOMS OF OBSTRUCTIVE SLEEP APNEA

- Excessive daytime sleepiness
- Noisy snoring
- Observed apnea
- Insomnia
- Heartburn
- Nocturia
- Morning headaches
- Dry mouth
- Erectile dysfunction
- Hypertension

Illustrations and Photos

The detailed, full-color illustrations will help you to build your own mental image of the content that is being presented. Each drawing has been developed to fully support and build upon the ideas in the text. Some illustrations are used to help you picture the complex interactions of the multiple phenomena that are involved in the development of a particular disease; others can help you visualize normal function or understand the mechanisms that enable the disease processes to exert their effects. In addition, photographs provide a realistic view of selected pathologic processes and lesions.

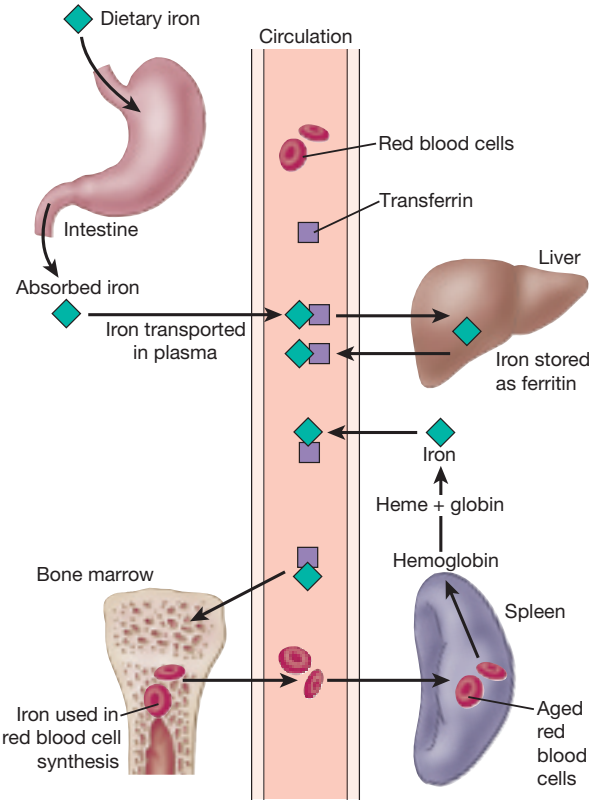


Figure 23.3 • Diagrammatic representation of the iron cycle, including its absorption from the gastrointestinal tract, transport in the circulation, storage in the liver, recycling from aged red cells destroyed in the spleen, and use in the bone marrow synthesis of red blood cells.

Concept Mastery Alerts

Concept Mastery Alerts clarify fundamental nursing concepts to improve the reader's understanding of potentially confusing topics, as identified by Lippincott's Adaptive Learning Powered by prepU.

Concept Mastery Alert

The electricity in nonsynchronized defibrillation depolarizes the entire heart, interrupting the chaotic rhythm and allowing the SA node to take control.

Review Exercises

The Review Exercises at the end of each chapter are designed to help you integrate and synthesize material and to help you verify your understanding of the material presented. If you are unable to answer a question, reread the relevant section in the chapter. (Answers are available for instructors at http://thepoint.lww.com/Porth11e.)

REVIEW EXERCISES

1. A 75-year-old woman with a history of congestive heart failure presents to the clinic complaining of feeling tired. Her heart rate is 121 beats/min, and the rhythm is irregular.
   - *A. What type of arrhythmia do you think she might be having? What would it look like if you were to obtain an ECG?*
   - *B. What causes this irregularity?*
   - *C. Why do you think she is feeling tired?*
   - *D. What are some of the concerns with this type of arrhythmia?*
2. A 45-year-old man appears at the urgent care center with complaints of chest discomfort, shortness of breath, and generally not feeling well. You assess vital signs and find that his temperature is 99.2°F, blood pressure 180/90, pulse 90 and slightly irregular, and respiratory rate 26. You do an ECG, and the readings from the anterior leads indicate that he is experiencing an ischemic episode.
   - *A. You attach him to a cardiac monitor and see that his underlying rhythm is normal sinus rhythm, but he is having frequent premature contractions that are more than 0.10 second in duration. What type of premature contractions do you suspect?*
   - *B. What would you expect his pulse to feel like?*
   - *C. What do you think the etiology of this arrhythmia might be? How might it be treated?*

Appendix

The appendix, "Lab Values," provides quick access to normal values for many laboratory tests, as well as a description of the prefixes, symbols, and factors (e.g., micro, μ, 10^{-6}) used for describing these values. Knowledge of normal values can help you to put abnormal values in context.

A COMPREHENSIVE PACKAGE FOR TEACHING AND LEARNING

To further facilitate teaching and learning, a carefully designed ancillary package has been developed to assist faculty and students.

Instructor Resources

Tools to assist you with teaching your course are available upon adoption of this text on thePoint® at http://thepoint.lww.com/Porth11e.

- A **Test Generator** features NCLEX-style questions mapped to chapter learning objectives.
- An extensive collection of materials is provided for each book chapter:
  - **PowerPoint Presentations** provide an easy way to integrate the textbook with your students' classroom experience; multiple-choice and true/false questions are included to promote class participation.
  - **Guided Lecture Notes** walk you through the chapter, learning objective by learning objective, with integrated references to the PowerPoint presentations.
  - **Discussion Topics** (and suggested answers) can be used in the classroom or in online discussion boards to facilitate interaction with your students.
  - **Assignments** (and suggested answers) include group, written, clinical, and Web assignments to engage students in varied activities and assess their learning.
  - **Case Studies** with related questions (and suggested answers) give students an opportunity to apply their knowledge to a client case similar to one they might encounter in practice.
  - **Answers to the Clinical Judgment Unfolding Cases** and **Answers to the Review Exercises** in the book facilitate review of student responses to the questions in these sections.
- Sample **Syllabi** are provided for 14-week and 28-week courses.
- An **American Association of Colleges of Nursing (AACN) Essentials Competency Map** identifies book content related to the AACN Essentials.
- An **Image Bank** allows you to use the photographs and illustrations from this textbook in your course materials.
- **Learning Objectives** from the book.
- An **ebook** serves as a handy resource.
- Access to all **Student Resources** is provided so that you can understand the student experience and use these resources in your course as well.

Student Resources

An exciting set of free learning resources is available on thePoint® to help students review and apply vital concepts. Multimedia engines have been optimized so that students can access many of these resources on mobile devices. Students can access all these resources at http://thepoint.lww.com/Porth11e using the codes printed in the front of their textbooks.

- **Concepts in Action Animations** bring physiologic and pathophysiologic concepts to life, explaining concepts that are difficult to understand.
- **Journal Articles** offer access to current articles relevant to each chapter and available in Wolters Kluwer journals to familiarize students with nursing literature.

LIPPINCOTT® COURSEPOINT

Lippincott® CoursePoint is an integrated, digital curriculum solution for nursing education that provides a completely interactive experience geared to help students understand, retain, and apply their course knowledge and be prepared for practice. The time-tested, easy-to-use, and trusted solution includes engaging learning tools, case studies, and in-depth reporting to meet students where they are in their learning, combined with the most trusted nursing education content on the market to help prepare students for practice. This easy-to-use digital learning solution of *Lippincott® CoursePoint,* combined with unmatched support, gives instructors and students everything they need for course and curriculum success!

Lippincott® CoursePoint includes:

- Engaging course content provides a variety of learning tools to engage students of all learning styles.
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- Unparalleled reporting provides in-depth dashboards with several data points to track student progress and help identify strengths and weaknesses.
- Unmatched support includes training coaches, product trainers, and nursing education consultants to help educators and students implement CoursePoint with ease.

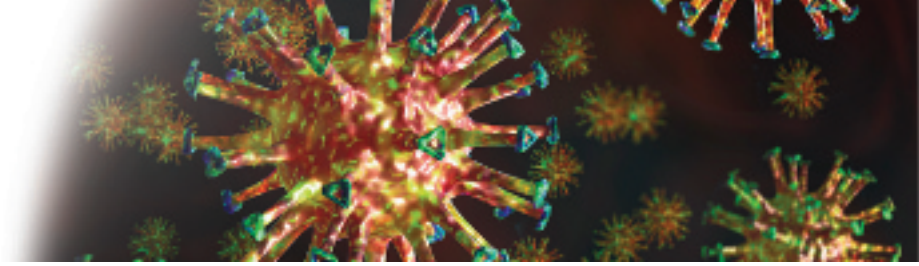
ACKNOWLEDGMENTS

The history of the text is substantial in part due to the vision of the original editor, Dr. Carol Porth, who forged the "nurse–physiologist" approach that is still the hallmark signature of the book. The expertise of the contributors, both current and previous, keeps the book at the forefront of advances in science, medicine, and healthcare. Their attention to detail and their desire to share current, relevant, and essential information with learners provides the comprehensive foundation to integrate pathophysiology into clinical decision making. Thanks also to Dr. Leila Casteel, who shared her expertise in nursing practice to review the currency of the information contained in the book.

I would like to thank the editorial team that worked diligently to review and revise this edition: Thanks to Jonathan Joyce, Senior Acquisitions Editor, for his leadership, providing guidance when facing hard deadlines; many thanks go to Meredith Brittain, Senior Development Editor, for her attention to detail and invaluable edits to improve readability; and thanks to Caroline Define, who tracked our progress and secured many improved images that especially benefit the visual learner.

I would also like to thank my work family, who shared my enthusiasm and provided encouragement while I was writing. Lastly, I want to thank my family for listening to me as I shared information gleaned from the new edition related to medical advances (especially when sharing a meal). Thanks to the many new professional friends who served as contributors to benefit our future healthcare providers. I especially want to thank all the students and faculty who choose the book and who share their perspectives on how the book improves understanding of course content in medical-surgical nursing, reproductive health, and pharmacology.

Contents



Disorders of Ventilation and Gas Exchange

31

Donna Brown-Richards

LEARNING OBJECTIVES

After completing this chapter, the learner will be able to meet the following objectives:

1. Define the terms *hypoxemia* and *hypercapnia and compare manifestations of each.*
2. Differentiate between the mechanisms causing disorders of ventilation and diffusion.
3. Characterize the pathogenesis and manifestations of transudative and exudative pleural effusion, chylothorax, and hemothorax.

4. Differentiate among the causes and manifestations of spontaneous pneumothorax, secondary pneumothorax, and tension pneumothorax.
5. Describe the causes of pleurisy (pleuritis) and differentiate the characteristics of pleural pain from other types of chest pain.
6. Describe the interaction between one's genetics, alteration of immune response, and environmental agents in the pathogenesis of asthma or reactive airway disease.
7. Differentiate between chronic bronchitis and emphysema in terms of pathology and clinical manifestations.
8. Describe the genetic abnormality responsible for the manifestations of CF.
9. State the difference between COPDs and interstitial lung diseases (ILDs) in terms of their pathology and manifestations.
10. Describe the pathophysiology of idiopathic pulmonary fibrosis.
11. Describe the causes of hypersensitivity pneumonitis.
12. Describe the systemic pathophysiology of organ involvement in sarcoidosis.
13. Describe the pathophysiology of pulmonary embolism and the clinical manifestations of the disorder.
14. Describe the pathophysiology of pulmonary hypertensive disorders.
15. Describe the rationale for right ventricular hypertrophy with cor pulmonale.
16. Describe the pathologic lung changes that occur in ARDS, the treatment for this condition, and the clinical manifestations of acute respiratory failure.

NURSING CONCEPTS

Acid–Base
Oxygenation

The major function of the lungs is to exchange oxygen (O_2) and carbon dioxide (CO_2) to support the metabolic functions of the body's tissues. The gas exchange function of the lungs depends on the **alveoli** being ventilated and perfused, which requires a system of open airways, expansion of the lungs, an adequate surface area for gas diffusion, and adequate blood flow through the pulmonary capillary bed.

Many types of diseases and disorders are capable of disrupting the normal gas-exchanging function of the lungs. In some cases, the disruption is temporary, and in other cases, it is marked and disabling. In some people, it is due to a system-wide deterioration most probably from an acute trauma or injury. Frequently seen respiratory disorders that disrupt ventilation and pulmonary gas exchange are discussed in the following six sections:

- Physiologic effects of ventilation and diffusion disorders
- Disorders of lung inflation
- Obstructive airway disorders
- Chronic interstitial (restrictive) lung diseases
- Disorders of the pulmonary circulation
- Acute respiratory disorders

It is important to realize that people with an underlying comorbidity such as **chronic obstructive pulmonary disease** (COPD) who then experience an acute event such as blunt trauma to the thorax or exacerbation of lupus erythematosus will require more ventilatory assistance and cardiovascular support than those who have "normal" lung function and no autoimmune dysfunction. Also, any person with inflammation from **sarcoidosis** or an infection such as **tuberculosis**, or excessive bronchoconstriction from reactive airway disease, will be challenged if they acquire a condition causing **acute respiratory failure.**

(Please note that in this chapter, "male" refers to a person assigned male at birth, and "female" refers to a person assigned female at birth.)

PHYSIOLOGIC EFFECTS OF VENTILATION AND DIFFUSION DISORDERS

The primary function of the respiratory system is to remove appropriate amounts of CO_2 from the blood entering the pulmonary circulation and to add adequate amounts of O_2 to the blood leaving the pulmonary circulation (Boron & Boulpaep, 2017; West & Luks, 2021b). This section of the chapter provides a brief overview of the causes and manifestations of the **hypoxemia** and **hypercapnia** that develop as the result of the impaired ventilation and gas exchange occurring with many of the disorders discussed in the chapter.

Ventilation involves the movement of atmospheric air to the alveoli for provision of O_2 and removal of CO_2. **Minute ventilation** is the volume of air exchanged per minute and is determined by both the amount of air exchanged with each breath (**tidal volume**) and the **respiratory rate** (breaths per minute). *Gas exchange* takes place within the lungs and involves the exchange of O_2 and CO_2 between air in the alveoli and the blood in the pulmonary capillaries. The process involves the diffusion or movement of O_2 from the air in the alveoli (which is rich in O_2 and low in CO_2) to the blood in the pulmonary capillaries. It also involves the transfer of CO_2 from the blood in the pulmonary capillaries (which has low amounts of O_2 and high amounts of CO_2) to the alveoli. Adequate oxygenation of the blood and removal of CO_2 also depend on adequate circulation of blood through the pulmonary blood vessels (**perfusion**) and appropriate contact between ventilated alveoli and perfused capillaries of the pulmonary circulation (ventilation and perfusion matching) (Fig. 31.1).

As a general rule, oxygenation of the blood depends primarily on factors that promote diffusion of O_2 from the alveoli into the pulmonary capillaries. Removal of CO_2 depends primarily on the minute ventilation (respiratory rate × tidal volume) and elimination of CO_2 from the alveoli (Fig. 31.2).

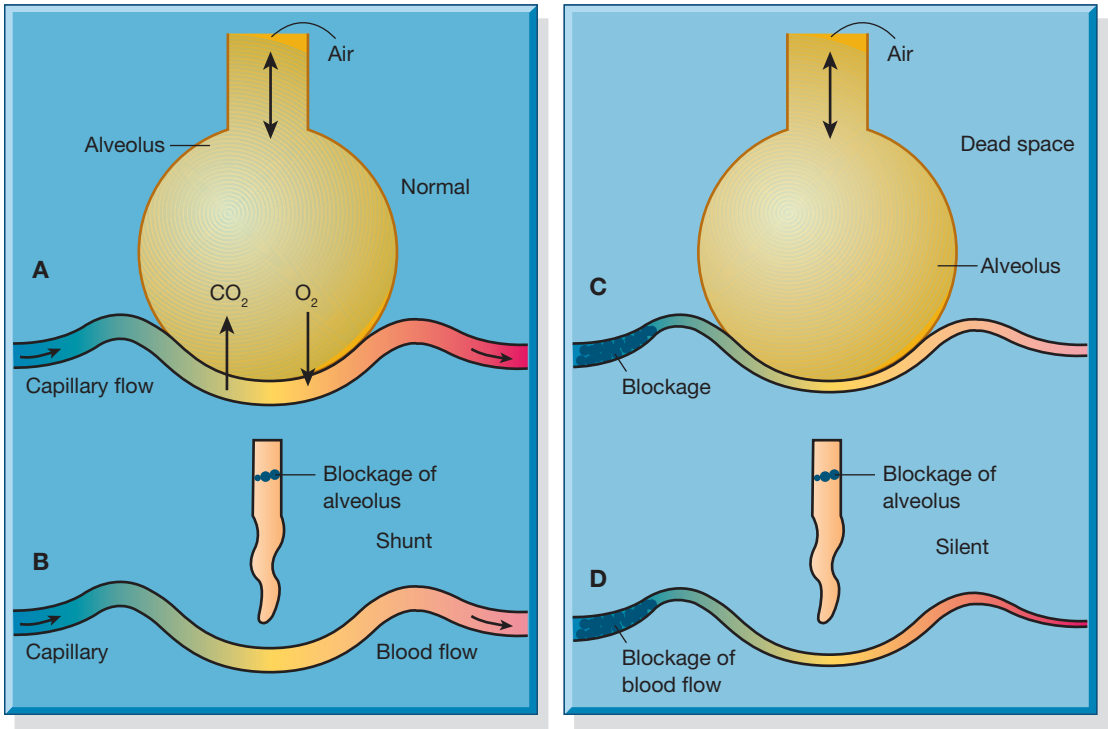


Figure 31.1 • Ventilation–perfusion ratios. Normal ratio **(A)**. In the healthy lung, a given amount of blood passes an alveolus and is matched with an equal amount of gas. The ratio is 1:1 (ventilation matches perfusion). Low ventilation–perfusion ratios: shunts **(B)**. Low ventilation–perfusion states may be called shunt-producing disorders. When perfusion exceeds ventilation, a shunt exists. Blood bypasses the alveoli without gas exchange occurring. This is seen with obstruction of the distal airways, such as with pneumonia, atelectasis, tumor, or a mucous plug. High ventilation–perfusion ratios: dead space **(C)**. When ventilation exceeds perfusion, dead space results. The alveoli do not have an adequate blood supply for gas exchange to occur. This is characteristic of a variety of disorders, including pulmonary emboli, pulmonary infarction, and cardiogenic shock. Silent unit **(D)**. In the absence of both ventilation and perfusion or with limited ventilation and perfusion, a condition known as a silent unit occurs. This is seen with pneumothorax and severe ARDS. (From Hinkle, J. L., & Cheever, K. H. (2018). *Brunner & Suddarth's textbook of medical-surgical nursing* (14th ed., figures in Chart 20-2, p. 486). Lippincott Williams & Wilkins.)

Hypoxemia

Hypoxemia refers to a reduction in arterial blood O_2 levels, which is considered a PaO_2 less than 95 mm Hg.

Etiology and Pathogenesis

Hypoxemia can result from an inadequate amount of O_2 in the air, a disorder of the respiratory system, dysfunction of the neurologic system, or alterations in circulatory function. The mechanisms whereby respiratory disorders lead to a significant reduction in PO_2 are hypoventilation, impaired diffusion of gases, inadequate circulation of blood through the pulmonary capillaries, and mismatching of ventilation and perfusion (Boron & Boulpaep, 2017; West & Luks, 2021b). Often, more than one mechanism contributes to hypoxemia in a person with respiratory or cardiac disease.

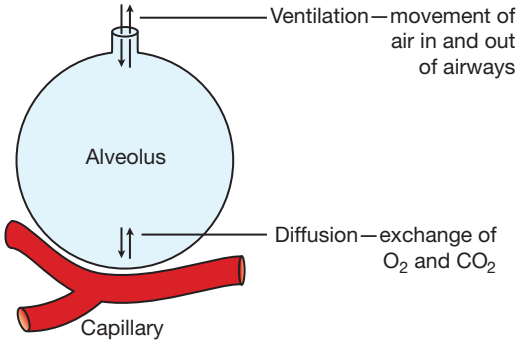


Figure 31.2 • Primary lung functions: ventilation and diffusion. (From Morton, P. G., & Fontaine, D. K. (2018). *Critical care nursing: A holistic approach* (11th ed., Fig. 25-1, p. 449). Lippincott Williams & Wilkins.)

Clinical Manifestations

Hypoxemia produces its effects through tissue hypoxia and the compensatory mechanisms that the body uses to adapt to the lowered oxygen level. Body tissues vary considerably in their vulnerability to hypoxia. Tissues with the greatest need are the brain, lungs, and heart. If the PO_2 of the tissues falls below a critical level, aerobic metabolism ceases and anaerobic metabolism takes over, with formation and release of lactic acid. This results in increased serum lactate levels and **metabolic acidosis**. The normal range of serum lactate levels is 1 to 0.5 mmol/L in nonacutely ill people.

Mild hypoxemia produces few manifestations. Recruitment of sympathetic nervous system compensatory

mechanisms produces an increase in heart rate, peripheral vasoconstriction, diaphoresis, and a mild increase in blood pressure. There may be slight impairment of mental performance and visual acuity and sometimes hyperventilation. This is because hemoglobin saturation still is approximately 90% when the PO_2 is only 60 mm Hg. More pronounced hypoxemia may produce confusion, personality changes, restlessness, agitated or combative behavior, uncoordinated muscle movements, euphoria, impaired judgment, delirium, and, eventually, stupor and coma.

The manifestations of chronic hypoxemia may be insidious in onset and attributed to other causes, particularly in people with chronic lung disease. The body compensates for chronic hypoxemia by increased ventilation, **pulmonary vasoconstriction**, and increased production of red blood cells. Pulmonary vasoconstriction occurs as a local response to alveolar hypoxia. It increases pulmonary arterial pressure and improves the matching of ventilation and blood flow. Increased production of red blood cells results from the release of erythropoietin from the kidneys in response to hypoxia. **Polycythemia** increases the red blood cell concentration and the oxygen-carrying capacity of the blood. Other adaptive mechanisms include a shift to the right in the oxygen dissociation curve, which increases O_2 release to the tissues (see Fig. 29.22).

Cyanosis refers to the bluish discoloration of the skin and mucous membranes that result from an excessive concentration of reduced or deoxygenated hemoglobin in the small blood vessels. It usually is most marked in the lips, nail beds, ears, and cheeks. The degree of cyanosis is modified by the amount of cutaneous pigment, skin thickness, and the state of the cutaneous capillaries. Cyanosis is more difficult to distinguish in people with dark skin and in areas of the body with increased skin thickness. Inspect the buccal tissue of the oral mucosa of dark-skinned people because this is the most accurate location to assess for cyanosis. Although cyanosis may be evident in people with respiratory failure, it often is a late sign. A concentration of approximately 5 g/dL of deoxygenated hemoglobin is required in the circulating blood for cyanosis to occur (Boron & Boulpaep, 2017). The absolute quantity of reduced hemoglobin, rather than the relative quantity, is important in producing cyanosis.

People with anemia and low hemoglobin levels are less likely than people with high hemoglobin concentrations to exhibit cyanosis (because they have less hemoglobin to deoxygenate), even though they may be relatively hypoxic because of their decreased ability to transport oxygen. A person with a high hemoglobin level due to polycythemia may be cyanotic without being hypoxic.

Cyanosis can be divided into two types: central and peripheral. **Central cyanosis** is evident in the tongue and lips. It is caused by an increased amount of deoxygenated hemoglobin or an abnormal hemoglobin derivative in the arterial blood. Abnormal hemoglobin derivatives include **methemoglobin**, in which the nitrite ion reacts with hemoglobin. Because methemoglobin has a low affinity for O_2, large doses of nitrites can result in cyanosis and tissue hypoxia. Although nitrites are used in treating angina, the therapeutic dose is too small to cause cyanosis. **Peripheral cyanosis** occurs in the extremities and on the tip of the nose or ears. It is caused by slowing of blood flow to an area of the body, with increased extraction of oxygen from the blood. It results from vasoconstriction and diminished peripheral blood flow, as occurs with cold exposure, shock, heart failure, or peripheral vascular disease. **Clubbing** may also be evident in people with COPD since there is long-term hypoxia. This is readily seen during a peripheral cardiovascular inspection when the provider assesses peripheral oxygenation/perfusion since the angle of the nail is 180° or greater (Fig. 31.3).

Diagnosis

Diagnosis of hypoxemia is based on clinical observation and diagnostic measures of **PO_2 levels**. The analysis of **arterial blood gases** (ABGs) provides a direct measure of the O_2 content of the blood and is the best indicator of the ability of the lungs to oxygenate the blood. **Venous oxygen saturation (SvO_2)** reflects the body's extraction and utilization of O_2 at the tissue levels. Venous blood samples can be obtained through either a pulmonary artery catheter or a central line. The latter is less invasive but slightly less accurate because the blood has not yet been mixed in the right ventricle.

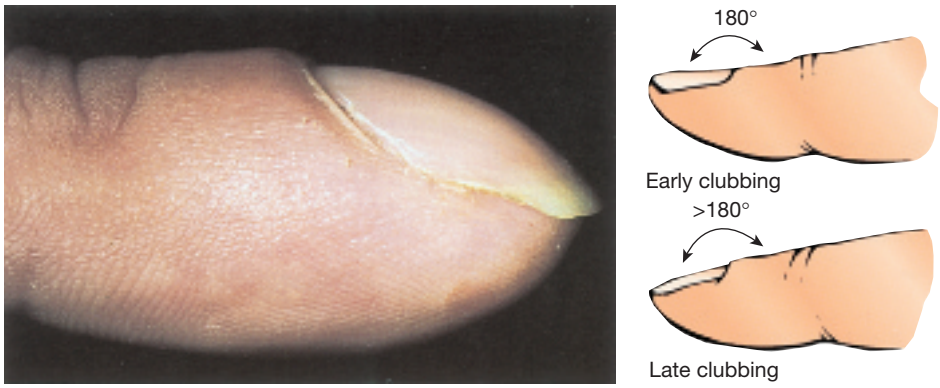


Figure 31.3 • Clubbing. The angle between the nail plate and the proximal nail fold increases to 180° or greater. (From Morton, P. G., & Fontaine, D. K. (2018). *Critical care nursing: A holistic approach* (11th ed., Fig. 24.2, p. 434). Lippincott Williams & Wilkins.)

Figure 31.4 • Measuring blood oxygenation with pulse oximetry reduces the need for invasive procedures, such as drawing blood for analysis of oxygen levels. **(A)** Self-contained digital fingertip pulse oximeter, which incorporates the sensor and the display into one unit. **(B)** Tabletop model with sensor attached. Memory permits tracking heart rate and oxygen saturation over time. (From Hinkle, J. L., & Cheever, K. H. (2018). *Brunner & Suddarth's textbook of medicalsurgical nursing* (14th ed., Fig. 20-12, p. 503). Lippincott Williams & Wilkins.)

Noninvasive measurements of arterial O_2 saturation of hemoglobin can be obtained using an instrument called the **pulse oximeter** (Fig. 31.4). The pulse oximeter uses light-emitting diodes and combines plethysmography (i.e., changes in light absorbance and vasodilation) with **spectrophotometry (Sp)** to measure oxygen saturation (Mechem, 2022). The normal **SpO_2** ranges from 90 to 100. Sp uses a red-wavelength light that passes through oxygenated hemoglobin and is absorbed by deoxygenated hemoglobin and an infrared wavelength light that is absorbed by oxygenated hemoglobin and passes through deoxygenated hemoglobin. Sensors that can be placed on the ear, finger, toe, or forehead are available. Sensors can be placed on the palm, penis, foot, and arm of infants. The pulse oximeter cannot distinguish between oxygen-carrying hemoglobin and carbon monoxide–carrying hemoglobin. In addition, the pulse oximeter cannot detect elevated levels of methemoglobin. Although pulse oximetry is not as accurate as ABG measurements, it provides the means for noninvasive and continuous monitoring of O_2 saturation. This is a useful trend indicator of respiratory and circulatory status. However, its reliability is questionable when used with people who are acutely ill. Using a formula that identifies arterial values of pH, PCO_2, and PO_2 from the person's venous values and pulse oximetry has also been effective (Ekstrom et al., 2019). The combination of venous blood gas analysis plus pulse oximetry provided accurate information, when compared to ABG analysis, on which to make bedside clinical decisions for critically ill individuals (Theodore, 2022).

The ratio between the arterial PaO_2 and the fraction of inspired oxygen (FiO_2), termed the **PF ratio**, is an additional indicator of alterations in diffusion of O_2 at the lung level. In determining this ratio, the PO_2 is divided by the FiO_2. For example, the FiO_2 of a person breathing room air is 0.21 because 21% of atmospheric air is O_2, whereas for the person receiving 40% O_2, the FiO_2 is 0.40. The normal value of the PF ratio is greater than 300 (Oyelade & Ezugwu, 2020). The PF ratio is useful for evaluating improvements or deteriorations in oxygen diffusion regardless of the percentage of supplemental oxygen that is being administered. In addition, the PF ratio is a diagnostic indicator of **acute lung injury** and **acute respiratory distress syndrome (ARDS)**.

Treatment

Treatment of hypoxemia is directed toward correcting the cause of the disorder and increasing the gradient for diffusion through the administration of supplemental oxygen. Oxygen may be delivered by nasal cannula, mask, or administered directly via an endotracheal or tracheostomy tube in people who are mechanically ventilated. A high-flow administration system is one in which the flow rate and reserve capacity are sufficient to provide all the inspired air (Weekley & Bland, 2022). A low-flow administration system delivers less than the total inspired air (Weekley & Bland, 2022). The concentration of O_2 being administered (usually determined by the flow rate) is based on the PO_2. A high-flow rate must be carefully monitored in people with chronic lung disease because increases in PO_2 above 60 mm Hg may depress the ventilatory drive. There also is the danger of oxygen toxicity with high concentrations of oxygen. Continuous breathing of oxygen at high concentrations can lead to diffuse parenchymal lung injury. People with healthy lungs begin to experience respiratory symptoms such as cough, sore throat, substernal tightness, nasal congestion, and painful inspiration after breathing pure oxygen for 24 hours (West & Luks, 2021b).

KEY POINTS

VENTILATION AND GAS EXCHANGE

- Ventilation is the movement of air volume from the atmosphere to the alveoli.
- Gas exchange is the delivery of oxygen and removal of carbon dioxide from the capillary membrane.

Hypercapnia

Hypercapnia refers to an increase in the carbon dioxide content of the arterial blood (Feller-Kopman & Schwartzstein, 2022). The carbon dioxide level in the arterial blood, or PCO_2, is proportional to carbon dioxide production and inversely related to alveolar ventilation.

Etiology and Pathogenesis

Hypercapnia can occur in a number of disorders that cause hypoventilation or mismatching of ventilation and perfusion (Feller-Kopman & Schwartzstein, 2022). The diffusing capacity of carbon dioxide is 20 times that of oxygen. Therefore, hypercapnia without hypoxemia is usually observed only in situations of hypoventilation (West & Luks, 2021b). In cases of ventilation–perfusion mismatching, hypercapnia is usually accompanied by a decrease in arterial PO_2 levels.

Conditions that increase carbon dioxide production, such as an increase in metabolic rate or a high-carbohydrate diet, can contribute to the degree of hypercapnia that occurs in people with impaired respiratory function. Changes in the metabolic rate resulting from an increase in activity, fever, or disease can have profound effects on carbon dioxide production. Alveolar ventilation usually rises proportionally with these changes, and hypercapnia occurs only when this increase is inappropriate.

The **respiratory quotient (RQ)**, which is the ratio of carbon dioxide production to oxygen consumption ($RQ = CO_2$ production/O_2 consumption), varies with the type of food metabolized (Boron & Boulpaep, 2017). A characteristic of carbohydrate metabolism is an RQ of 1.0, with equal amounts of carbon dioxide being produced and oxygen being consumed. Because fats contain less oxygen than carbohydrates, their oxidation produces less carbon dioxide (RQ = 0.7). The metabolism of pure proteins (RQ = 0.81) results in the production of more carbon dioxide than the metabolism of fat, but less than the metabolism of carbohydrates. The type of food that is eaten or the types of nutrients that are delivered through enteral feedings (i.e., through a tube placed in the small intestine) or parenteral nutrition (i.e., through a central venous catheter) may influence PCO_2 levels.

Clinical Manifestations and Diagnosis

Hypercapnia affects a number of body functions, including acid–base balance and renal, neurologic, and cardiovascular function. Elevated levels of PCO_2 produce a decrease in pH and **respiratory acidosis**. The body normally compensates for an increase in PCO_2 by increasing renal bicarbonate $\left(HCO_3^-\right)$ retention, which results in an increase in serum HCO_3^- and pH levels. As long as the pH is within normal range, the main complications of hypercapnia are those resulting from the accompanying hypoxia. Because the body adapts to chronic increases in blood levels of carbon dioxide, people with chronic hypercapnia may not have symptoms until the PCO_2 becomes markedly elevated. At this point, they will display symptoms of increased work of breathing (WOB) since they will also be experiencing hypoxemia (Chart 31.1).

The diagnosis of hypercapnia is based on physiologic manifestations, arterial pH, and ABG levels. $PACO_2$ can also be measured on individuals receiving mechanical ventilation via end-tidal carbon dioxide ($EtCO_2$) measuring at the end of exhalation (Nooralishahi et al., 2021). Samples of the carbon dioxide at the end of the exhaled breath can be used to identify an estimated $PACO_2$ (Nooralishahi et al., 2021).

Treatment

The treatment of hypercapnia is directed at decreasing the WOB and improving the ventilation–perfusion balance. The use of intermittent rest therapy, such as nocturnal negative pressure ventilation or continuous positive airway pressure, in people with chronic obstructive disease or chest wall disease may be effective in increasing the strength and endurance of the respiratory muscles and improving the PCO_2. Respiratory muscle retraining aimed at improving respiratory muscle strength and their endurance, or both, has been used to improve exercise tolerance and diminish the likelihood of respiratory fatigue. Use of a ventilator may become necessary in situations of acute hypercapnia.

CHART 31.1 SYMPTOMS OF WORK OF BREATHING

Shortness of breath
Diaphoresis
Pursed-lip breathing
Tachypnea or bradypnea/irregular breathing rhythm
Use of accessory muscles
Tachycardia
Abdominal breathing
Cyanosis

IN SUMMARY

The primary function of the respiratory system is to remove appropriate amounts of CO_2 from the blood entering the pulmonary circulation and provide adequate O_2 to blood leaving the pulmonary circulation. This is accomplished through the process of ventilation, in which air moves into and out of the lungs, and diffusion, in which gases move between the alveoli and the pulmonary capillaries. Although both diffusion and ventilation affect gas exchange, oxygenation of the blood largely depends on diffusion and removal of carbon dioxide on ventilation.

Hypoxemia refers to a decrease in arterial blood oxygen levels that results in a decrease in tissue oxygenation. Hypoxemia can occur as the result of hypoventilation, diffusion impairment, shunt, and ventilation–perfusion impairment. Acute hypoxemia is manifested by increased respiratory effort (increased respiratory and heart rates, use of accessory muscles, pursed-lip breathing, and diaphoresis), cyanosis, and impaired sensory and neurologic function, which is also referred to as WOB. The body compensates for chronic hypoxemia by increased ventilation, pulmonary vasoconstriction, and increased production of red blood cells.

Hypercapnia refers to an increase in carbon dioxide levels. In the clinical setting, four factors contribute to hypercapnia: alterations in carbon dioxide production, disturbance in the gas exchange function of the lungs, abnormalities in function of the chest wall and respiratory muscles, and changes in neural control of respiration. Alterations in respiratory function or the rate decrease minute volume, which is the most common cause of hypercapnia. The manifestations of hypercapnia consist of those associated with a decreased pH (respiratory acidosis); vasodilation of blood vessels, including those in the brain; and depression of central nervous system (CNS) function.

DISORDERS OF LUNG INFLATION

Air entering through the airways inflates the lung, and the negative pressure in the pleural cavity keeps the lung from collapsing. Disorders of lung inflation are caused by conditions that obstruct the airways, cause lung compression, or produce lung collapse. There can be compression of the lung by an accumulation of fluid in the intrapleural space; complete collapse of an entire lung, as in **pneumothorax**; or collapse of a segment of the lung due to airway obstruction, as in atelectasis.

Disorders of the Pleura

The **pleura** is a thin, double-layered serous membrane that encases the lungs (Fig. 31.5). The outer **parietal layer** lines the thoracic wall and superior aspect of the diaphragm. It continues around the heart and between the lungs, forming the lateral walls of the mediastinum. The inner **visceral layer** covers the lung and is adherent to all its surfaces. The pleural cavity or space between the two layers contains a thin layer of serous fluid that lubricates the pleural surfaces and allows the parietal and visceral pleurae to slide smoothly over each other during breathing movements. The pressure in the pleural cavity, which is negative in relation to atmospheric pressure, holds the lungs against the chest wall and keeps them from collapsing. Disorders of the pleura include pleural effusion, hemothorax, pneumothorax, and pleural inflammation.

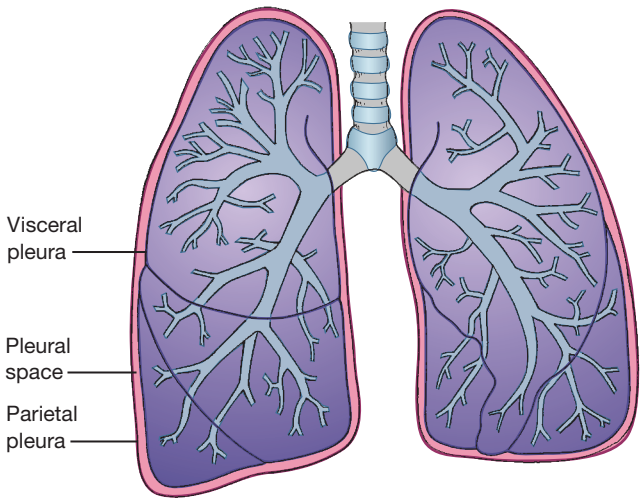


Figure 31.5 • The relationship between the parietal and visceral pleurae and the plural space, which is the site of fluid accumulation in pleural effusions.

Pleural Effusion

Pleural effusion refers to an abnormal collection of fluid in the pleural cavity (West & Luks, 2021a). Like fluid developing in other transcellular spaces in the body, pleural effusion occurs when the rate of fluid formation exceeds the rate of its removal.

Etiology and Pathogenesis. Normally, fluid enters the pleural space from capillaries in the parietal pleura and is removed by the lymphatics situated in the parietal pleura. Fluid can also enter from the interstitial spaces of the lung through the visceral pleura or from small holes in the diaphragm. Accordingly, fluid may accumulate when there is excess fluid formation (from the interstitium of the lung, the parietal pleura, or peritoneal cavity) or when there is decreased removal by the lymphatics.

The fluid that accumulates in a pleural effusion may be a **transudate** or **exudate**, **purulent** (containing pus), **chyle**, or **sanguineous** (bloody). The accumulation of a serous transudate (clear fluid) in the pleural cavity often is referred to as **hydrothorax**. The condition may be unilateral or bilateral. The most common cause of hydrothorax is congestive heart failure. Other causes are renal failure, nephrosis, liver failure, and malignancy. An **exudate** is a pleural fluid that has a specific gravity greater than 1.020 and often contains inflammatory cells.

Transudative and exudative pleural effusions are distinguished by measuring the lactate dehydrogenase (LDH) and protein levels in the pleural fluid (West & Luks, 2021a). LDH is an enzyme that is released from inflamed and injured pleural tissue. Because measurements of LDH are easily obtained from a sample of pleural fluid, it is a useful marker for diagnosis of exudative pleural disorders. Exudative pleural effusion meets at least one of the following criteria:

1. A pleural fluid protein/serum protein ratio greater than 0.5
2. A pleural fluid LDH/serum LDH ratio greater than 0.6
3. A pleural fluid LDH greater than two thirds the upper limit of normal serum LDH (West & Luks, 2021a)

Conditions that produce exudative pleural effusions are bacterial pneumonia, viral infection, pulmonary infarction, and malignancies. Seventy percent of pleural effusion cases have a single cause (Jany & Welte, 2019).

Parapneumonic effusions are a common type of pleural effusion and are largely caused by bacterial infections such as pneumonia. A common type of parapneumonic effusion is **empyema**, an infection in the pleural cavity that results in exudate (pus) containing glucose, proteins, leukocytes, and debris from dead cells and tissue (Jany & Welte, 2019). It is caused by an adjacent bacterial pneumonia, rupture of a lung abscess into the pleural space, invasion from a subdiaphragmatic infection, or infection associated with trauma.

Chylothorax is the effusion of lymph in the thoracic cavity. **Chyle**, a milky fluid containing chylomicrons, is found in the lymph fluid originating in the gastrointestinal tract. The thoracic duct transports chyle to the central circulation. Chylothorax also results from trauma, inflammation, or malignant infiltration obstructing chyle transport from the thoracic duct into the central circulation. It is the most common cause of pleural effusion in the fetus and neonate, resulting from congenital malformation of the thoracic duct or lymph channels. Chylothorax also can occur as a complication of intrathoracic surgical procedures and use of the great veins for total parenteral nutrition and hemodynamic monitoring (West & Luks, 2021a).

Clinical Manifestations. The manifestations of parapneumonic effusions vary with the cause. Empyemas may be accompanied by fever, increased white blood cell count, and other signs of inflammation. Fluid in the pleural cavity acts as a space-occupying mass; it causes a decrease in lung expansion on the affected side that is proportional to the amount of fluid collected. Characteristic signs of pleural effusion are dullness or flatness to percussion and diminished breath sounds. Hypoxemia may occur due to the decreased surface area and usually is corrected with supplemental oxygen. Dyspnea, the most common symptom, occurs when fluid compresses the lung, resulting in increased effort or rate of breathing. Pleuritic pain usually occurs only when inflammation is present. However, constant discomfort may be felt with large effusions.

Diagnosis and Treatment. Diagnosis of pleural effusion is based on chest radiographs, chest ultrasonography, and computed tomography (CT). Thoracentesis (aspiration of fluid from the pleural space) can be used to obtain a sample of pleural fluid for diagnosis. The treatment of pleural effusion is directed at the cause of the disorder. With large effusions, thoracentesis may be used to remove fluid from the intrapleural space and allow for reexpansion of the lung. A palliative method used for treatment of pleural effusions caused by a malignancy is the injection of a sclerosing agent into the pleural cavity. This method of treatment causes obliteration of the pleural space and prevents the reaccumulation of fluid. Chest tube drainage may be necessary in cases of continued effusion.

Hemothorax

Hemothorax is a specific type of pleural effusion in which there is blood in the pleural cavity.

Etiology and Pathogenesis. Bleeding may be the result of chest injury, a complication of chest surgery, malignancies, or rupture of a great vessel such as an aortic aneurysm. Hemothorax may be classified as minimal, moderate, or large (Loscalzo et al., 2022). A minimal hemothorax involves the presence of at least 250 mL of blood in the pleural space (West & Luks, 2021a). Small amounts of blood usually are absorbed from the pleural space, and the hemothorax usually clears in 10 to 14 days without complication. A moderate hemothorax fills approximately one-third of the pleural space and may produce signs of lung compression and loss of intravascular volume. It requires immediate drainage and replacement of intravascular fluids. A large hemothorax fills one half or more of one side of the chest and is usually caused by bleeding from a high-pressure vessel such as an intercostal or mammary artery. It requires immediate drainage and, if the bleeding continues, surgery to control the bleeding.

Clinical Manifestations. In addition to alterations in oxygenation, ventilation, respiration effort, and breath sounds, signs of blood loss, including increased heart rate, may accompany hemothorax. Because hemothorax is abrupt in onset, the manifestations are usually sudden and distressing. One of the complications of untreated moderate or large hemothorax is **fibrothorax**—the fusion of the pleural surfaces by fibrin, hyaline, and connective tissue—and, in some cases, calcification of the fibrous tissue, which restricts lung expansion.

Diagnosis and Treatment. Diagnosis of hemothorax is based on chest radiographs and decreased arterial saturation, which is indicative of decreased oxygen exchange. If the person is symptomatic or oxygen exchange is compromised, chest tube drainage is indicated.

Pneumothorax

Pneumothorax refers to the presence of air in the pleural space. Pneumothorax causes partial or complete collapse of the affected lung.

Etiology and Pathogenesis. Pneumothorax can occur without an obvious cause or injury (i.e., **spontaneous pneumothorax**) or as a result of direct injury to the chest or major airways (i.e., **traumatic pneumothorax**). **Tension pneumothorax** describes a life-threatening condition in which increased pressure within the pleural cavity impairs both respiratory and cardiac function.

Spontaneous Pneumothorax. Spontaneous pneumothorax is hypothesized to occur due to the rupture of an air-filled **bleb**, or blister, on the surface of the lung. Rupture of these blebs allows atmospheric air from the airways to enter the pleural cavity (Fig. 31.6). Because alveolar pressure normally is greater than pleural pressure, air flows from the alveoli into the pleural space, causing the involved portion of the lung to collapse as a result of its own recoil. Air continues to flow into the pleural space until a pressure gradient no longer exists or until the decline in lung size causes the leak to seal. Spontaneous pneumothoraces can be divided into primary and secondary pneumothoraces. Primary pneumothorax occurs in otherwise healthy people, whereas secondary pneumothorax occurs in people with underlying lung disease.

In primary spontaneous pneumothorax, the blebs usually are located at the top of the lungs. The condition is seen most often in tall boys and young males between 10 and 30 years of age. (As noted previously, in this chapter, "males" refers to people assigned male at birth.) It has been suggested that the difference in pleural pressure from the top to the bottom of the lung is greater in tall people and that this difference in pressure may contribute to the development of blebs. Smoking and family history are factors associated with primary spontaneous pneumothorax (West & Luks, 2021b). Inflammation of the small airways related to smoking probably contributes to the condition, and cessation of smoking may reduce the recurrence.

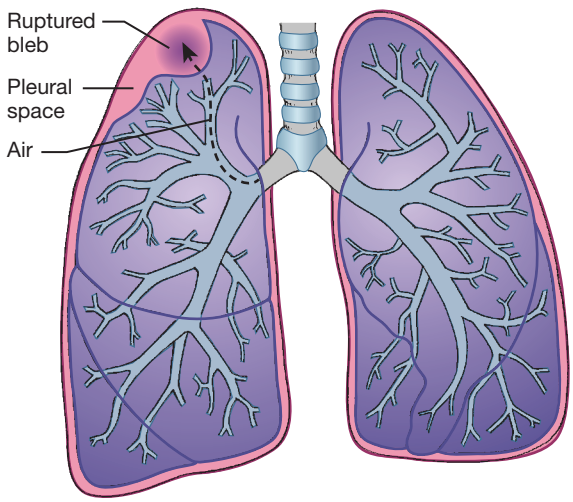


Figure 31.6 • Mechanism for development of spontaneous pneumothorax, in which an air-filled bleb on the surface of the lung ruptures, allowing atmospheric air from the airways to enter the pleural space.

Secondary spontaneous pneumothoraces usually are more serious because they occur in people with lung disease. They are associated with many different types of lung conditions that cause trapping of gases and destruction of lung tissue, including asthma, tuberculosis, cystic fibrosis (CF), sarcoidosis, bronchogenic carcinoma, and metastatic pleural diseases. A common cause of secondary spontaneous pneumothorax is emphysema. Secondary spontaneous pneumothorax may be life-threatening because of the underlying lung injury and poor compensatory reserves.

Catamenial pneumothorax occurs in relation to the menstrual cycle and usually is recurrent (Gil & Tulandi, 2020). It typically occurs in females between 30 and 40 years of age who have a history of endometriosis. (As noted previously, in this chapter, "females" refers to people assigned female at birth.) Although catamenial pneumothorax is unusual, it represents 23% to 30% of pneumothoraxes in females (Ciriaco et al., 2022). It usually affects the right lung and develops within 72 hours of onset of menses. Although the cause of catamenial pneumothorax is unknown, it has been suggested that air may gain access to the peritoneal cavity during menstruation and then enter the pleural cavity through a diaphragmatic defect (Gil & Tulandi, 2020). Pleural and diaphragmatic endometrioses also have been implicated as causes of the condition.

Traumatic Pneumothorax. Traumatic pneumothorax may be caused by penetrating or nonpenetrating injuries. Fractured or dislocated ribs that penetrate the pleura are the most common cause of pneumothorax from nonpenetrating chest injuries. Hemothorax may accompany these injuries. Pneumothorax also may accompany fracture of the trachea or major bronchus or rupture of the esophagus. People with pneumothorax due to chest trauma frequently have other complications and may require chest surgery. Medical procedures such as transthoracic needle aspirations, central line insertion, intubation, and positive-pressure ventilation occasionally may cause pneumothorax. Traumatic pneumothorax also can occur as a complication of cardiopulmonary resuscitation.

Tension Pneumothorax. Tension pneumothorax occurs when the intrapleural pressure exceeds atmospheric pressure. It is a life-threatening condition and occurs when injury to the chest or respiratory structures permits air to enter but not leave the pleural space (Fig. 31.7). This results in a rapid increase in pressure within the chest that causes compression atelectasis of the unaffected lung, a shift in the mediastinum to the opposite side of the chest, and compression of the vena cava, which results in a decrease in venous return to the heart and reduced cardiac output (Loscalzo et al., 2022). Although tension pneumothorax can develop in people with spontaneous pneumothoraces, it is seen most often in people with traumatic pneumothoraces. It may also result from barotrauma caused by mechanical ventilation and should be suspected in people who deteriorate suddenly while on a ventilator (Broaddus et al., 2021).

Tension pneumothorax should also be suspected in the person receiving CPR who becomes difficult to ventilate (Broaddus et al., 2021).

Clinical Manifestations. The manifestations of pneumothorax depend on its size and the integrity of the underlying lung. In spontaneous pneumothorax, manifestations of the disorder sometimes include development of ipsilateral chest pain. There is an almost immediate increase in respiratory rate, often accompanied by dyspnea that occurs as a result of the activation of receptors that monitor lung volume. Asymmetry of the chest may occur because of the air being trapped in the pleural cavity on the affected side. This asymmetry may be evidenced during inspiration as a lag in the movement of the affected side, with inspiration delayed until the unaffected lung reaches the same level of pressure as the lung with the air trapped in the pleural space. Percussion of the chest produces a more **hyperresonant** sound, and breath sounds are decreased or absent over the area of the pneumothorax.

With tension pneumothorax, the structures in the mediastinal space shift toward the opposite side of the chest (see Fig. 31.7). When this occurs, the position of the trachea, normally located in the midline of the neck, deviates with the mediastinum. The position of the trachea can be used as a means of assessing for a mediastinal shift. Because of the increase in intrathoracic pressure, stroke volume is impaired to such an extent that cardiac output is decreased despite an increase in heart rate. There may be jugular neck vein distention, **subcutaneous emphysema** (i.e., presence of air in the subcutaneous tissues of the chest and neck), and clinical signs of shock due to impaired cardiac function.

Hypoxemia usually develops immediately after a large pneumothorax, followed by vasoconstriction of the blood vessels in the affected lung, causing the blood flow to shift to the unaffected lung. In people with primary spontaneous pneumothorax, this mechanism usually returns oxygen saturation to normal within 24 hours. Hypoxemia usually is more serious in people with underlying lung disease in whom secondary spontaneous pneumothorax develops or in people with underlying heart disease who are unable to compensate with an increase in heart rate and stroke volumes. Regardless of etiology, the hypoxemia caused by the partial or total loss of lung function can be life-threatening. Without immediate intervention, the increased thoracic pressure will further impair both cardiac and pulmonary function, resulting in severe hypoxemia and hypotension, which often leads to respiratory and cardiac arrest.

Diagnosis and Treatment. Chest radiograph or CT scan confirms diagnosis of pneumothorax. Perform pulse oximetry and blood gas analysis to determine the effect on blood oxygen levels. Treatment of pneumothorax varies with the cause and extent of the disorder. In small spontaneous pneumothoraces, the air usually reabsorbs spontaneously. Therefore, only observation and follow-up chest radiographs are required. Supplemental oxygen may be used to correct the hypoxemia until the air is reabsorbed. In larger pneumothoraces, the air is removed by needle aspiration or a closed drainage system used with or without suction. This type of drainage system uses a one-way valve or a water-seal chamber to allow air to exit the pleural space and prevent it from reentering the chest.

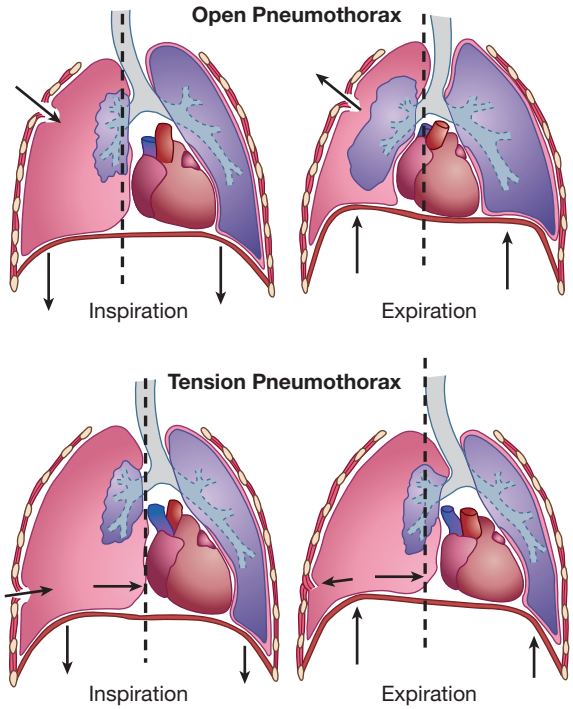


Figure 31.7 • Open or communicating pneumothorax **(top)** and tension pneumothorax **(bottom)**. In an open pneumothorax, air enters the chest during inspiration and exits during expiration. There may be slight inflation of the affected lung because of a decrease in pressure as air moves out of the chest. In tension pneumothorax, air can enter but not leave the chest. As the pressure in the chest increases, the heart and great vessels are compressed and the mediastinal structures are shifted toward the opposite side of the chest. The trachea is pushed from its normal midline position toward the opposite side of the chest, and the unaffected lung is compressed.

Emergency treatment of tension pneumothorax involves the prompt insertion of a large-bore needle or chest tube into the affected side of the chest along with one-way valve drainage or continuous chest suction to aid in reinflating the affected lung. Sucking chest wounds, which allow air to pass in and out of the chest cavity, should be treated by promptly covering the area with an airtight bandage (e.g., Vaseline gauze, firm piece of plastic). Chest tubes are inserted as soon as possible to reexpand the lung. Because of the risk for recurrence, people with primary spontaneous pneumothorax should be advised against cigarette smoking, exposure to high altitudes, flying in nonpressurized aircraft, and scuba diving.

KEY POINTS

DISORDERS OF LUNG INFLATION

- The pleura encases the lungs and is made up of two layers, which create the pleural cavity where pathology is often caused by air getting into the space, which is called a pneumothorax, or blood in the pleural space, which would cause a hemothorax.
- Atelectasis is a partial expansion of the lung, which is caused by obstruction or compression of lung tissue.

Pleuritis

Pleuritis (also called *pleurisy*) refers to inflammation of the pleura. Pleuritis is common in infectious processes such as respiratory infections that extend to involve the pleura. Pain is a frequent symptom and most commonly is unilateral and abrupt in onset. When the central part of the diaphragm is irritated, the pain may be referred to the shoulder. Chest movements such as deep breathing and coughing that exaggerate pressure changes in the pleural cavity and increase movement of the inflamed or injured pleural surfaces usually make the pain worse. Because deep breathing is painful, tidal volumes usually are kept small, and breathing becomes more rapid to maintain minute volume. Reflex splinting of the chest muscles may occur, causing a lesser respiratory expansion on the affected side.

It is important to differentiate pleural pain from pain produced by other conditions, such as musculoskeletal strain of chest muscles, bronchial irritation, and myocardial disease. Musculoskeletal pain may occur as the result of frequent, forceful coughing. This type of pain usually is bilateral and located in the inferior portions of the rib cage, where the abdominal muscles insert into the anterior rib cage. Movements associated with contraction of the abdominal muscles make it worse. The pain associated with irritation of the bronchi usually is substernal and dull in character rather than sharp; it is often described as tightening. This type of pain is made worse with coughing but is not affected by deep breathing. Myocardial discomfort or pain usually is located in the substernal area and is not affected by respiratory movements.

Treatment of pleuritis consists of treating the underlying disease and inflammation. Analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., ibuprofen, indomethacin) may be used for pleural pain. Although these agents reduce inflammation, they may not entirely relieve the discomfort associated with deep breathing and coughing.

Atelectasis

Atelectasis refers to an incomplete expansion of a lung or portion of a lung. It can be caused by airway obstruction, lung compression such as occurs in pneumothorax or pleural effusion, or increased recoil of the lung due to loss of pulmonary surfactant. The disorder may be present at birth (i.e., primary atelectasis) or develop during the neonatal period or later in life (i.e., acquired or secondary atelectasis).

Etiology and Pathogenesis

Primary atelectasis of the newborn implies that the lung has never been inflated. It is seen most frequently in premature and high-risk infants. A secondary form of atelectasis can occur in infants who established respiration and subsequently experienced impairment of lung expansion. Among the causes of secondary atelectasis in the newborn is respiratory distress syndrome associated with lack of surfactant, airway obstruction due to aspiration of amniotic fluid or blood, and bronchopulmonary dysplasia.

Acquired atelectasis occurs mainly in adults. It is caused most commonly by airway obstruction and lung compression (Fig. 31.8). A mucus plug in the airway or external compression by fluid, tumor mass, exudate, or other matter in the area surrounding the airway can cause obstruction. Portions of alveoli, a small segment of lung, or an entire lung lobe may be involved in obstructive atelectasis. Complete obstruction of an airway is followed by the absorption of air from the dependent alveoli and collapse of that portion of the lung. Breathing high concentrations of oxygen increases the rate at which gases are absorbed from the alveoli and predisposes to atelectasis. The danger of obstructive atelectasis increases after surgery. Administration of narcotics or anesthesia, pain, and immobility tend to promote retention of viscid bronchial secretions and can cause airway obstruction. The encouragement of coughing and deep breathing, frequent change of position, adequate hydration, and early ambulation decrease the likelihood of atelectasis developing.

Another cause of atelectasis is compression of lung tissue. It occurs when the pleural cavity is partially or completely filled with fluid, exudate, blood, a tumor mass, or air.

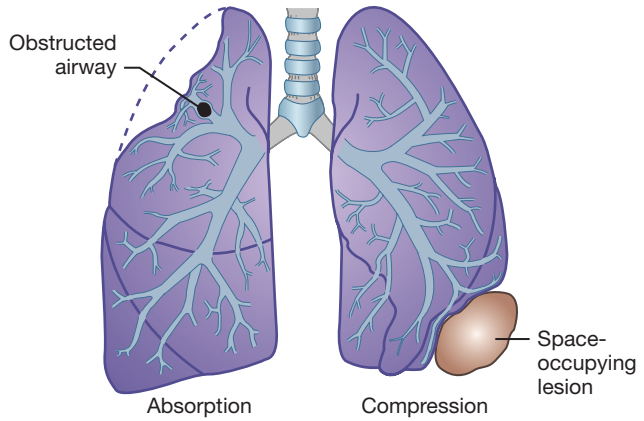


Figure 31.8 • Atelectasis caused by airway obstruction and absorption of air from the involved lung area **(left)** and by compression of lung tissue **(right)**.

It is observed most commonly in people with pleural effusion from congestive heart failure or cancer.

Clinical Manifestations

The clinical manifestations of atelectasis include tachypnea, tachycardia, dyspnea, cyanosis, signs of hypoxemia, diminished chest expansion, decreased breath sounds, and intercostal retractions. There may be **intercostal retraction** (pulling in of the intercostal spaces) over the involved area during inspiration. Signs of respiratory distress are proportional to the extent of lung collapse. If the collapsed area is large, the mediastinum and trachea shift to the affected side. In compression atelectasis, the mediastinum shifts away from the affected lung.

Diagnosis and Treatment

The diagnosis of atelectasis is based on signs and symptoms. Chest radiographs are used to confirm the diagnosis. CT scans may be used to show the exact location of the obstruction.

Treatment depends on the cause and extent of lung involvement. It is directed at reducing the airway obstruction or lung compression and at reinflating the collapsed area of the lung. Ambulation, deep breathing, and body positions that favor increased lung expansion are used when appropriate. Administration of oxygen may be needed to correct the hypoxemia. There are new minimally invasive bronchoscopic procedures that may be used as both a diagnostic and treatment method.

IN SUMMARY

Disorders of the pleura include pleural effusion, hemothorax, pneumothorax, and pleuritis. Pleural effusion refers to the abnormal accumulation of fluid in the pleural cavity. The fluid may be a transudate (i.e., hydrothorax), exudate (i.e., parapneumonic effusion, empyema), or chyle (i.e., chylothorax). Hemothorax refers to the presence of blood in the pleural cavity. Pain is a common symptom of conditions that produce pleuritis or inflammation of the pleura. Characteristically, the pain is unilateral, abrupt in onset, and exaggerated by respiratory movements. Pneumothorax refers to an accumulation of air in the pleural cavity that causes partial or complete collapse of the lung. Pneumothorax can result from rupture of an air-filled bleb on the lung surface or from penetrating or nonpenetrating injuries. A tension pneumothorax is a life-threatening event in which air progressively accumulates in the thorax, collapsing the lung on the injured side and progressively shifting the mediastinum to the opposite side of the thorax, producing severe cardiac and respiratory impairment.

Atelectasis refers to an incomplete expansion of the lung. Primary atelectasis occurs most often in premature and high-risk infants. Acquired atelectasis occurs mainly in adults and is caused most commonly by a mucus plug in the airway or by external compression by fluid, tumor mass, exudate, or other matter in the area surrounding the airway.

OBSTRUCTIVE AIRWAY DISORDERS

Obstructive airway disorders are caused by disorders that limit expiratory airflow. **Asthma** represents an acute and reversible form of airway disease caused by narrowing of airways due to bronchospasm, inflammation, and increased airway secretions. Chronic obstructive disorders include a variety of airway diseases, such as chronic bronchitis, emphysema, bronchiectasis, and CF.

Physiology of Airway Disease

Air moves through the upper airways (i.e., trachea and major bronchi) into the lower or pulmonary airways (i.e., bronchi and alveoli). In the pulmonary airways, the cartilaginous layer that provides support for the trachea and major bronchi gradually disappears and is replaced with crisscrossing strips of smooth muscle. The contraction and relaxation of the smooth muscle layer, which is innervated by the autonomic nervous system, controls the diameter of the bronchial airways and consequent resistance to airflow. Parasympathetic stimulation, through the vagus nerve and cholinergic receptors, produces bronchial constriction, whereas sympathetic stimulation, through β_2-adrenergic receptors, increases bronchial dilation. At rest, a slight vagal-mediated bronchoconstrictor tone predominates. When there is need for increased airflow, as during exercise, the bronchodilator effects of the sympathetic nervous system are stimulated and the bronchoconstrictor effects of the parasympathetic nervous system are inhibited. Bronchial smooth muscle also responds to inflammatory mediators, such as histamine, that act directly on bronchial smooth muscle cells to produce constriction.

KEY POINTS

AIRWAY DISORDERS

- Changes in airway patency involve changes in airway diameter due to bronchial smooth muscle hyperreactivity or changes in bronchial wall structure, injury to the mucosal lining of the airways, or excess respiratory tract secretions.
- Bronchial asthma is a chronic disorder of the airways that causes episodes of airway obstruction due to bronchial smooth muscle hyperreactivity and airway inflammation. The episodes usually are reversible.
- **COPD** represents a group of disorders that cause chronic and recurrent obstruction of the pulmonary airways. These disorders can affect patency of the bronchial structures (chronic bronchitis), the gas-diffusing airspaces distal to the terminal bronchioles (emphysema), or a combination of both.

Asthma

Asthma is a chronic disorder of the airways that causes episodes of airway obstruction, bronchial hyperresponsiveness, airway inflammation, and, in some, airway remodeling (Centers for Disease Control and Prevention, 2022). More than 25 million people have asthma in the United States. An estimated 7.1 million children have asthma (U.S. Department of Health and Human Services, n.d.). As adults are living longer, the prevalence of asthma in older adults is increasing.

The strongest risk factor for developing asthma is a genetic predisposition for the development of an immunoglobulin E (IgE)–mediated response to common allergens (Loscalzo et al., 2022). IgE is the antibody involved in causing allergic reactions and inflammation (Loscalzo et al., 2022). Other risk factors for childhood asthma include family history of asthma, allergies, antenatal exposure to tobacco smoke and pollution, and obesity (Litonjua & Weiss, 2021b). Asthma severity is impacted by several factors including genetics, age of onset, pollution exposure, atopy, degree of exposure to triggers, environmental triggers such as tobacco smoke and dust mites, and the presence of gastroesophageal reflux disease or respiratory infections (Loscalzo et al., 2022; U.S. Department of Health and Human Services, n.d.) (see "Severe or Refractory Asthma").

Etiology and Pathogenesis

The common denominator underlying asthma is an exaggerated hyperresponsiveness to a variety of stimuli. Airway inflammation manifested by the presence of inflammatory cells (particularly eosinophils, lymphocytes, and mast cells) and by damage to the bronchial epithelium contributes to the pathogenesis of the disease. There are two subsets of T-helper cells (T_1H and T_2H) that develop from the same precursor $CD4^+$ T lymphocyte (Heimall, 2023; Loscalzo et al., 2022). T_1H cells differentiate in response to microbes and stimulate the differentiation of B cells into immunoglobulin M (IgM)– and IgG-producing plasma cells. T_2H cells, on the other hand, respond to allergens and helminths (intestinal parasites) by stimulating B cells to differentiate into IgE-producing plasma cells, produce growth factors for mast cells, and recruit and activate eosinophils. In people with allergic asthma, T-cell differentiation appears to be skewed toward a proinflammatory T_2H response. Although the molecular basis for this preferential differentiation is unclear, it seems likely that both genetic and environmental factors play a role (Loscalzo et al., 2022).

Cytokines also have an apparent role in the chronic inflammatory response and complications of asthma. Tumor necrosis factor (TNF)-α and interleukins 4 and 5 (IL-4, IL-5) participate in the pathogenesis of bronchial asthma through their effects on the bronchial epithelial and smooth muscle cells (Castells & Bankova, 2020; Litonjua & Weiss, 2021a; O'Byrne, 2020). Studies suggest that TNF-α, an inflammatory cytokine that is stored and released from mast cells, plays a critical role in the initiation and amplification of airway inflammation in people with asthma. TNF-α is credited with increasing the migration and activation of inflammatory cells (i.e., eosinophils and neutrophils) and contributing to all aspects of airway remodeling, including proliferation and activation of fibroblasts, increased production of extracellular matrix glycoproteins, and mucous cell hyperplasia (Litonjua & Weiss, 2021a).

It has been determined that frequent viral respiratory infections predispose people with asthma to experience an exacerbation of their disease. In fact, frequent viral respiratory infections may also cause the development of asthma in some people (Strayer et al., 2020). When these respiratory infections are frequent at an early age, there is evidence that the T-helper 2 (T_2H) response is exaggerated. When the CD4 T_2H cytokines IL-4, IL-5, and IL-13 are released, the airways are predisposed for an allergic response, which favors the production of IgE (Hammand & Lambrecht, 2021; National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group, 2020).

The National Heart, Lung, and Blood Institute's Expert Panel Report 3 (NHLBI EPR 3): Guidelines for the Diagnosis and Management of Asthma defined asthma as a chronic inflammatory disorder of the airways. The immunologic aspects of asthma including the cascade of neutrophils, eosinophils, lymphocytes, and mast cells cause epithelial injury. This causes airway inflammation, which further increases hyperresponsiveness and decreased airflow (Loscalzo et al., 2022). There are multiple mediators and cell types that cause the inflammation and airway bronchoconstriction in asthma. When mast cells are activated, the release of histamine; prostaglandin D_2; cytokines such as IL-1 to IL-5, interferon, TNF, and granulocyte–macrophage colony-stimulating factor; and leukotrienes causes massive bronchoconstriction and inflammation of pulmonary vasculature endothelium. **Mast cells** can trigger multiple cytokine release, which causes major inflammation of the airway. The contraction of the airways and subsequent swelling leads to further airway obstruction.

The mast cell release may be linked to exercise-induced asthma (EIA), which is when individuals only experience wheezing and bronchospasm during exercise (Syabbalo, 2019). The cause of EIA is unclear but the following two theories are possible explanations. One theory explaining the cause of EIA is based on the loss of heat and water from the tracheobronchial tree because of the need for warming and humidifying large volumes of air (Castells & Bankova, 2020). The response commonly is exaggerated when the person exercises in a cold environment. The second theory supporting EIA is the airway rewarming hypothesis, which states that airways cool and then warm during any exercise (Castells & Bankova, 2020). This causes congestion in the bronchiolar vessels that surround the bronchial tree and allows fluid exudates to move into the mucosa of the airway, which triggers the inflammatory cascade. It is important to assess the type of air (polluted, cold, or warm), level of exercise, presence/absence of respiratory infectious process, and individual's asthma stability when identifying if a person has EIA (Syabbalo, 2019).

Eosinophils tend to be present in airways of people with asthma and generate inflammatory enzymes and release leukotrienes and many proinflammatory enzymes (Litonjua & Weiss, 2021a; Loscalzo et al., 2022). It is common to have increased neutrophils in sputum and airways of people experiencing asthma exacerbations (Litonjua & Weiss, 2021a). The release of leukotrienes causes more mucus secretion, which often obstructs the airway further and causes more histamine release from the mast cells (Castells & Bankova, 2020).

This inflammatory process produces recurrent episodes of airway obstruction, characterized by wheezing, breathlessness, chest tightness, and a cough that often is worse at night and in the early morning. These episodes, which usually are reversible either spontaneously or with treatment, also cause an associated increase in bronchial responsiveness to a variety of stimuli (American Lung Association, 2020). Chronic inflammation can lead to airway remodeling, in which case airflow limitations may be only partially reversible (Loscalzo et al., 2022). This may be due to the long-term effects of the inflammation on the airway structures (Loscalzo et al., 2022).

There is a small group of people with the clinical triad of asthma, chronic **rhinosinusitis** with nasal polyps, and precipitation of asthma and **rhinitis** attacks in response to aspirin and other NSAIDs (Litonjua & Weiss, 2021a). The mechanism of the hypersensitivity reaction is complex and not fully understood, but most evidence points toward an abnormality in arachidonic acid (AA) metabolism. Cyclooxygenase (COX), the rate-limiting enzyme in AA metabolism, exists in two main forms: COX-1 and COX-2. COX-1 is responsible for the synthesis of protective prostaglandins and COX-2 for the synthesis of mediators of inflammation and bronchoconstriction. It has been hypothesized that in people with aspirin-induced asthma, the inhibition of COX-1 shunts the metabolism of AA away from the production of protective prostaglandins and toward the generation of COX-2 and other mediators of inflammation and bronchoconstriction (Litonjua & Weiss, 2021a). Avoidance of aspirin and all NSAIDs is a necessary part of the treatment program.

In addition, both emotional factors and changes in hormone levels are thought to contribute to an increase in asthma symptoms. Emotional factors produce bronchospasm by way of vagal pathways. They can act as a bronchospastic trigger, or they can increase airway responsiveness to other triggers through noninflammatory mechanisms. The role of sex hormones in asthma is unclear, although there is much circumstantial evidence to suggest that they may be important. In fact, research shows girls with an early menarche (<11.5 years) had twice the chance of developing asthma in their twenties than girls with average menarche (Miller, 2021). Up to 30% of females with asthma report a premenstrual increase in asthma symptoms (Martin, 2021). Female sex hormones have a regulatory role on β_2-adrenergic function, and it has been suggested that abnormal regulation may be a possible mechanism for premenstrual asthma (Martin, 2021). A study comparing premenopausal females with asthma, menopausal females with asthma, and a control group found that menopausal females with asthma had decreased estradiol concentrations, had high sputum neutrophils, and exhaled IL-6, which is indicative of a neutrophilic inflammation. Females with premenopausal asthma had an eosinophilic inflammatory phenotype (Martin, 2021).

Clinical Manifestations

Asthma attacks may occur spontaneously or in response to various triggers, respiratory infections, emotional stress, or weather changes. Asthma is often worse at night, referred to as **nocturnal asthma**. Studies of nocturnal asthma suggest that there is a circadian and sleep-related variation in hormones and respiratory function (Adcock & Barnes, 2020). The greatest decrease in respiratory function occurs at about 4:00 A.M. and is associated with low levels of cortisol and epinephrine along with high levels of the bronchoconstrictor mediator, histamine (WebMD, 2022).

People with asthma exhibit a wide range of signs and symptoms, from episodic wheezing and feelings of chest tightness to an acute, immobilizing attack. The attacks differ from person to person, and between attacks, many people are symptom-free. A mild attack may produce a feeling of chest tightness, a slight increase in respiratory rate with prolonged expiration, and mild wheezing. A cough may accompany the wheezing. More severe attacks are accompanied by use of the accessory muscles, distant breath sounds due to air trapping, and loud wheezing. As the condition progresses, fatigue develops, the skin becomes moist, and anxiety and apprehension are obvious. Sensations of shortness of breath may be severe, and often the person is able to speak only one or two words before taking a breath. At the point at which airflow is markedly decreased, breath sounds become inaudible with diminished wheezing, and the cough becomes ineffective despite being repetitive and hacking (American Lung Association, 2020). This point often marks the onset of respiratory failure.

During an asthmatic attack, the airways narrow because of **bronchospasm**, edema of the bronchial mucosa, and **mucus plugging**. Expiration becomes prolonged because of progressive airway obstruction. The amount of air that can be forcibly expired in 1 second (forced expiratory volume in 1 second [$FEV_{1.0}$]) and the peak expiratory flow (PEF) rate, measured in liters per second, are decreased. A fall in the PEF to levels below 50% of the predicted value during an acute asthmatic attack indicates a severe exacerbation and the need for emergency department treatment (Guntern & Eggel, 2020).

During a prolonged attack, air becomes trapped behind the occluded and narrowed airways, causing hyperinflation of the lungs. This produces an increase in the residual volume (RV) along with a decrease in the inspiratory reserve capacity (tidal volume + inspiratory reserve volume [IRC]) and forced vital capacity (FVC), such that the person breathes close to their functional residual capacity (residual volume + expiratory reserve volume). As a result, more energy is needed to overcome the tension already present in the lungs, and the accessory muscles (e.g., sternocleidomastoid muscles) are required to maintain ventilation and gas exchange. This

increased WOB further increases oxygen demands and causes dyspnea and fatigue. Because air is trapped in the alveoli and inspiration is occurring at higher residual lung volumes, the cough becomes less effective. As the condition progresses, the effectiveness of alveolar ventilation declines, and mismatching of ventilation and perfusion occurs, causing hypoxemia and hypercapnia. Pulmonary vascular resistance may increase as a result of the hypoxemia and hyperinflation, leading to a rise in pulmonary arterial pressure and increased work demands on the right heart.

Diagnosis

The diagnosis of asthma is based on a careful history and physical examination, laboratory findings, and pulmonary function studies. Spirometry provides a means for measuring FVC, $FEV_{1.0}$, PEF, tidal volume, expiratory reserve capacity, and inspiratory reserve capacity. The $FEV_{1.0}$/FVC ratio can then be calculated. The level of airway responsiveness can be measured by inhalation challenge tests using methacholine (a cholinergic agonist), histamine, or exposure to a nonpharmacologic agent such as cold air.

Small, inexpensive, portable meters that measure PEF are available. Although not intended for use in the diagnosis of asthma, they can be used in clinics and primary care providers' offices and in the home to provide frequent measures of flow rates. Day–night (circadian) variations in asthma symptoms and PEF variability can be used to indicate the severity of bronchial hyperresponsiveness. The person's best performance is established from readings taken over several weeks. This often is referred to as the individual's *personal best* and is used as a reference to indicate changes in respiratory function (Loscalzo et al., 2022).

Treatment

The NHLBI EPR 3 classifies four stages of asthma for children greater than 12 years and adults, including intermittent, mild persistent, moderate persistent, and severe persistent (National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group, 2020). The Expert Panel developed these classification systems in order to direct asthma treatment and to assist in identifying people at high risk for development of life-threatening asthma attacks (Loscalzo et al., 2022) (Table 31.1). Asthma treatment consists of prevention measures, nonpharmacologic measures, desensitization, and pharmacologic management.

Prevention measures to control factors contributing to asthma severity are aimed at limiting exposure to irritants and factors that increase asthma symptoms and precipitate asthma exacerbations. They include education of the person and family regarding measures used in avoiding exposure to irritants and allergens that are known to induce or trigger an attack. A careful history often is needed to identify all the contributory factors. Factors such as nasal polyps, a history of aspirin sensitivity, and gastroesophageal reflux should be considered. Annual influenza vaccination is recommended for people with persistent asthma.

Nonpharmacologic management includes relaxation techniques and controlled breathing, which often help to allay the panic and anxiety that aggravate breathing difficulties. The hyperventilation that often accompanies anxiety and panic is

TABLE 31.1 CLASSIFICATION OF ASTHMA SEVERITY (ADOLESCENTS AND ADULTS)

	SYMPTOMS	LUNG FUNCTION
Intermittent Step 1	Daytime symptoms ≤2 times a week Asymptomatic and normal PEF between exacerbations Exacerbations <1 time/year Nighttime awakening ≤2 times/month	Normal $FEV_{1.0}$
Mild Step 2	Daytime symptoms >2 times a week but <7 days/week Nighttime awakening 3-4 times/month Exacerbations >2 times/year May have minimal effect on activity	$FEV_{1.0}$ normal
Moderate Step 3	Daily symptoms Daily use of inhaled combined low-dose ICS and 1-2 inhalations (alternative options may be recommended) Some limitation on activity Exacerbations ≥2 times a year; 1/nighttime awakening >1/week	$FEV_{1.0}$ > 60% to < 80%
Severe Step 4	Continual symptoms Very limited physical activity Exacerbations >2 times/year Need for SABA several times/day Combination medium-dose ICS and 1-2 inhalations/day Nighttime awakening each pm	$FEV_{1.0}$ ≤ 60% predicted

Adapted from Fanta, D., & Barrett, N. (2022). *National asthma education and prevention program: Expert panel working group (NAEPP 2020).* Retrieved February 5, 2023, from https://www.uptodate.com/contents/an-overview-of-asthma-management

known to act as an asthmatic trigger. In a child, measures to encourage independence as it relates to symptom control, along with those directed at helping to develop a positive self-concept, are essential.

A *program of* ***desensitization*** may be undertaken in people with persistent asthma who react to allergens, such as house dust mites, that cannot be avoided. This involves the injection of selected antigens (based on skin tests) to stimulate the production of IgG antibodies that block the IgE response. A course of allergen immunotherapy is typically of 3 to 5 years' duration (Loscalzo et al., 2022).

The Expert Panel recommends a stepwise approach to *pharmacologic therapy* based on the classification systems discussed previously (Loscalzo et al., 2022). The first line of treatment with any of the persistent forms of asthma includes an inflammatory controller drug that would include inhaled corticosteroids (ICS), mast cell stabilizers, and leukotriene modifiers. ICS are considered the most effective in preventing airway inflammation and generally the drug used.

The *quick-relief medications* such as the short-acting β_2-adrenergic agonists (e.g., albuterol, levalbuterol, pirbuterol) relax bronchial smooth muscle and provide prompt relief of symptoms, usually within 30 minutes. They are administered by inhalation (i.e., metered-dose inhaler or nebulizer), and their recommended use is in alleviating acute attacks of asthma because regular use does not produce beneficial effects (Loscalzo et al., 2022). The anticholinergic medications (e.g., ipratropium) block the postganglionic efferent vagal pathways that cause bronchoconstriction. These medications, which are administered by inhalation, produce bronchodilation by direct action on the large airways and do not change the composition or viscosity of the bronchial mucus. It is thought that they may provide some additive benefit for treatment of asthma exacerbations when administered with inhaled β_2-adrenergic agonists (Loscalzo et al., 2022). A short course of systemic corticosteroids, administered orally or parenterally, may be used for treating an acute flare. Although their onset of action is slow (>4 hours), systemic corticosteroids may be used in the treatment of moderate to severe exacerbations because of their action in preventing the progression of the exacerbation, speeding recovery, and preventing early relapses (Loscalzo et al., 2022).

The antiinflammatory agents sodium cromolyn and nedocromil are also used to prevent an asthmatic attack. These agents act by stabilizing mast cells, thereby preventing release of the inflammatory mediators that cause an asthmatic attack. They are used prophylactically to prevent early and late responses but are of no benefit when taken during an attack. Due to the immunomodulatory properties of vitamin D and its abilities to modify proinflammatory and antiinflammatory responses in the immunologic system, there have been studies suggesting a correlation of vitamin D and more effective management of childhood and asthma exacerbations as well as with steroid-resistant asthma (Litonjua, 2019).

Severe or Refractory Asthma

Severe or **refractory asthma** represents a subgroup of approximately 0.5% of people with asthma who have more troublesome disease as evidenced by high medication requirements to maintain good symptom control or those who continue to have persistent symptoms despite high medication use (Backman et al., 2019). These people are at increased risk for fatal or near-fatal asthma.

Little is known about the causes of severe asthma. Among the proposed risk factors are genetic predisposition, continued allergen or tobacco exposure, infection, intercurrent sinusitis or gastroesophageal reflux disease, and lack of compliance or adherence with treatment measures (Beckman et al., 2019). It has been proposed that because asthma is a disease involving multiple genes, mutations in genes regulating cytokines, growth factors, or receptors for medications used in treatment of asthma (β_2-adrenergic agonist or glucocorticoid) could be involved. Environmental factors include both allergen and tobacco exposure, with the strongest response occurring in response to house dust, cockroach allergen, and *Alternaria* exposure. Infections may also play a role. **Respiratory syncytial virus** infections are implicated in children, and pathogens such as mycoplasma and chlamydiae may play a role in adults. Gastroesophageal reflux and chronic sinusitis may also play a role. Although the cause of death during an acute asthmatic attack is largely unknown, both cardiac arrhythmias and asphyxia due to severe airway obstruction have been implicated. It has been suggested that an underestimation of the severity of the attack may be a contributing factor. Deterioration often occurs rapidly during an acute attack, and underestimation of its severity may lead to a life-threatening delay in seeking medical attention. Frequent and repetitive use of β_2-adrenergic agonist inhalers far in excess of the recommended doses may temporarily blunt symptoms and mask the severity of the condition. It has been suggested that people who have a fatal or near-fatal asthmatic attack may not perceive its severity (Beckman et al., 2019; Loscalzo, 2017). That is, they may not perceive the severity of their condition and consequently not take appropriate measures in terms of seeking medical or emergency treatment.

The long-acting β_2-agonists such as salmeterol and formoterol are used to treat severe refractory asthma only if no other treatment is effective. The long-acting β_2-adrenergic agonists have durations of action of at least 12 hours and should not be used to treat acute symptoms or exacerbations. These drugs have a black box warning from the U.S. Food and Drug Administration due to their possibility of causing asthma death, especially if they are used as a monotherapy. Research is also focused on the use of allergen immunotherapy treatment aimed at T_2H cytokines in specific groups of people with severe asthma. However, only one is currently available (Azhar & Ballas, 2020; Stokes & Casale, 2021). At this time, the only approved anti-IgE therapy for severe asthma is omalizumab, which has severe potential systemic

side effects (Azhar & Ballas, 2020). Several anti-IgE biologicals are now in various phases of clinical trials (Guntern & Eggel, 2020).

Asthma in Older Adults

For older adults with asthma, who already have a decreased immunologic function due to aging, it is important to be aware of how this lowered immunity impacts their airway inflammation. Studies demonstrate these changes in immune function can seriously affect their conditions (HSU et al., 2017).

Asthma in Children

Asthma is a leading cause of chronic illness in children and is responsible for more than 10 million lost school days annually (Global Initiative for Asthma, 2019). It is the most frequent admitting diagnosis in children's hospitals. Based on information collected by the Centers for Disease Control and Prevention, asthma may have its onset at any age. In addition, asthma is more prevalent in non-Hispanic Black children than in White children and results in more frequent disability and more frequent hospitalizations in non-Hispanic Black children (Jartti & Gern, 2017).

As with adults, asthma in children commonly is associated with an IgE-related reaction. It has been suggested that IgE directed against respiratory viruses in particular may be important in the pathogenesis of wheezing illnesses in infants (i.e., bronchiolitis), which often precede the onset of asthma. Other contributing factors include exposure to environmental allergens such as pet dander, dust mite antigens, and cockroach allergens. Exposure to environmental tobacco smoke also contributes to asthma in children.

The signs and symptoms of asthma in infants and small children vary with the stage and severity of an attack. Because airway patency decreases at night, many children have acute signs of asthma at this time. Infants with undiagnosed asthma may have a prolonged cough without cold symptoms, independent of wheezing (COPD Foundation, n.d.). Often, previously well infants and children develop what may seem to be a cold with rhinorrhea, rapidly followed by irritability, a tight and nonproductive cough, wheezing, tachypnea, dyspnea with prolonged expiration, and use of accessory muscles of respiration. Cyanosis, hyperinflation of the chest, and tachycardia indicate increasing severity of the attack. Wheezing may be absent in children with extreme respiratory distress. The symptoms may progress rapidly and require a trip to the emergency department or hospitalization.

The expert panel of the Global Initiative for Asthma (GINA) has developed a global strategy with guidelines for management and prevention of asthma in infants and children from 0 to 5 years, 6 to 11 years, and for adults and children 12 years of age and older. As with adults and older children, GINA recommends a stepwise approach to diagnosing and managing asthma in infants and children (COPD Foundation, n.d.).

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is characterized by chronic and recurrent obstruction of airflow in the pulmonary airways. Airflow obstruction usually is progressive and is accompanied by inflammatory responses to noxious particles or gases. COPD is a leading cause of morbidity and mortality worldwide. It has been estimated that approximately 30 million Americans (Global Initiative for Chronic Obstructive Lung Disease, 2020) have some degree of COPD, but millions may have the disease and not be aware. The burden of COPD is highest in females and residents of rural areas (Global Initiative for Chronic Obstructive Lung Disease, 2020). In the United States, COPD is the fourth leading cause of death following heart disease, cancer, and unintentional injuries (Global Initiative for Chronic Obstructive Lung Disease, 2020). According to the COPD National Action Plan, the economic cost ($32.1 billion) was spent on direct costs related to COPD care, and more than 16.4 million days of work were lost due to COPD (Global Initiative for Chronic Obstructive Lung Disease, 2020; Stoller et al., 2020).

The most common cause of COPD is smoking (Stoller et al., 2020). A second, less common factor is a hereditary deficiency in α_1-antitrypsin (AAT). Other predisposing factors are asthma and airway hyperresponsiveness. Although clinical findings may be absent during the early stages of COPD, any person with a chronic cough, sputum production, dyspnea and a history to exposures of risk factors such as smoking or indoor/outdoor pollution should be considered for the diagnosis of COPD (Global Initiative for Chronic Obstructive Lung Disease, 2020; Stoller et al., 2020). By the time symptoms appear or are recognized, the disease is usually far advanced. For smokers with early signs of airway disease, there is hope that early recognition, combined with appropriate treatment and smoking cessation, may prevent or delay the usually relentless progression of the disease.

Etiology and Pathogenesis

The mechanisms involved in the pathogenesis of COPD usually are multiple and include inflammation and fibrosis of the bronchial wall, hypertrophy of the submucosal glands and hypersecretion of mucus, and loss of elastic lung fibers and alveolar tissue (Stoller et al., 2020). Inflammation and fibrosis of the bronchial wall, along with excess mucus secretion, obstruct airflow and cause mismatching of ventilation and perfusion. Destruction of alveolar tissue decreases the surface area for gas exchange, and loss of elastic fibers impairs the expiratory flow rate, increases air trapping, and predisposes to airway collapse.

The term *chronic obstructive pulmonary disease* encompasses two types of obstructive airway disease: *emphysema*, with enlargement of airspaces and destruction of lung tissue, and *chronic obstructive bronchitis*, with increased mucus production, obstruction of small airways, and a chronic productive cough. People with COPD often have overlapping features of both disorders (Beckman et al., 2019; Stoller et al., 2020).

Emphysema. **Emphysema** is characterized by a loss of lung elasticity and abnormal enlargement of the airspaces distal to the terminal bronchioles, with destruction of the alveolar walls and capillary beds (Fig. 31.9). Enlargement of the airspaces leads to hyperinflation of the lungs and produces an increase in total lung capacity (TLC). Two of the recognized causes of emphysema are smoking, which incites lung injury, and an inherited deficiency of AAT, an antiprotease enzyme that protects the lung from injury. AAT deficiency (AATD) is a genetic risk factor for COPD (Mejza et al., 2017). Mutations in the SERPINA1 gene can cause AATD. Isoelectric focusing is considered to be the gold standard in diagnosis of ATTD (Mejza et al., 2017).

Emphysema is thought to result from the breakdown of elastin and other alveolar wall components by enzymes, called *proteases*, which digest proteins. Normally, antiprotease enzymes, including AAT, protect the lung. Cigarette smoke and other irritants stimulate the movement of inflammatory cells into the lungs, resulting in increased release of elastase and other proteases. In smokers in whom COPD develops, antiprotease production and release may be inadequate to neutralize the excess protease production such that the process of elastic tissue destruction goes unchecked (Fig. 31.10).

The type and amount of AAT that a person has is determined by a pair of codominant genes referred to as *PI* (protein inhibitor) genes. An AATD is inherited as an autosomal recessive disorder. Most people with clinically diagnosed emphysema before the age of 40 years have an AATD. Smoking and repeated respiratory tract infections, which also decrease AAT levels, contribute to the risk for emphysema in people with AATD. Laboratory methods are available for measuring AAT levels. Human AAT is available for replacement therapy in people with a hereditary deficiency of the enzyme.

There are two commonly recognized types of emphysema: centriacinar or centrilobular, and panacinar (Fig. 31.11). Centriacinar emphysema is mostly associated with cigarette smoking and affects the respiratory bronchioles predominantly in the upper lobes and in the superior lower lobes (Beckman et al., 2019). It is the most common type of emphysema and is seen predominantly in male smokers. The **panacinar type** produces initial involvement of the peripheral alveoli and later extends to involve the more central bronchioles. This type of emphysema is more common in people with AATD. It also is found in smokers in association with **centriacinar emphysema**. In such cases, the panacinar pattern tends to occur in the lower parts of the lung and centriacinar emphysema is seen in the upper parts of the lung.

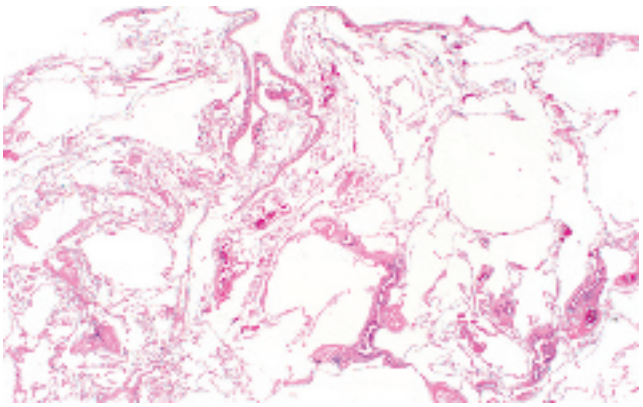


Figure 31.9 • Panacinar emphysema in a patient with α_1-antitrypsin deficiency. Low power shows enlargement of airspaces throughout the lung parenchyma with severe destruction of the alveolar septa. (From Butt, Y. M., & Tazelaar, H. D. (2021). *Atlas of pulmonary pathology* (Fig. 6-44). Wolters Kluwer.)

Chronic Bronchitis. Chronic **bronchitis** represents airway obstruction of the major and small airways (Cystic Fibrosis Foundation, 2021). The condition is seen most commonly in middle-aged males and is associated with chronic irritation from smoking and recurrent infections. A clinical diagnosis of chronic bronchitis requires the history of a chronic productive cough for at least 3 consecutive months in at least 2 consecutive years (Cystic Fibrosis Foundation, 2021). Typically, the cough has been present for many years, with a gradual increase in acute exacerbations that produce frankly purulent sputum.

The earliest feature of chronic bronchitis is hypersecretion of mucus in the large airways, associated with hypertrophy of the submucosal glands in the trachea and bronchi (Beckman et al., 2019). Although mucus hypersecretion in the large airways is the cause of sputum overproduction, it is now thought that accompanying changes in the small airways (small bronchi and bronchioles) are physiologically important in the airway obstruction that develops in chronic bronchitis (Beckman et al., 2019). Histologically, these changes include a marked increase in goblet cells and excess mucus production with plugging of the airway lumen, inflammatory infiltration, and fibrosis of the bronchiolar wall. It is thought that both the submucosal hypertrophy in the larger airways and the increase in goblet cells in the smaller airways are a protective reaction against tobacco smoke and other pollutants. Viral and bacterial infections are common in people with chronic bronchitis and are thought to be a result rather than a cause of the problem.

Clinical Manifestations

The clinical manifestations of COPD usually have an insidious onset. People characteristically seek medical attention in the fifth or sixth decade of life, with manifestations such as fatigue, exercise intolerance, cough, sputum production, or shortness of breath. The productive cough usually occurs in the morning and the dyspnea becomes more severe as the disease progresses. Frequent exacerbations of infection and respiratory insufficiency are common, causing absence from work and eventual disability. The late stages of COPD are characterized by recurrent respiratory infections and chronic respiratory failure. Death usually occurs during an exacerbation of illness associated with infection and respiratory failure.

The mnemonics "pink puffer" and "blue bloater" have been used to differentiate the clinical manifestations of

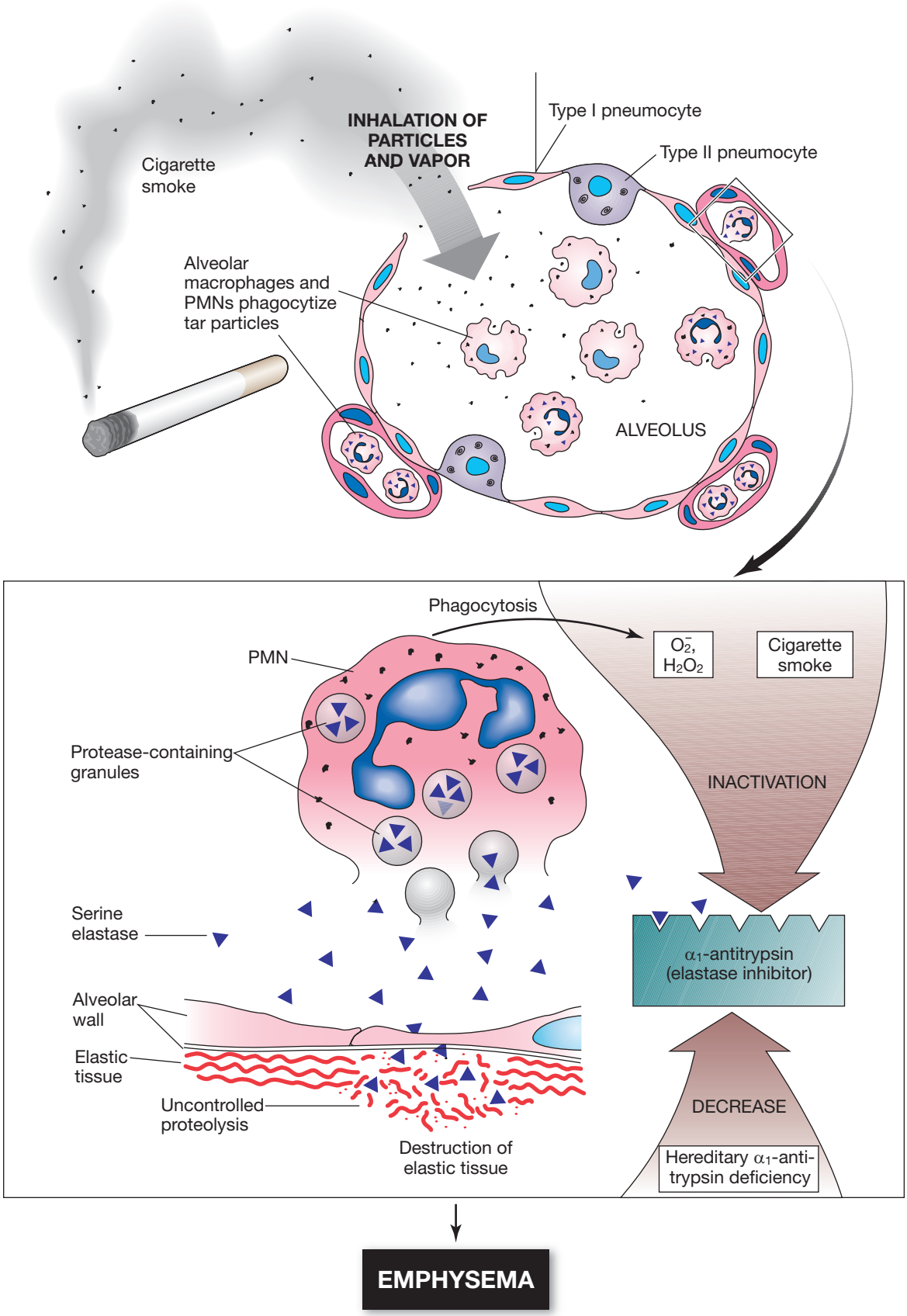


Figure 31.10 • The proteolysis–antiproteolysis theory of the pathogenesis of emphysema. Cigarette (tobacco) smoking is closely related to the development of emphysema. Some products in tobacco smoke induce an inflammatory reaction. The serine elastase in polymorphonuclear leukocytes, a particularly potent elastolytic agent, injures the elastic tissue of the lung. Normally, this enzyme activity is inhibited by α_1-antitrypsin, but tobacco smoke, directly or through the generation of free radicals, inactivates AAT (protease inhibitor). (From Strayer, D., , Saffitz, J., , & Rubin, R. (Eds.) (2020). *Rubin's pathology: Clinicopathologic foundations of medicine* (8th ed., Fig. 18-42, p. 723). Lippincott Williams & Wilkins.)

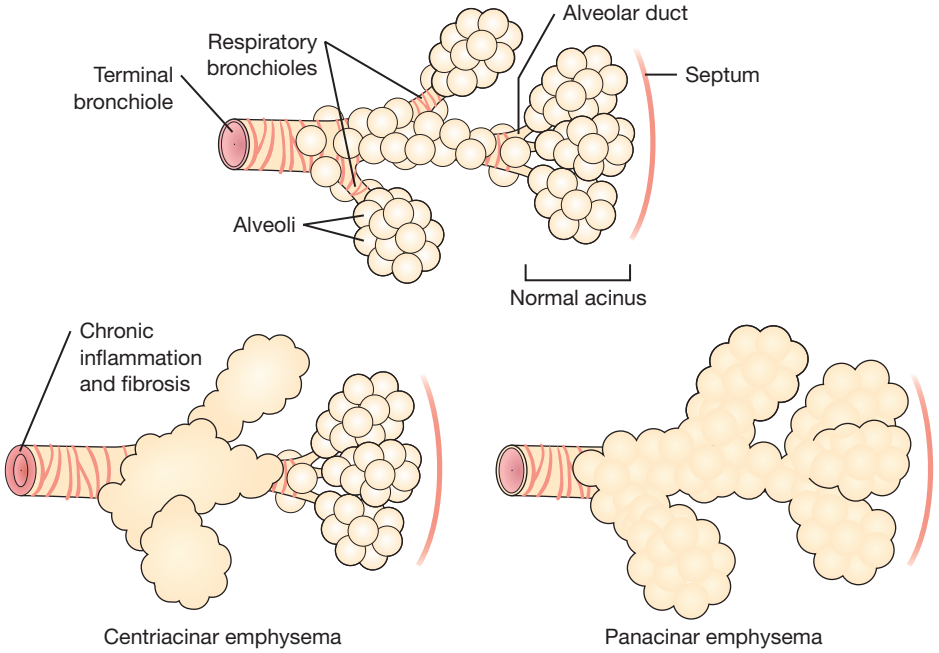


Figure 31.11 • Types of emphysema. The acinus, the gas-exchanging structure of the lung distal to the terminal bronchiole, consists of the terminal bronchiole, respiratory bronchioles, alveolar ducts, and alveoli. In centriacinar emphysema, the respiratory bronchioles are mainly involved. In panacinar emphysema, the acinus is uniformly damaged. (From Nath, J., & Braun, C. (2022). *Applied pathophysiology* (4th ed., Fig. 15-7). Wolters Kluwer.)

emphysema and chronic obstructive bronchitis. People with predominant emphysema are classically referred to as **pink puffers**, a reference to the lack of cyanosis, the use of accessory muscles, and **pursed-lip** ("puffer") **breathing**. With loss of lung elasticity and hyperinflation of the lungs, the airways often collapse during expiration because pressure in surrounding lung tissues exceeds airway pressure. Air becomes trapped in the alveoli and lungs, producing an increase in the anteroposterior dimensions of the chest, the so-called **barrel chest** that is typical of people with emphysema (Fig. 31.12). Such people have a dramatic decrease in breath sounds throughout the chest. Because the diaphragm may be functioning near its maximum ability, the person is vulnerable to diaphragmatic fatigue and acute respiratory failure.

People with a clinical syndrome of chronic bronchitis are classically labeled **blue bloaters**, a reference to cyanosis and fluid retention associated with right-sided heart failure. In practice, differentiation between the two types of COPD is often difficult. This is because people with COPD often have some degree of both emphysema and chronic bronchitis.

The manifestations of COPD represent a progressive change in respiratory function. There is moderate to severe respiratory impairment due to obstruction of airflow, which is greater on expiration than inspiration, resulting in increased WOB but decreased effectiveness. The development of exertional dyspnea, often described as increased effort to breathe, heaviness, air hunger, or gasping, can be insidious and is often reported in the sixth decade. Activities involving significant arm work, particularly above the shoulders, are particularly difficult for people with COPD. Activities that allow the person to brace the arms and use the accessory muscles are better tolerated. As the disease progresses, breathing becomes increasingly more labored, even at rest. The expiratory phase of respiration is prolonged, and expiratory wheezes and crackles can be heard on auscultation. People with severe airflow obstruction may also exhibit use of the accessory muscles, sitting in the characteristic "tripod" position to facilitate use of the sternocleidomastoid, scalene, and intercostal muscles (Beckman et al., 2019). Pursed-lip breathing enhances airflow because it increases the resistance to the outflow of air and helps to prevent airway collapse by increasing airway pressure. Eventually, people with COPD are unable to maintain normal blood gases by increasing their breathing effort. Hypoxemia, hypercapnia, and cyanosis develop, reflecting an imbalance between ventilation and perfusion.

Severe hypoxemia, in which arterial PO_2 levels fall below 55 mm Hg, causes reflex vasoconstriction of the pulmonary vessels and further impairment of gas exchange in the lung. It is more common in people with the chronic bronchitis form of COPD. Hypoxemia also stimulates red blood cell production, causing polycythemia. The increase in pulmonary vasoconstriction and subsequent elevation in pulmonary artery pressure further increase the work of the right ventricle. As a result, people with COPD may develop right-sided heart failure with peripheral edema (i.e., cor pulmonale). However, signs of overt right-sided heart failure are seen less frequently since the advent of supplemental oxygen therapy.

Diagnosis

The diagnosis of COPD is based on a careful history and physical examination, pulmonary function studies, chest

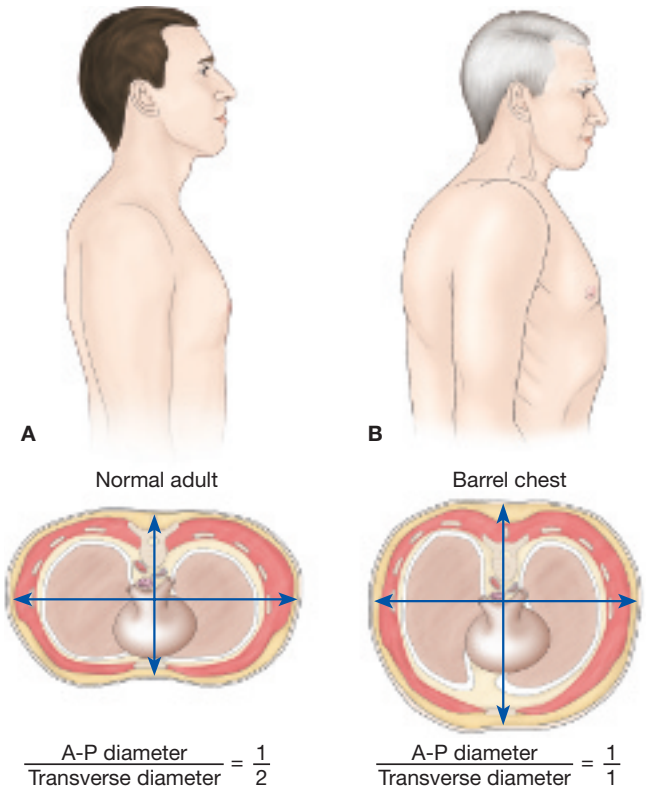


Figure 31.12 • Characteristics of normal chest wall and chest wall in emphysema. **(A)** The normal chest wall and its cross-section. **(B)** The barrel-shaped chest of emphysema and its cross-section. (From Hinkle, J. L., Cheever, K. H., & Overbaugh, K. J. (2022). *Brunner & Suddarth's textbook of medical-surgical nursing* (15th ed., Fig. 20-3, p. 606). Lippincott Williams & Wilkins.)

radiographs, and laboratory tests. Airway obstruction prolongs the expiratory phase of respiration and affords the potential for impaired gas exchange because of mismatching of ventilation and perfusion. The FVC is the amount of air that can be forcibly exhaled after maximal inspiration. In an adult with normal respiratory function, this should be achieved in 4 to 6 seconds. In people with chronic lung disease, the time required for FVC is increased, the $FEV_{1.0}$ is decreased, and the ratio of $FEV_{1.0}$ to FVC is decreased. In severe disease, the FVC is markedly reduced. Lung volume measurements reveal a marked increase in RV, an increase in TLC, and elevation of the RV-to-TLC ratio. These and other measurements of expiratory flow are determined by spirometry and are used in the diagnosis of COPD. Spirometry measurements can be used in staging disease severity. For example, an $FEV_{1.0}$-to-FVC ratio of less than 70% with an $FEV_{1.0}$ of 80% or more, with or without symptoms, indicates mild disease, and an $FEV_{1.0}$-to-FVC ratio of less than 70% with an $FEV_{1.0}$ of less than or equal to 50%, with or without symptoms, indicates moderate disease. Severe disease is indicated by an $FEV_{1.0}$ range of 30% to 50%, and very severe COPD is indicated with an $FEV_{1.0}$ of less than 30%; both with $FEV_{1.0}$-to-FVC ratios less than 70% (U.S. Department of Health and Human Services, n.d.). Other diagnostic measures become important as the disease advances. Measures of exercise tolerance, nutritional status, hemoglobin saturation, and ABGs can be used to assess the overall impact of COPD on health status and to direct treatment.

Treatment

The treatment of COPD depends on the stage of the disease and often requires an interdisciplinary approach. Smoking cessation is the only measure that slows the progression of the disease. Education of people with COPD and their families is a key to successful management of the disease. Psychosocial rehabilitation must be individualized to meet the specific needs of people with COPD and their families. These needs vary with age, occupation, financial resources, social and recreational interests, and interpersonal and family relationships.

People in more advanced stages of the disease often require measures to maintain and improve physical and psychosocial functioning, pharmacologic interventions, and oxygen therapy. Avoidance of cigarette smoke and other environmental airway irritants is imperative. Wearing a cold-weather mask often prevents dyspnea and bronchospasm due to cold air and wind exposure.

Respiratory tract infections can prove life-threatening to people with severe COPD. A person with COPD should avoid exposure to others with known respiratory tract infections and should avoid attending large gatherings during periods of the year when influenza or respiratory tract infections are prevalent. Immunization for influenza and pneumococcal infections decreases the likelihood of their occurrence.

Maintaining and improving physical and psychosocial functioning is an important part of the treatment program for people with COPD. A long-term pulmonary rehabilitation program can significantly reduce episodes of hospitalization and add measurably to a person's ability to manage and cope with their impairment in a positive way. This program includes breathing exercises that focus on restoring the function of the diaphragm, reducing the WOB, and improving gas exchange. Physical conditioning with appropriate exercise training increases maximal oxygen consumption and reduces ventilatory effort and heart rate for a given workload. Work simplification and energy conservation strategies may be needed when impairment is severe.

The pharmacologic treatment of COPD includes the use of **bronchodilators**, including inhaled adrenergic and anticholinergic agents. Inhaled β_2-adrenergic agonists have been the mainstay of treatment of COPD. It has been suggested that long-acting inhaled β_2-adrenergic agonists may be even more effective than the short-acting forms of the drug. The anticholinergic drugs (e.g., ipratropium bromide, tiotropium bromide), which are administered by inhalation, produce bronchodilation by blocking parasympathetic cholinergic receptors that produce contraction of bronchial smooth muscle. These medications, which are administered by inhalation, produce bronchodilation by direct action on the large airways and do not change the composition or viscosity of the bronchial mucus. They also reduce the volume of sputum without altering its viscosity. Because these drugs have a slower onset and longer duration of action, they usually are used on

a regular basis rather than on an as-needed basis. Inhalers that combine an anticholinergic drug with a β_2-adrenergic agonist are available.

ICSs often are used in treatment of COPD; there is controversy regarding their usefulness. An explanation for this lack of effect may be related to the fact that corticosteroids prolong the action of neutrophils and hence do not suppress the neutrophilic inflammation seen in COPD. Because corticosteroids are useful in relieving asthma symptoms, they may benefit people with asthma concomitant with COPD. ICSs also may be beneficial in treating acute exacerbations of COPD, minimizing the undesirable effects that often accompany systemic use.

Oxygen therapy is prescribed for selected people with significant hypoxemia (arterial PO_2 < 55 mm Hg). Administration of continuous low-flow (1 to 2 L/minute) oxygen to maintain arterial PO_2 levels between 55 and 65 mm Hg decreases dyspnea and pulmonary hypertension and improves neuropsychologic function and activity tolerance. The overall goal of oxygen therapy is to maintain a hemoglobin oxygen saturation of 88% to 92% (U.S. Department of Health and Human Services, n.d.). Because the ventilatory drive associated with hypoxic stimulation of the peripheral chemoreceptors does not occur until the arterial PO_2 has been reduced to about 60 mm Hg or less, increasing the arterial PO_2 above 60 mm Hg tends to depress the hypoxic stimulus for ventilation and often leads to hypoventilation and carbon dioxide retention. Therefore, clinicians should use caution and not over oxygenate COPD people to seek a higher spirometry goal, as this may depress the drive to breathe.

Bronchiectasis

Bronchiectasis is an uncommon type of COPD characterized by a permanent dilation of the bronchi and bronchioles caused by destruction of the muscle and elastic supporting tissue as the result of a continuous cycle of infection and inflammation (Fig. 31.13). It is not a primary disease but is considered secondary to acquiring frequent infections. In the past, bronchiectasis often followed a necrotizing bacterial pneumonia that frequently complicated measles, pertussis, or influenza. Tuberculosis was also commonly associated with bronchiectasis. Thus, with the advent of antibiotics that more effectively treat respiratory infections such as tuberculosis and with immunization against pertussis and measles, there has been a marked decrease in the prevalence of bronchiectasis except with people who are living longer with CF.

Etiology and Pathogenesis

Mucus obstruction and chronic persistent infection are the etiology of bronchiectasis. Regardless of which may come first, both cause damage to the bronchial walls, leading to weakening and dilation. On gross examination, bronchial dilation is classified as **saccular**, **cylindrical**, or **varicose**. Saccular bronchiectasis involves the proximal third to fourth generation of bronchi (Stoller et al., 2020). These bronchi become severely dilated and end blindly in dilated sacs, with collapse and fibrosis of more distal lung tissue. Cylindrical bronchiectasis involves uniform and moderate dilation of the sixth to eighth generations of airways. It is a milder form of disease than saccular bronchiectasis and leads to fewer symptoms. Varicose bronchiectasis involves the second through eighth branchings of bronchi and results in bronchi that resemble varicose veins. Bronchiolar obliteration is not as severe and various symptoms can occur.

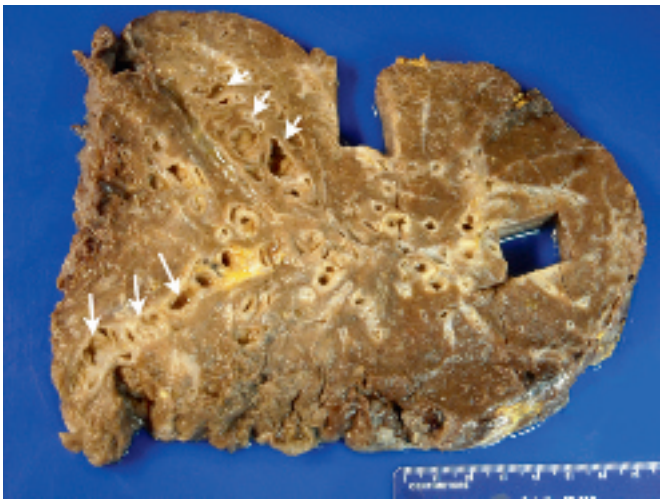


Figure 31.13 • Bronchiectasis, explanted lung. There is diffuse airway dilatation, without significant consolidation. The bronchi are tortuous and focally extend to near the pleural surface (arrows). The patient suffered diffuse airway injury following inhalation of smoke in a house fire. (From Burke, A. P, Aubry, M.-C., Maleszewski, J., Alexiev, B., & Tavora, F. (2016). *Practical thoracic pathology* (Fig. 31-3). Wolters Kluwer.)

Bronchiectasis can present in either of two forms: a local obstructive process involving a lobe or segment of a lung or a diffuse process involving much of both lungs. *Localized or focal bronchiectasis* is most commonly caused by conditions such as tumors, foreign bodies, and mucus plugs that produce atelectasis and infection due to obstructed drainage of bronchial secretions. It can affect any area of the lung, the area being determined by the site of obstruction or infection. *Generalized or diffuse bronchiectasis* usually is bilateral and most commonly affects the lower lobes (Beckman et al., 2019). It is due largely to inherited impairments of host mechanisms or acquired disorders that permit introduction of infectious organisms into the airways. They include inherited conditions such as CF, in which airway obstruction is caused by impairment of normal mucociliary function; congenital and acquired immunodeficiency states, which predispose to respiratory tract infections; lung infection (e.g., tuberculosis, fungal infections, lung abscess); and exposure to toxic gases that cause airway obstruction.

Clinical Manifestations

Bronchiectasis is associated with a number of abnormalities that profoundly affect respiratory function, including atelectasis, obstruction of the smaller airways, and diffuse bronchitis.

People with bronchiectasis have recurrent bronchopulmonary infection; coughing; production of copious amounts of foul-smelling, purulent sputum; and hemoptysis. Weight loss and anemia are common.

In addition, the manifestations of bronchiectasis are similar to those seen in chronic bronchitis and emphysema. As in the latter two conditions, chronic bronchial obstruction leads to marked dyspnea and cyanosis. Clubbing of the fingers, which is not usually seen in other types of obstructive lung diseases, is more common in moderate to advanced bronchiectasis.

Diagnosis and Treatment

Diagnosis is based on history and imaging studies. The condition often is evident on chest radiographs. High-resolution CT scanning of the chest allows for definitive diagnosis. Accuracy of diagnosis is important because interventional bronchoscopy or surgery may be palliative or curative in some types of obstructive disease.

Treatment consists of early recognition and treatment of infection along with regular postural drainage and chest physical therapy. People with this disorder benefit from many of the rehabilitation and treatment measures used for chronic bronchitis and emphysema.

Cystic Fibrosis

Cystic fibrosis, which is the major cause of severe chronic respiratory disease in children, is an autosomal recessive disorder involving the exocrine glands in the epithelial lining of the respiratory, gastrointestinal, and reproductive tracts (U.S. National Library of Medicine, n.d.). In 2021, CF affected about 30,000 children and adults in the United States; more than 10 million people are asymptomatic carriers of the defective gene (U.S. National Library of Medicine, n.d.). The defective gene, **cystic fibrosis transmembrane regulator** (CFTR), and its protein product cause excessive thick mucus that obstructs lungs and the pancreas. In addition to chronic respiratory disease, CF is manifested by pancreatic exocrine deficiency and elevation of sodium chloride in the sweat. Nasal polyps, sinus infections, pancreatitis, and cholelithiasis also are seen with CF. Most boys with CF have congenital bilateral absence of the vas deferens with azoospermia.

Etiology and Pathogenesis

CF is caused by mutations in a single gene on the long arm of chromosome 7 that encodes for the CFTR, which functions as a chloride (Cl^-) channel in epithelial cell membranes. Mutations in the CFTR gene render the epithelial membrane relatively impermeable to the chloride ion (Fig. 31.14). There are greater than 1,000 possible CFTR changes that can occur. However, the most common CFTR gene mutation is called the delta F508, in which the deletion of the amino acid phenylalanine at the 508 position results in a severe phenotype. Due to the deletion of this amino acid, chloride channels are misfolded and are not inserted into the cell membrane (Gemma et al., 2017). Others have a partial loss or mutation of the CFTR gene so their phenotype is less severe and often goes unnoticed until they have an acute injury such as pneumonia and may need intubation and mechanical ventilation.

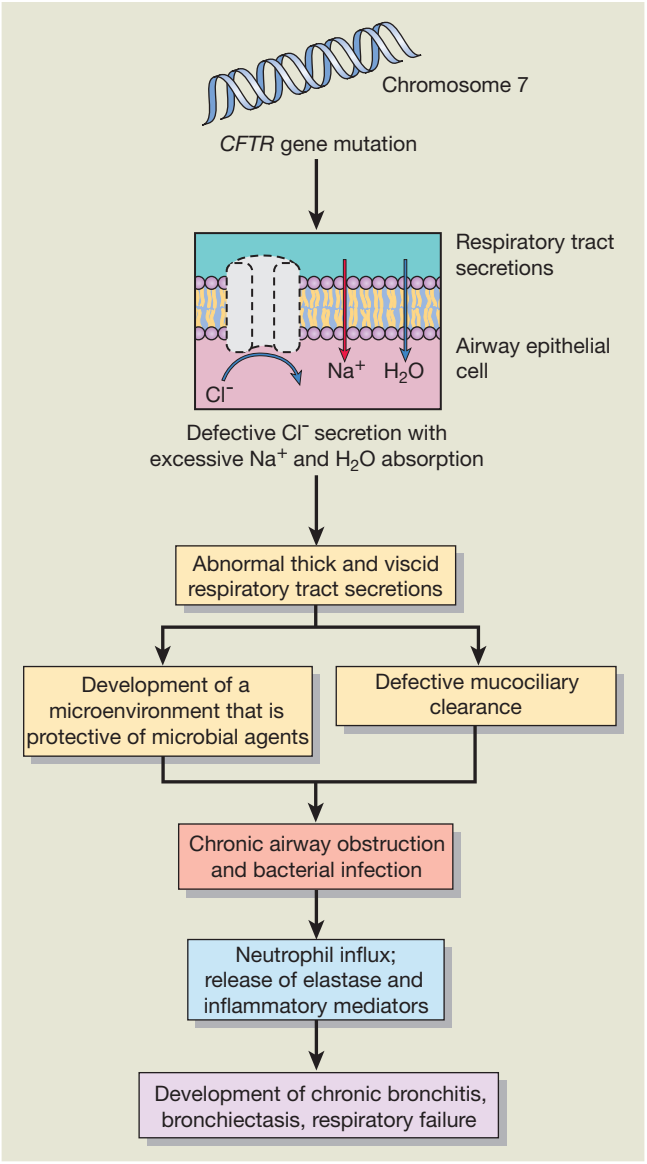


Figure 31.14 • Pathogenesis of CF.

The impact on impaired Cl^- transport due to the CFTR gene mutation ultimately affects the reabsorption of NaCl, which results in high concentrations of NaCl in the sweat of individuals with CF (Farell et al., 2017). The impaired transport of Cl^- ultimately leads to a series of secondary events, including increased absorption of Na^+ and water from the airways into the blood. This lowers the water content of the mucociliary blanket coating the respiratory epithelium, causing it to become more viscid. The resulting dehydration of the mucous layer leads to defective mucociliary function and accumulation of viscid secretions that obstruct the airways and predispose to recurrent pulmonary infections. Similar

transport abnormalities and pathophysiologic events take place in the pancreatic and biliary ducts and in the vas deferens in boys.

Clinical Manifestations

Respiratory manifestations of CF are caused by an accumulation of viscid mucus in the bronchi, impaired mucociliary clearance, and lung infections. Chronic bronchiolitis and bronchitis are the initial lung manifestations. However, after months and years, structural changes in the bronchial wall lead to bronchiectasis. In addition to airway obstruction, the basic genetic defect that occurs with CF predisposes to chronic infection with a surprisingly limited number of organisms, the most common being *Pseudomonas aeruginosa* (Gemma et al., 2017). *P. aeruginosa*, in particular, has a propensity to undergo pathogenesis. Early colonization can cause recurring pulmonary infections (Beckman et al., 2019). Pulmonary inflammation is another cause of decline in respiratory function in people with CF and may precede the onset of chronic infection.

Pancreatic function is often abnormal to some degree with individuals with CF. Malabsorption and malnutrition may often be present along with symptoms of abdominal discomfort and diarrhea. Steatorrhea, diarrhea, and abdominal pain and discomfort are common associated symptoms. In the newborn, meconium ileus may cause intestinal obstruction, a fatal condition if left untreated. The degree of pancreatic involvement is highly variable. In some children, the defect is relatively mild, and in others, the involvement is severe and impairs intestinal absorption. In addition, individuals with CF should be tested for diabetes mellitus, as 30% of adults develop diabetes (Farell et al., 2017).

Diagnosis and Treatment

Early diagnosis and treatment are important in delaying the onset and severity of chronic illness in children with CF. Diagnosis is based on the presence of respiratory and gastrointestinal manifestations typical of CF, a history of CF in a sibling, or a positive newborn screening test result. Confirmatory laboratory tests include the sweat chloride test, CFTR functional testing and CFTR genetic analysis. The **sweat test** is performed by collecting the individual's sweat followed by chemical analysis of its chloride content. Sweat with a sodium and chloride content more than twice of normal is consistent with CF. The sweat test remains the standard approach to diagnosis. Newborns with CF have elevated blood levels of immunoreactive trypsinogen, presumably because of secretory obstruction in the pancreas. **Newborn screening** consists of a test for determination of immunoreactive trypsinogen (National Institute of Health, 2020).

Twenty years after cloning the CFTR gene, there are still no approved treatments for correcting the genetic defects in CF or to reverse the ion transport abnormalities associated with the dysfunctional CFTR. Thus, treatment measures are directed toward slowing the progression of secondary organ dysfunction and sequelae such as chronic lung infection and pancreatic insufficiency. They include the use of oral and inhaled antibiotics to prevent and manage infections, bronchodilators, antiinflammatory medications, CFTR modulators, the use of chest physical therapy (chest percussion and postural drainage) and mucolytic agents to prevent airway obstruction, and nutritional therapy (Kamangar, 2020).

Appropriate antibiotic therapy directed against bacterial pathogens isolated from the respiratory tract is an essential component in the management of CF lung disease. Indications for oral antibiotics include the presence of respiratory tract symptoms and identification of pathogenic organisms in respiratory tract cultures. Intravenous antibiotics are used for progressive and unrelenting symptoms.

People with CF who have complete loss of exocrine pancreas function and have inadequate digestion of fats and proteins require diet adjustment, pancreatic enzyme replacement, and supplemental vitamins and minerals. Many people with CF have a higher-than-normal caloric need because of the increased WOB and perhaps because of the increased metabolic activity related to the basic defect. Pancreatic enzyme dosage and product type are individualized for each person.

Progression of the disease is variable. Improved medical management has led to longer survival. Lung transplantation is being used as a treatment for people with end-stage lung disease. Pulmonary rehabilitation is also used in medical management of CF (Kamangar, 2020). Current hopes reside in research that would make gene therapy a feasible alternative for people with the disease.

IN SUMMARY

Obstructive ventilatory disorders are characterized by airway obstruction and limitation in expiratory airflow. Asthma is a chronic inflammatory disorder of the airways characterized by airway hyperreactivity, airway narrowing, and airway remodeling. T_1H cells differentiate in response to microbes and stimulate the differentiation of B cells into IgM- and IgG-producing plasma cells, whereas T_2H cells respond to allergens by stimulating B cells to differentiate into IgE-producing plasma cells, produce growth factors for mast cells, and recruit and activate eosinophils. In people with allergic asthma, T-cell differentiation appears to be skewed toward a proinflammatory T_2H response. It appears that both genetic and environmental factors play a role in the development of asthma or reactive airway disease.

COPD describes a group of conditions characterized by obstruction to airflow in the lungs. Among the conditions associated with COPD are emphysema, chronic bronchitis, and bronchiectasis. Emphysema is characterized by a loss of lung elasticity, abnormal, permanent enlargement of the airspaces distal to the terminal bronchioles, and hyperinflation of the lungs. Chronic bronchitis is caused by inflammation of major and small airways and

is characterized by edema and hyperplasia of submucosal glands and excess mucus secretion into the bronchial tree. A history of a chronic productive cough that has persisted for at least 3 months and for at least 2 consecutive years in the absence of other disease is necessary for the diagnosis of chronic bronchitis. Emphysema and chronic bronchitis are manifested by eventual mismatching of ventilation and perfusion. As the condition advances, signs of respiratory distress and impaired gas exchange become evident, with development of hypercapnia and hypoxemia. Bronchiectasis is a less common form of COPD that is characterized by an abnormal dilation of the large bronchi associated with infection and destruction of the bronchial walls.

CF is an autosomal recessive genetic disorder manifested by chronic lung disease, pancreatic exocrine deficiency, and elevation of sodium chloride in the sweat. The disorder is caused by a mutation of a single gene on the long arm of chromosome 7 that codes for the CFTR, which functions in the transepithelial transport of the chloride ion. The defect causes exocrine gland secretions to become exceedingly viscid, and it promotes colonization of the respiratory tract with *P. aeruginosa* and other organisms such as *Staphylococcus aureus*. Accumulation of viscid mucus in the bronchi, impaired mucociliary function, and infection contribute to the development of chronic lung disease and a decreased life expectancy.

CHRONIC INTERSTITIAL (RESTRICTIVE) LUNG DISEASES

The diffuse **interstitial lung diseases** are a diverse group of lung disorders that produce similar inflammatory and fibrotic changes in the interstitium or interalveolar septa of the lung. Because the ILDs result in a stiff and noncompliant lung, they are commonly classified as restrictive lung disorders. In contrast to obstructive lung diseases, the lungs are stiff and difficult to expand, despite normally functioning airways.

Etiology and Pathogenesis of Interstitial Lung Diseases

The ILDs may be acute or insidious in onset. They may be rapidly progressive, slowly progressive, or static in their course. They include occupational lung diseases such as the **pneumoconioses**, which are caused by the inhalation of dusts, gases, fumes, and asbestos; hypersensitivity pneumonitis; lung diseases caused by exposure to toxic drugs (e.g., methotrexate, bleomycin, phenytoin, amiodarone); and granulomatous disorders such as sarcoidosis (Chart 31.2). Some of the most common ILDs are caused by exposure to inhaled dust and particles and, in others, no specific cause can be found.

In contrast to the obstructive lung diseases, which primarily involve the airways of the lung, the interstitial lung disorders exert their effects on the collagen and elastic connective tissue found in the delicate interstitium of the alveolar walls. Certain ILDs affect the distal part of the alveoli and this causes physiologic restrictions and decreased lung volumes (Loscalzo et al., 2022). Other ILDs impact the interstitium closer to the proximal aspect of the acinus near the bronchioles, which causes physiologic obstruction but does not impact the lung volumes (West & Luks, 2021a). Many of these diseases also involve the airways, arteries, and veins. In general, these lung diseases share a pattern of lung dysfunction that includes diminished lung volumes, reduced diffusing capacity of the lung, and varying degrees of hypoxemia.

It is thought that these disorders are initiated by some type of injury to the alveolar epithelium, followed by an inflammatory process that involves the alveoli and interstitium of the lung. An accumulation of inflammatory and immune cells causes continued damage to lung tissue and replacement of normally functioning lung tissue with fibrous scar tissue.

Clinical Manifestations

In general, the ILDs are characterized by clinical changes consistent with restrictive rather than obstructive changes in the lung, although some people have both components. People with ILDs have dyspnea, tachypnea, and eventual cyanosis, without evidence of wheezing or signs of airway obstruction. Usually, there is an insidious onset of breathlessness that initially occurs during exercise and may progress to the point at which the person is totally incapacitated. Typically, a person with a restrictive lung

CHART 31.2 CAUSES OF INTERSTITIAL LUNG DISEASE*

Occupational and Environmental Inhalants
Pneumoconioses
- Coal miner's pneumoconiosis
- Silicosis
- Asbestosis

Hypersensitivity pneumonitis
- Farmer's lung
- Pigeon breeder's lung

Drugs and Therapeutic Agents
Cancer drugs
- Bleomycin
- Busulfan
- Cyclophosphamide
- Methotrexate

Amiodarone

Immunologic Lung Disease
Sarcoidosis
Collagen vascular disease
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Scleroderma

*This list is not intended to be inclusive.

disease breathes with a tachypneic pattern of breathing, in which the respiratory rate is increased and the tidal volume is decreased. This pattern of breathing serves to maintain minute volume yet reduces the WOB because it takes less work to move air through the airways at an increased rate than it does to stretch a stiff lung to accommodate a larger tidal volume. A nonproductive cough may develop, particularly with continued exposure to the inhaled irritant, along with clubbing of the fingers and toes.

Lung volumes, including vital capacity and TLC, are reduced in ILD. In contrast to COPD, in which expiratory flow rates are reduced, the $FEV_{1.0}$ usually is preserved, even though the ratio of $FEV_{1.0}$ to FVC may increase. Although resting ABGs usually are normal early in the course of the disease, arterial PO_2 levels may fall during exercise. In people with advanced disease, hypoxemia often is present, even at rest. In the late stages of the disease, hypercapnia and respiratory acidosis develop. Alterations in the alveolar–capillary membrane, as well as an increase in shunt resulting from unventilated regions of the lung, are thought to cause the impaired diffusion of gases in people with ILD.

Diagnosis and Treatment

The diagnosis of ILD requires a comprehensive personal and family history, with particular emphasis on exposure to environmental, occupational, and other injurious agents. Chest radiographs and other imaging may be used as an initial diagnostic method, and serial chest films often are used to follow the progress of the disease. A surgical lung biopsy specimen for histologic study and culture is the preferred diagnostic examination (Loscalzo et al., 2022).

The treatment goals for people with ILD focus on identifying and removing the injurious agent, suppressing the inflammatory response, preventing progression of the disease, and providing supportive therapy for people with advanced disease. In general, the treatment measures vary with the type of lung disease. Immunosuppressants and corticosteroid drugs frequently are used. Many of the supportive treatment measures used in the late stages of the disease, such as oxygen therapy and measures to prevent infection, are similar to those discussed for people with COPD. For some people a lung transplant may be the only potentially effective treatment.

KEY POINTS

INTERSTITIAL LUNG DISEASES

- ILDs result from inflammatory conditions that affect the interalveolar structures of the lung and produce lung fibrosis and a stiff lung.
- A stiff and noncompliant lung is difficult to inflate, increasing the WOB and causing decreased exercise tolerance due to hypoxemia.
- Because of the increased effort needed for lung expansion, people with ILD tend to take small but more frequent breaths.

Occupational and Environmental Interstitial Lung Diseases

The **occupational and environmental ILDs** include the pneumoconioses, drug-induced ILD, and the hypersensitivity diseases. The **pneumoconioses** are caused by the inhalation of inorganic dusts and particulate matter. The **hypersensitivity diseases** result from the inhalation of organic dusts and related occupational antigens. A third type of occupational lung disease, byssinosis, a disease that affects cotton workers, has characteristics of the pneumoconioses and hypersensitivity lung diseases.

Among the pneumoconioses are silicosis, found in hard-rock miners, foundry workers, sandblasters, pottery makers, and workers in the slate industry; coal miner's pneumoconiosis; **asbestosis,** found in asbestos miners, manufacturers of asbestos products, and installers and removers of asbestos insulation; **talcosis**, found in talc miners, millers, or those who misuse drugs and in infants or small children who accidently inhale powder containing talc; and berylliosis, found in ore extraction workers and alloy production workers. The danger of exposure to asbestos dust is not confined to the workplace. The dust pervades the general environment because it was used in the construction of buildings and in other applications before its health hazards were realized. It has been mixed into paints and plaster, wrapped around water and heating pipes, used to insulate hair dryers, and woven into theater curtains, hot pads, and ironing board covers.

Important etiologic determinants in the development of the pneumoconioses are the size of the dust particle, its chemical nature and ability to incite lung destruction, and the concentration of dust and the length of exposure to it. Particles that are deposited below the larynx are less than 10 μm in size and are divided into three categories bases on their source and size (Schwab, 2021). Coarse particles (2.5 to 10 μm) are elements such as iron, silica, and aluminum. Fine-mode fraction (<2.5 μm) are products of gases, fumes and vapors. Finally, ultrafine particles, also known as nanoparticles (<0.1 μm), make up the largest category of particles (Schwab, 2021).

All particles in the alveoli must be cleared by the lung macrophages. Macrophages are thought to transport engulfed particles from the small bronchioles and the alveoli, which have neither cilia nor mucus-secreting cells, to the mucociliary escalator or to the lymphatic channels for removal from the lung. This clearing function is hampered when the function of the macrophage is impaired by factors such as cigarette smoking, consumption of alcohol, and hypersensitivity reactions. This helps to explain the increased incidence of lung disease among smokers exposed to asbestos. In silicosis, the ingestion of silica particles leads to the destruction of the lung macrophages and the release of substances resulting in inflammation and fibrosis (Schwab, 2021). Tuberculosis and other diseases caused by mycobacteria are common in people with silicosis. Because the macrophages are responsible for protecting the lungs from tuberculosis, the destruction of macrophages accounts for an increased susceptibility to tuberculosis in people with silicosis.

The concentration of some dusts in the environment strongly influences their effects on the lung. For example, acute silicosis is seen only in people whose occupations entail intense exposure to silica dust over a short period. It is seen in sandblasters, who use a high-speed jet of sand to clean and polish bricks and the insides of corroded tanks; in tunnelers; and in rock drillers, particularly if they drill through sandstone. Acute silicosis is a rapidly progressive disease, usually leading to severe disability and death within 5 years of diagnosis. In contrast to acute silicosis, which is caused by exposure to extremely high concentrations of silica dust, the symptoms related to chronic, low-level exposure to silica dust usually do not begin to develop until after many years of exposure, and then the symptoms often are insidious in onset and slow to progress.

Drug-Induced Interstitial Lung Disease

Drugs can cause a variety of both acute and chronic alterations in lung function. For example, some of the cytotoxic drugs (e.g., bleomycin, busulfan, methotrexate, cyclophosphamide) used in treatment of cancer cause pulmonary damage as a result of direct toxicity of the drug and by stimulating the influx of inflammatory cells into the alveoli (Loscalzo et al., 2022). Amiodarone, a drug used to treat cardiac arrhythmias, is preferentially sequestered in the lung and can cause significant pneumonitis in individuals receiving more than 400 mg/day (Loscalzo et al., 2022).

Hypersensitivity Pneumonitis

The hypersensitivity occupational lung disorders (e.g., hypersensitivity pneumonitis or also termed extrinsic allergic alveolitis) are caused by intense and often prolonged exposure to inhaled organic dusts and related occupational antigens (Schwab, 2021). Those affected have a heightened sensitivity to the antigen. The most common forms of hypersensitivity pneumonitis are farmer's lung, which results from exposure to moldy hay; pigeon breeder's lung, provoked by exposure to the serum, excreta, or feathers of birds; **bagassosis**, from contaminated sugar cane; and humidifier or air conditioner lung, caused by mold in the water reservoirs of these appliances. Unlike asthma, this type of hypersensitivity reaction involves primarily the alveoli. These disorders cause progressive fibrotic lung disease, which can be prevented by the removal of the environmental agent.

Sarcoidosis

Sarcoidosis is a systemic disorder in which granulomas are found in affected tissues and organ systems, particularly the lung and lymphatic system (Loscalzo et al., 2022). The cause of sarcoidosis, an inflammatory disease, remains unknown but is associated with increased activity of the immune system, causing groups of granulomas to form. The disorder predominantly affects people between 10 and 40 years of age, although it can occur in older people. The incidence of sarcoidosis in the United States is approximately 11 cases per 100,000 people per year for Whites and 34 of 100,000 people per year for Blacks (Loscalzo et al., 2022).

Etiology and Pathogenesis

The characteristic lesion of sarcoidosis is the noncaseating granuloma. Unlike the granulomatous lesions that develop in tuberculosis and histoplasmosis, the collection of tissue macrophages composing the granulomas in sarcoidosis do not show evidence of necrosis or caseation. In addition to granulomas, in which multinuclear giant cells are frequently seen, there is often alveolitis or inflammation of the alveoli.

The cause of sarcoidosis remains obscure. It is thought that the disorder may result from exposure of genetically predisposed people to specific environmental agents (Loscalzo et al., 2022). Support for a genetic influence comes from epidemiologic studies that have demonstrated the higher incidence in American Blacks and Scandinavian populations. Additional evidence comes from familial clustering of the disease. Analysis of human leukocyte antigen (HLA) genes located in the major histocompatibility complex also suggests that unique HLA genes can be linked to disease susceptibility and prognosis. Despite advances, including the identification of sarcoidosis genetic factors, a specific etiologic agent has yet to be identified.

Clinical Manifestations

Sarcoidosis has variable manifestations and an unpredictable course of progression in which any organ system can be affected. Routine chest screenings detect 20% to 30% of pulmonary cases in asymptomatic individuals (Loscalzo et al., 2022). The most commonly manifested symptoms occur in the lungs skin, eyes, and neurologic system. People with sarcoidosis frequently seek healthcare either as a result of abnormalities detected on an incidental chest film or because of insidious onset of respiratory symptoms (shortness of breath, nonproductive cough, chest pain) or constitutional signs and symptoms (e.g., fever, sweating, anorexia, weight loss, fatigue, myalgia) (Loscalzo et al., 2022). Eye involvement (anterior uveitis) and skin involvement (skin papules and plaques) are particularly common extrathoracic manifestations. However, symptoms of sarcoidosis may affect any organ system and there may be cardiac, neuromuscular, hematologic, hepatic, endocrine, or lymph node findings (Loscalzo et al., 2022).

Sarcoidosis follows an unpredictable course characterized by either progressive chronicity or periods of activity interspersed with remissions, sometimes permanent, that may be spontaneous or induced by corticosteroid therapy. The disease is thought to be connected to abnormal immunologic function since there is an increase in ratio of $CD4^+$ and $CD8^+$ lymphocytes and increased proinflammatory cytokines (Loscalzo et al., 2022). Although there is low risk of death or disability, the course of the disease varies. Approximately one third of individuals diagnosed with sarcoidosis have the progressive disease (Loscalzo et al., 2022).

Diagnosis and Treatment

The diagnosis of sarcoidosis is based on history and physical examination, tests to exclude other diseases, chest radiography, and biopsy to obtain confirmation of noncaseating granulomas. The use of CT scans and magnetic resonance imaging as routine methods for diagnosis of sarcoidosis remains controversial. For example, increased angiotensin-converting enzyme is commonly seen with sarcoidosis; however, it is not specific so is deemed controversial (Loscalzo et al., 2022).

Treatment is directed at interrupting the granulomatous inflammatory process that is characteristic of the disease and managing the associated complications. When treatment is indicated, corticosteroid drugs are used. These agents produce clearing of the lung, as seen on the chest radiograph, and improve pulmonary function, but it is not known whether they affect the long-term outcome of the disease.

IN SUMMARY

The ILDs are characterized by fibrosis and decreased compliance of the lung. They include the occupational and environmental lung diseases and granulomatous disorders, such as sarcoidosis. These disorders are thought to result from an inflammatory process that begins in the alveoli and extends to involve the interstitial tissues of the lung. Unlike COPD, which affects the airways, ILDs affect the supporting collagen and elastic tissues that lie between the airways and blood vessels. These lung diseases generally decrease lung volumes, reduce the diffusing capacity of the lung, and cause various degrees of hypoxemia. Because lung compliance is reduced, people with this form of lung disease tend to maintain their minute volume by a rapid, shallow breathing pattern.

KEY POINTS

DISORDERS OF THE PULMONARY CIRCULATION

- **Pulmonary thromboemboli** are blood clots that originate in the systemic venous system and become lodged in a pulmonary blood vessel as they move from the right heart into and through the pulmonary circulation.
- **Pulmonary hypertension** is an elevated pulmonary arterial pressure. It may arise as a primary disorder of the pulmonary arteries in which an abnormal thickening of the vessel wall increases the resistance to blood flow, or as a secondary disorder due to chronic lung disorders or environmental conditions that produce hypoxemia and a resultant constriction of small pulmonary arteries, cardiac disorders that increase pulmonary venous pressure, or thromboembolic disorders that occlude pulmonary blood vessels.

DISORDERS OF THE PULMONARY CIRCULATION

As blood moves through the pulmonary capillaries, oxygen content increases and carbon dioxide decreases. These processes depend on the matching of ventilation (i.e., gas exchange) and perfusion (i.e., blood flow). This section discusses two major problems of the pulmonary circulation: pulmonary embolism and pulmonary hypertension.

Pulmonary Embolism

Pulmonary embolism develops when a bloodborne substance lodges in a branch of the pulmonary artery and obstructs blood flow. The embolism may consist of a thrombus (Fig. 31.15), air that has accidently been injected during intravenous infusion, fat that has been mobilized from the bone marrow after a fracture or from a traumatized fat depot, or amniotic fluid that has entered the maternal circulation after rupture of the membranes at the time of delivery. When a pulmonary embolism occurs during the setting of a malignancy, the fatality rate is 25% (Loscalzo et al., 2022).

Etiology and Pathogenesis

Pulmonary emboli are thrombi that generally occur from deep vein thrombosis (DVT) in the lower and upper extremities (Loscalzo et al., 2022). The presence of thrombosis in the deep veins of the legs or pelvis often is unsuspected until embolism occurs. The effects of emboli on the pulmonary circulation are related to mechanical obstruction of the pulmonary circulation and neurohumoral reflexes causing vasoconstriction. Obstruction of pulmonary blood flow causes reflex bronchoconstriction in the affected area of the lung, wasted ventilation

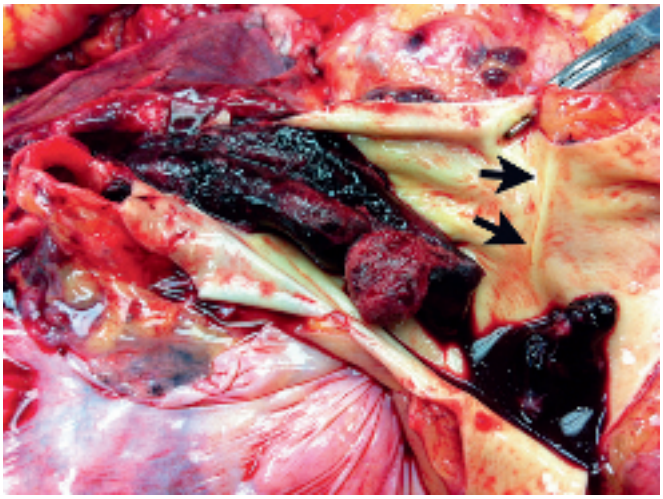


Figure 31.15 • Pulmonary embolism, gross. There is occlusion of the right and left pulmonary arteries at the junction of the pulmonary trunk. The arrows point to the flow divider. (From Burke., A. P, Aubry, M.-C., Maleszewski, J., Alexiev, B., & Tavora, F. (2016). *Practical thoracic pathology* (Fig. 65-1A). Wolters Kluwer.)

and impaired gas exchange, and loss of alveolar surfactant. Pulmonary hypertension and right heart failure may develop when there is massive vasoconstriction because of a large embolus. Although small areas of infarction may occur, frank pulmonary infarction is uncommon.

Among the physiologic factors that contribute to venous thrombosis is Virchow triad, which consists of venous stasis, venous endothelial injury, and hypercoagulability states. The thrombophilias (e.g., antithrombin III deficiency, protein C and S deficiencies, factor V Leiden mutation) are a group of inherited disorders affecting coagulation that make an individual prone to development of venous thromboemboli (Loscalzo et al., 2022). Venous stasis and venous endothelial injury can result from prolonged bed rest, trauma, surgery, childbirth, fractures of the hip and femur, myocardial infarction and congestive heart failure, and spinal cord injury. People undergoing orthopedic surgery and gynecologic cancer surgery are at particular risk, as are immobilized people. **Hypercoagulability** is related to various factors. Cancer cells can produce thrombin and synthesize procoagulation factors, increasing the risk for thromboembolism. Use of oral contraceptives, pregnancy, and hormone replacement therapy are thought to increase the resistance to endogenous anticoagulants.

CLINICAL JUDGMENT UNFOLDING CASE

Refer back to Ms. French in discussion about pulmonary embolism etiology. Ms. French, who was introduced at the beginning of the unit, presented to the emergency department with soreness in her right calf. This was because the embolus originated in the saphenous vein of her right leg and then broke free and traveled to the pulmonary circulation. Ms. French's history of cigarette smoking and use of estrogen-based oral contraceptives increased her risk for thrombus development, because these agents cause vasoconstriction and inflammation.

1. Ms. French's history presents a clear example of Virchow triad, a term associated with the physiologic factors that contribute to venous thrombosis. Describe the components of Virchow triad and their relationship to the noted history in this case.
2. In Ms. French's case, reported calf pain was related to the saphenous vein, where the embolism originated. In addition to a thrombus, what else might an embolism consist of?

Clinical Manifestations

The manifestations of pulmonary embolism depend on the size and location of the obstruction. Chest pain, dyspnea, and increased respiratory rate are the most frequent signs and symptoms of pulmonary embolism. Pulmonary infarction often causes pleuritic pain that changes with respiration; it is more severe on inspiration and less severe on expiration. Moderate hypoxemia without carbon dioxide retention occurs as a result of impaired gas exchange. Small emboli that become lodged in the peripheral branches of the pulmonary artery may go unrecognized unless the person is compromised, such as occurs in older adults or people who are acutely ill. Repeated small emboli gradually reduce the size of the pulmonary capillary bed, resulting in pulmonary hypertension. People with moderate-sized emboli often present with breathlessness accompanied by pleuritic pain, apprehension, slight fever, and cough productive of blood-streaked sputum. Tachycardia often occurs to compensate for decreased oxygenation, and the breathing pattern is rapid and shallow. People with massive emboli usually present with sudden collapse, crushing substernal chest pain, shock, and sometimes loss of consciousness. The pulse is rapid and weak, the blood pressure is low, the neck veins are distended, and the skin is cyanotic and diaphoretic. Massive pulmonary emboli often are fatal.

CLINICAL JUDGMENT UNFOLDING CASE

Refer back to Ms. French in discussion about pulmonary embolism clinical features. On presentation, Ms. French's heart rate was elevated (132 beats/minute) and the electrocardiogram (ECG) showed sinus tachycardia. Her breathing was rapid and shallow. In a person with pulmonary embolism, tachycardia and tachypnea often occur to compensate for decreased oxygenation.

1. Many of Ms. French's symptoms would be considered common for a patient presenting with a pulmonary embolism. Based on the specific symptoms noted in this case, would it be more likely that the emboli present are small, moderate, or massive? Include a rationale for this determination.

Diagnosis

The diagnosis of pulmonary embolism is based on clinical signs and symptoms, blood gas determinations, venous thrombosis studies, troponin, D-dimer testing, lung scans, and helical CT scans of the chest. Laboratory studies and radiologic films are useful in ruling out other conditions that might give rise to similar symptoms. Because emboli can cause an increase in pulmonary vascular resistance, the ECG may be used to detect signs of right heart strain.

Because most pulmonary emboli originate from DVT, venous studies such as *lower limb compression ultrasonography*, *impedance plethysmography,* and *contrast venography* are often used as initial diagnostic procedures. Of these, lower limb compression ultrasonography has become an important noninvasive means for detecting DVT. **D-dimer testing** involves the measurement of plasma D-dimer, a degradation product of coagulation factors that have been

activated as the result of a thromboembolic event. **Troponin levels** may be increased due to stretching of the right ventricle by a large pulmonary infarction. The **ventilation–perfusion scan** uses radiolabeled albumin, which is injected intravenously, and a radiolabeled gas, which is inhaled. A scintillation (gamma) camera is used to scan the various lung segments for blood flow and distribution of the radiolabeled gas. Ventilation–perfusion scans are useful only when their results are either normal or indicate a high probability of pulmonary embolism. **Helical (spiral) CT angiography** requires administration of an intravenous radiocontrast medium. It is sensitive for the detection of emboli in the proximal pulmonary arteries and provides another method of diagnosis. **Pulmonary angiography** involves the passage of a venous catheter through the right heart and into the pulmonary artery under fluoroscopy. Although it remains the most accurate method of diagnosis, it is infrequently done since it is such an invasive procedure. An embolectomy sometimes is performed during this procedure.

CLINICAL JUDGMENT UNFOLDING CASE

Refer back to Ms. French in discussion about pulmonary embolism diagnostics. D-dimer testing involves the measurement of plasma D-dimer, a degradation product of coagulation factors that have been activated as the result of a thromboembolic event. Recall that Ms. French's D-dimer levels were elevated.

1. In addition to D-dimer testing, what diagnostic studies may be used to assist in identifying pulmonary embolism? Describe the studies that may be used and the significance of each.

Treatment

The treatment goals for pulmonary emboli focus on preventing DVT and the development of thromboemboli; protecting the lungs from exposure to thromboemboli when they occur; and, in the case of large and life-threatening pulmonary emboli, sustaining life and restoring pulmonary blood flow. Thrombolytic therapy using recombinant tissue plasminogen activator may be indicated in people with multiple or large emboli.

Prevention focuses on identifying people at risk, avoidance of venous stasis and hypercoagulability states, and early detection of venous thrombosis. It is important that people start to become mobile as soon as possible after surgery or illness. For people at risk, graded compression elastic stockings and intermittent pneumatic compression boots can be used to prevent venous stasis. Surgical interruption of the vena cava may be indicated when pulmonary embolism poses a life-threatening risk.

Pharmacologic prophylaxis involves the use of anticoagulant drugs. Anticoagulant therapy may be used to decrease the likelihood of DVT, thromboembolism, and fatal pulmonary embolism after major surgical procedures. Low molecular weight heparin, which can be administered subcutaneously on an outpatient basis, often is used. Warfarin, an oral anticoagulation drug, may be used for people with a long-term risk for development of thromboemboli.

Pulmonary Hypertension

The pulmonary circulation is a low-pressure system designed to accommodate varying amounts of blood delivered from the right heart and to facilitate gas exchange. The main pulmonary artery and major branches are relatively thin-walled, compliant vessels. The distal pulmonary arterioles also are thin walled and have the capacity to dilate, collapse, or constrict depending on the presence of vasoactive substances released from the endothelial cells of the vessel, neurohumoral influences, flow velocity, oxygen tension, and alveolar ventilation.

Pulmonary hypertension is a disorder characterized by an elevation of pressure within the pulmonary circulation, namely, the pulmonary arterial system. The elevation in pressure may be acute or chronic, depending on the causative factors.

Etiology and Pathogenesis

A number of factors can contribute to the pathogenesis of pulmonary arterial hypertension (PAH), including a decrease in the cross-sectional area of the pulmonary arteries, a loss of blood vessels from either scarring or destructive processes affecting the alveolar walls, vasoconstriction in response to hypoxia, the need to accommodate excessive inflow of blood flow without any anatomic changes in the pulmonary arteries or arterioles, or the occlusion of outflow from the pulmonary circulation due to elevated pressures within the left atrium or ventricle.

The disorder may be due to changes in the arterial wall, often referred to as **pulmonary arterial hypertension**, or it may occur as a secondary condition related to the occlusion of the pulmonary circulation by pulmonary emboli or to disruption of the pulmonary circulation due to heart or lung disease.

Pulmonary Arterial Hypertension

The term **pulmonary arterial hypertension** (PAH) is used to describe a type of pulmonary hypertension that has its origin in the pulmonary arteries. The World Health Organization categorizes PAH into five groups related to their disease mechanism (Girerd et al., 2017):

- Group I is pulmonary arterial or idiopathic hypertension.
- Group II is pulmonary venous hypertension.
- Group III is pulmonary hypertension associated with hypoxemia.
- Group IV is pulmonary hypertension due to chronic thrombotic or embolic disease or both.

- Group V comprises miscellaneous disorders that cause PAH (Girerd et al., 2017).

PAH is a rare and debilitating disorder characterized by abnormal proliferation and contraction of vascular smooth muscle, coagulation abnormalities, and marked intimal fibrosis leading to obliteration or obstruction of the pulmonary arteries and arterioles (Fig. 31.16). The resulting increase in pressure results in progressive right heart failure, low cardiac output, and death if left untreated. The past decade has witnessed dramatic advances in the treatment of PAH, with medical therapies targeting specific pathways that are believed to play pathogenetic roles in development of the disorder. Despite these achievements, PAH remains a serious, life-threatening condition.

Etiology and Pathogenesis. The familial form of PAH appears to be inherited as an autosomal dominant trait with a variable but low penetrance, with some people inheriting the trait without exhibiting the disease. The bone morphogenetic protein receptor type II gene (*BMPR2*), which codes for a member of the transforming growth factor-β (TGF-β) superfamily of receptors, was identified as causative of familial PAH. Mutations in these receptors are thought to prevent TGF-β and related molecules from exerting an inhibitory effect on smooth muscle and endothelial cell proliferation (Griggs et al., 2021). Other conditions associated with PAH include collagen vascular disorders (e.g., **scleroderma**), drugs and toxins, human immunodeficiency virus infection, portal hypertension, and persistent pulmonary hypertension in the newborn (Girerd et al., 2017).

Although the specific mechanisms responsible for the vascular changes that occur in PAH remain unknown, a number of mechanisms have been proposed. These include enhanced expression of the serotonin transporter, diminished levels of nitric oxide and prostacyclin, and increased levels of several growth factors, including endothelin, vascular endothelial growth factor, and platelet-derived growth factor. The endothelium-relaxing factor, nitric oxide, is a potent pulmonary vasodilator that is produced locally in the lung and has profound effects on smooth muscle relaxation and proliferation. Endothelin 1 is a peptide produced by the vascular endothelium that has potent vasoconstrictor and paracrine effects on vascular smooth muscle. The endothelium also produces prostacyclin (PGI2), an inhibitor of platelet aggregation and potent vasodilator. Results of studies relating these mechanisms to the structure and function of the pulmonary arterial circulation have already been translated into targeted therapies for PAH, with the probability that more will be investigated in the future.

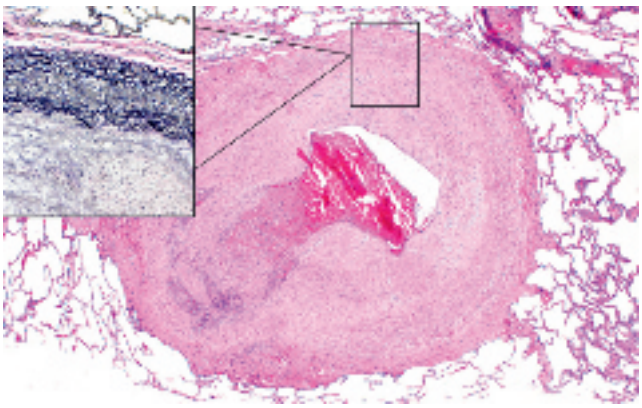


Figure 31.16 • Acute and organizing thrombus, pulmonary artery. Recent and organizing thromboemboli in a case of chronic thromboembolic pulmonary hypertension (CTEPH). The older organizing thrombus consists of fibrosis with the newer thrombus consisting of fibrin. The inset shows that there is mild medial hypertrophy, but the wall of the vessel is not disrupted by the thrombus. (From Butt, Y. M., & Tazelaar, H. D. (2021). *Atlas of Pulmonary Pathology* (Fig. 6-108). Wolters Kluwer.)

Clinical Manifestations. PAH is defined by persistent elevation in pulmonary artery pressure with normal left ventricular pressures, differentiating it from left-sided heart failure. Symptoms typically progress from shortness of breath and decreasing exercise tolerance to right heart failure, with marked peripheral edema and functional limitations. Other common symptoms include fatigue, angina, and syncope (fainting) or near-syncope.

Diagnosis and Treatment. The diagnosis of primary pulmonary hypertension is based on an absence of disorders that cause secondary hypertension and mean pulmonary artery pressures greater than 25 mm Hg at rest or 30 mm Hg with exercise.

Treatment consists of measures to improve right heart function as a means of reducing fatigue and peripheral edema. Supplemental oxygen may be used to increase exercise tolerance. This agent often improves symptoms, sometimes dramatically, in people who have not responded to other vasodilators. Sildenafil (e.g., Viagra) a highly selective phosphodiesterase-5 inhibitor, which acts in a manner similar to nitric oxide to produce vasodilation, is another treatment of pulmonary hypertension (Girerd et al., 2017). Lung transplantation may be an alternative for people who do not respond to other forms of treatment.

Secondary Pulmonary Hypertension

Although pulmonary hypertension can develop as a primary disorder, most cases develop secondary to conditions such as chronic hypoxemia due to COPD, ILD, or sleep-disordered breathing; increased resistance to pulmonary venous drainage due to conditions such as diastolic dysfunction of the left heart or disorders of mitral or aortic valves; or chronic thromboembolic disorders.

Etiology and Pathogenesis. Continued exposure of the pulmonary vessels to hypoxemia is a common cause of pulmonary hypertension. Unlike blood vessels in the systemic circulation, most of which dilate in response to hypoxemia and hypercapnia, the pulmonary vessels constrict. The stimulus for constriction seems to originate in the airspaces near the

smaller branches of the pulmonary arteries. In regions of the lung that are poorly ventilated, the response is adaptive in that it diverts blood flow away from the poorly ventilated areas to those areas that are more adequately ventilated. This effect, however, becomes less beneficial as more and more areas of the lung become poorly ventilated. Pulmonary hypertension is a common problem in people with advanced COPD or ILD. It also may develop at high altitudes in people with normal lungs. People who experience marked hypoxemia during sleep (such as those with sleep apnea) often experience marked elevations in pulmonary arterial pressure.

Elevation of pulmonary venous pressure is common in conditions such as mitral valve disorders or left ventricular diastolic dysfunction. In each of these alterations, the elevated left atrial pressure is transmitted to the pulmonary circulation. Continued increases in left atrial pressure can lead to medial hypertrophy and intimal thickening of the small pulmonary arteries, causing sustained hypertension. Another cause of secondary pulmonary hypertension is obstruction of pulmonary blood flow due to pulmonary thromboemboli. People who are promptly treated for acute pulmonary thromboembolism with anticoagulants rarely develop pulmonary hypertension. However, in some people, chronic obstruction of the pulmonary vascular bed develops because of impaired resolution of the thromboemboli.

Clinical Manifestations, Diagnosis, and Treatment. The signs and symptoms of secondary pulmonary hypertension reflect both the elevated pulmonary arterial pressure and the underlying heart or lung disease. As with primary pulmonary hypertension, diagnosis is based on radiographic findings, echocardiography, and Doppler ultrasonography. Treatment measures are directed toward the underlying disorder. Vasodilator therapy may be indicated for some people.

Cor Pulmonale

The term **cor pulmonale** refers to right heart failure resulting from primary lung disease or pulmonary hypertension. The increased pressures and work result in hypertrophy and eventual failure of the right ventricle. The manifestations of cor pulmonale include the signs and symptoms of the primary lung disease and the signs of right-sided heart failure. Signs of right-sided heart failure include venous congestion, peripheral edema, shortness of breath, and a productive cough, which becomes worse during periods of heart failure. Plethora (i.e., redness), cyanosis, and warm, moist skin may result from the compensatory polycythemia and desaturation of arterial blood that accompany chronic lung disease. Drowsiness and altered consciousness may occur as the result of carbon dioxide retention. Management of cor pulmonale focuses on the treatment of the lung disease and heart failure (Fig. 31.17). Low-flow oxygen therapy may be used to reduce the pulmonary hypertension and polycythemia associated with severe hypoxemia caused by chronic lung disease.

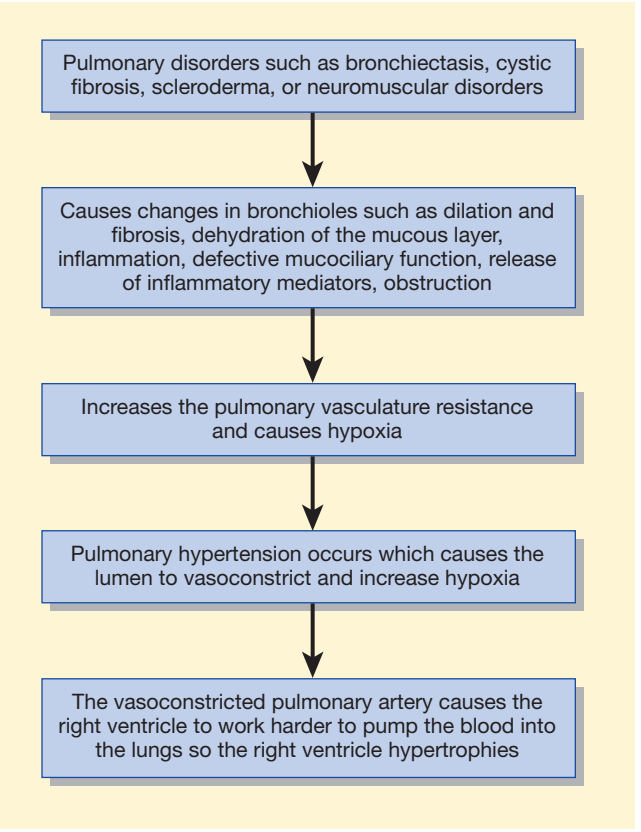


Figure 31.17 • Pathogenesis of cor pulmonale.

IN SUMMARY

Pulmonary vascular disorders include pulmonary embolism and pulmonary hypertension. Pulmonary embolism develops when a bloodborne substance lodges in a branch of the pulmonary artery and obstructs blood flow. The embolus can consist of a thrombus, air, fat, or amniotic fluid. The most common form is thromboemboli arising from the deep venous channels of the lower extremities. Pulmonary hypertension is the elevation of pulmonary arterial pressure. It has been categorized into five groups. *Cor pulmonale* describes right heart failure caused by primary pulmonary disease and long-standing pulmonary hypertension.

ACUTE RESPIRATORY DISORDERS

The function of the respiratory system is to add oxygen to the blood and remove carbon dioxide. Disruptions in this function occur with ALI/respiratory distress syndrome and acute respiratory failure. Although the mechanisms that disrupt gas exchange may vary, both conditions represent a life-threatening situation with high risks of morbidity and mortality.

Acute Lung Injury/Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome is the most severe form of **Acute lung injury**. The symptoms generally manifest with symptoms of diffuse crackles, dyspnea, cyanosis, tachypnea, tachycardia and diaphoresis. The severity of lung dysfunction is evaluated by the PaO_2/FiO_2ratio (Loscalzo et al., 2022). ARDS is a more severe aspect of ALI and is differentiated primarily for early intervention, prevention, and research purposes.

ARDS may result from a number of conditions, including aspiration of gastric contents, major trauma (with or without fat emboli), sepsis secondary to pulmonary or nonpulmonary infections, acute pancreatitis, hematologic disorders, metabolic events, and reactions to drugs and toxins (Chart 31.3).

Etiology and Pathogenesis

Although a number of conditions may lead to ALI/ARDS, they all produce similar pathologic lung changes that include diffuse epithelial cell injury with increased permeability of the alveolar–capillary membrane (Fig. 31.18). The increased permeability permits fluid, plasma proteins, and blood cells to move out of the vascular compartment into the interstitium and alveoli of the lung (Loscalzo et al., 2022). Diffuse alveolar cell damage leads to accumulation of fluid, surfactant inactivation, and formation of a hyaline membrane that is impervious to gas exchange. As the disease progresses, the WOB becomes greatly increased as the lung stiffens and becomes more difficult to inflate. There is increased intrapulmonary shunting of blood, impaired gas exchange, and refractory hypoxemia despite high supplemental oxygen therapy. Gas exchange is further compromised by alveolar collapse resulting from abnormalities in surfactant production. When injury to the alveolar epithelium is severe, disorganized epithelial repair may lead to fibrosis (Fig. 31.19).

The pathogenesis of ALI/ARDS is unclear, although both local and systemic inflammatory responses occur so often when a person has been diagnosed with ARDS; they already have leaky capillary syndrome in other organs such

CHART 31.3 CONDITIONS IN WHICH ARDS CAN DEVELOP*

Aspiration
Near drowning
Aspiration gastric contents

Drugs, Toxins, and Therapeutic Agents
Free-base cocaine smoking
Heroin
Inhaled gases (e.g., smoke, ammonia)
Breathing high concentrations of oxygen
Radiation

Infections
Septicemia

Trauma and Shock
Burns
Fat embolism
Chest trauma

Disseminated Intravascular Coagulation

Multiple Blood Transfusions

*This list is not intended to be inclusive.

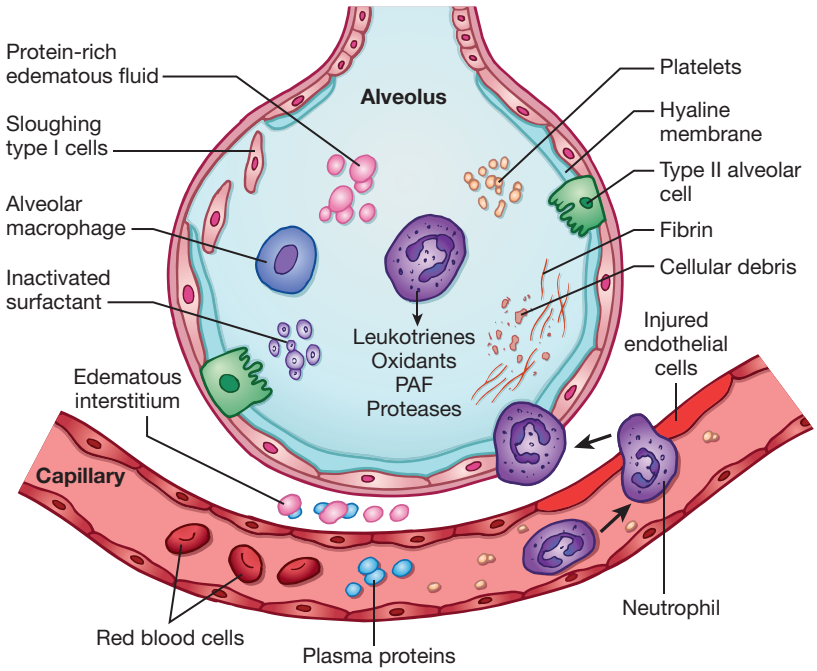


Figure 31.18 • The mechanism of lung changes in ARDS. Injury and increased permeability of the alveolar capillary membrane allow fluid, protein, cellular debris, platelets, and blood cells to move out of the vascular compartment and enter the interstitium and alveoli. Activated neutrophils release a variety of products that damage the alveolar cells and lead to edema, surfactant inactivation, and formation of a hyaline membrane. PAF, platelet-activating factor.

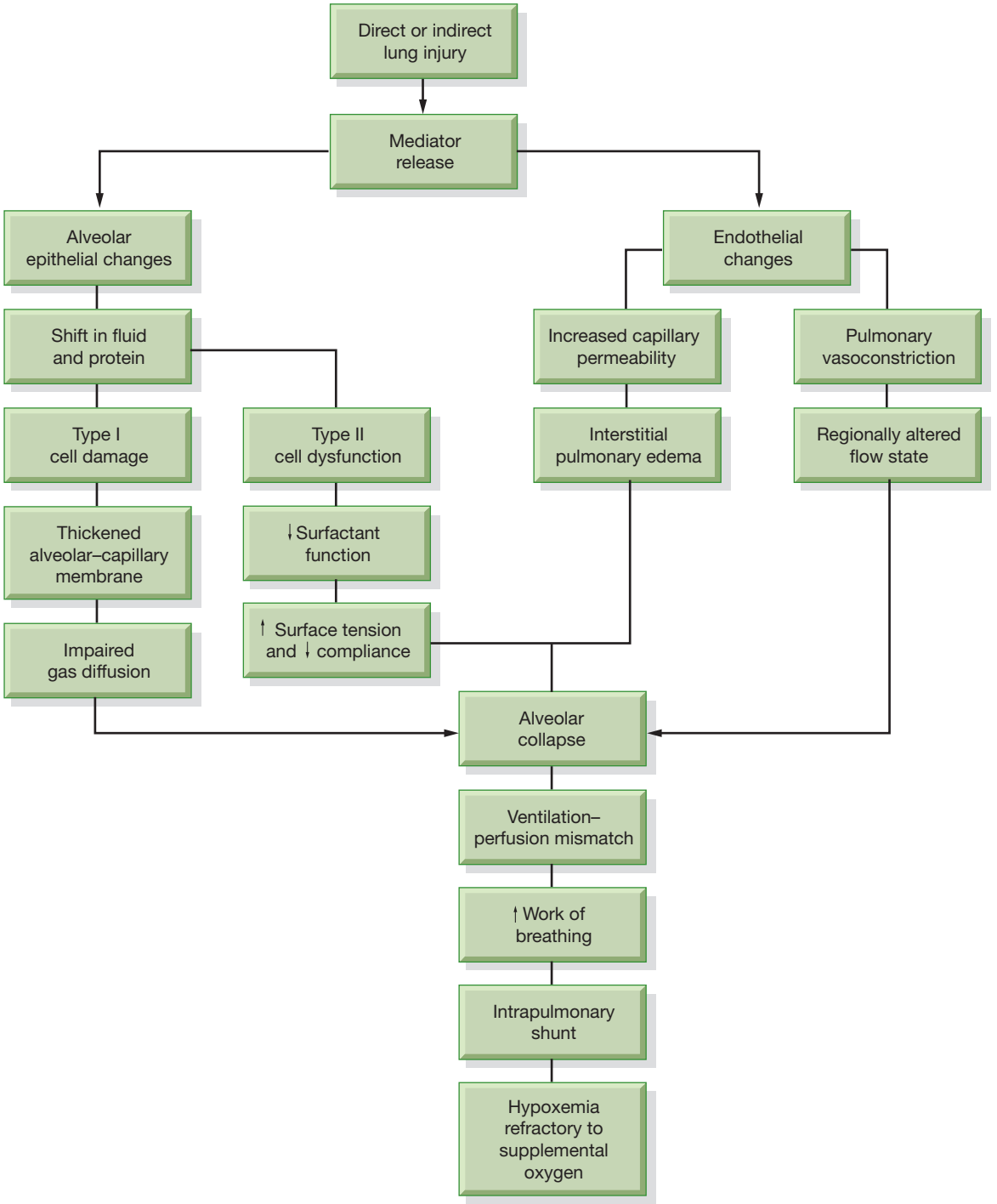


Figure 31.19 • Pathophysiologic cascade is initiated by an injury resulting in mediator release. The multiple effects result in changes to the alveoli, vascular tissue, and bronchi. The ultimate effect is ventilation–perfusion mismatching and refractory hypoxemia. (From Morton, P. G., & Fontaine, D. K. (2018). *Critical care nursing: A holistic approach* (11th ed., Fig. 27-2, p. 522). Lippincott Williams & Wilkins.)

as the pancreas. Neutrophils accumulate early in the course of the disorder and are considered to play a role in the pathogenesis of ALI/ARDS. Activated neutrophils synthesize and release a variety of products, including proteolytic enzymes, toxic oxygen species, and phospholipid products that increase the inflammatory response and cause further injury to the capillary endothelium and alveolar epithelium.

Clinical Manifestations and Diagnosis

Clinically, ALI/ARDS is marked by a rapid onset of respiratory distress, usually within 12 to 18 hours of the initiating event, an increase in respiratory rate, and signs of respiratory failure. Marked hypoxemia occurs that is refractory to treatment with supplemental oxygen therapy, which results in a decrease in the PF ratio. Many people

with ARDS have a systemic response that results in multiple organ failure, particularly of the renal, gastrointestinal, cardiovascular, and CNSs. Chest radiography shows diffuse bilateral infiltrates of the lung tissue in the absence of cardiac dysfunction.

Treatment

The treatment goals in ARDS are to (1) adequately oxygenate the lungs and vital organs, (2) recognize and treat underlying medical and surgical disorders, (3) prevent further lung injury and complications, including but not limited to venous thromboembolism, aspiration, nosocomial infections, and (4) ultimately decrease mortality (Eliopoulos, 2022). Assisted ventilation using high concentrations of oxygen may be required to correct the hypoxemia. Extensive study has been conducted to determine optimal pressures and volumes to correct the hypoxemia yet prevent further lung injury due to the barotrauma often seen with mechanics of ventilation (Eliopoulos, 2022). Prone ventilation, which is ventilation delivered with the individual lying in the prone position, has demonstrated improved oxygenation with ventilation and is used as a treatment for ARDS along with traditional modes of ventilation when ventilation alone fails to increase PaO_2 levels (U.S. Department of Health and Human Services, 2021). Prone ventilation has demonstrated improvement in lung perfusion (improvement in ventilation/perfusion matching), reduction in ventral-dorsal transpulmonary pressure difference, and reduced lung compression (U.S. Department of Health and Human Services, 2021).

Acute Respiratory Failure

Respiratory failure can be viewed as a failure in gas exchange due to either heart or lung failure, or both. It is not a specific disease but can occur in the course of a number of conditions that impair ventilation, compromise the matching of ventilation and perfusion, or impair gas diffusion. Acute respiratory failure may occur in previously healthy people as the result of acute disease or trauma involving the respiratory system, or it may develop in the course of a chronic neuromuscular or lung disease.

Respiratory failure is a condition in which the respiratory system fails in one or both of its gas exchange functions—oxygenation of mixed venous blood and elimination of carbon dioxide. The function of the respiratory system can be said to consist of two aspects: gas exchange (movement of gases across the alveolar–capillary membrane) and ventilation (movement of gases into and out of the alveoli due to the action of the respiratory muscles, respiratory center in the CNS, and the pathways that connect the centers in the CNS with the respiratory muscles). Thus, respiratory failure is commonly divided into two types:

1. Hypoxemic respiratory failure due to failure of the gas exchange function of the lung
2. Hypercapnic/hypoxemic respiratory failure due to ventilatory failure (Loscalzo et al., 2022)

The classification should not be viewed as rigid since lung disorders that cause impaired gas exchange can be complicated by ventilatory failure. In addition, ventilatory failure can be accompanied by lung disorders that impair gas diffusion. Causes of respiratory failure are summarized in Chart 31.4.

Hypoxemic Respiratory Failure

In people with **hypoxemic respiratory failure**, two major pathophysiologic factors contribute to the lowering of arterial PO_2–ventilation–perfusion mismatching or impaired diffusion.

Mismatching of Ventilation and Perfusion. The mismatching of ventilation and perfusion occurs when areas of the lung are ventilated but not perfused or when areas are perfused but not ventilated. Usually the hypoxemia seen in situations of ventilation–perfusion mismatching is more severe in relation to hypercapnia than that seen in hypoventilation. Severe mismatching of ventilation and perfusion often is seen in people with advanced COPD. These disorders contribute to the retention of carbon dioxide by reducing the effective alveolar ventilation, even when total ventilation is maintained. This occurs because a region of the lung is not perfused and gas exchange

CHART 31.4 CAUSES OF RESPIRATORY FAILURE*

Hypoxemic Respiratory Failure
Chronic obstructive pulmonary disease
Interstitial (restrictive) lung disease
Severe pneumonia
Atelectasis

Hypercapnic/Hypoxemic Respiratory Failure
Upper airway obstruction
- Infection (e.g., epiglottitis)
- Laryngospasm
- Tumors

Weakness or paralysis of respiratory muscles
- Brain injury
- Drug overdose
- Guillain-Barré syndrome
- Muscular dystrophy
- Spinal cord injury

Chest wall injury

Impaired Diffusion
Pulmonary edema
Acute lung injury/ARDS

*This list is not intended to be inclusive.

cannot take place or because an area of the lung is not being ventilated. Maintaining a high ventilation rate effectively prevents hypercapnia but also increases the WOB.

The hypoxemia associated with ventilation–perfusion disorders often is exaggerated by conditions such as hypoventilation and decreased cardiac output. For example, sedation can cause hypoventilation in people with severe COPD, resulting in further impairment of ventilation. Likewise, a decrease in cardiac output because of myocardial infarction can exaggerate the ventilation–perfusion impairment in a person with mild pulmonary edema or COPD.

The beneficial effect of oxygen administration on PO_2 levels in ventilation–perfusion disorders depends on the degree of mismatching that is present. Because oxygen administration increases the diffusion gradient in ventilated portions of the lung, it usually is effective in raising arterial PO_2 levels. However, high-flow oxygen may decrease the respiratory drive and produce an increase in PCO_2.

Impaired Diffusion. Impaired **diffusion** describes a condition in which gas exchange between the alveolar air and pulmonary blood is impeded because of an increase in the distance for diffusion or a decrease in the permeability or surface area of the respiratory membranes to the movement of gases. It most commonly occurs in conditions such as ILD, ALI/ARDS, pulmonary edema, and pneumonia.

Conditions that impair diffusion may produce severe hypoxemia but no hypercapnia because of the increase in ventilation and greater diffusion rate of carbon dioxide. Hypoxemia resulting from impaired diffusion can be partially or completely corrected by the administration of high concentrations of oxygen. In this case, the high concentration of oxygen serves to overcome the decrease in diffusion by establishing a larger alveolar-to-capillary diffusion gradient.

Hypercapnic/Hypoxemic Respiratory Failure

In the hypercapnic form of respiratory failure, people are unable to maintain a level of alveolar ventilation sufficient to eliminate CO_2 and keep arterial O_2 levels within normal range. Because ventilation is determined by a sequence of events ranging from generation of impulses in the CNS to movement of air through the conducting airways, there are several stages at which problems can adversely affect the total minute ventilation.

Hypoventilation or ventilatory failure occurs when the volume of "fresh" air moving into and out of the lung is significantly reduced. It is commonly caused by conditions outside the lung such as depression of the respiratory center (e.g., drug overdose, brain injury), diseases of the nerves supplying the respiratory muscles (e.g., Guillain-Barré syndrome, spinal cord injury), disorders of the respiratory muscles (e.g., muscular dystrophy), exacerbation of chronic lung disease (e.g., COPD), or thoracic cage disorders (e.g., severe scoliosis or crushed chest).

Hypoventilation has two important effects on ABGs. First, it almost always causes an increase in PCO_2. The rise in PCO_2 is directly related to the level of ventilation; reducing the ventilation by one half causes a doubling of the PCO_2. Thus, the PCO_2 level is a good diagnostic measure for hypoventilation. Second, it may cause hypoxemia, although the hypoxemia that is caused by hypoventilation can be readily abolished by the administration of supplemental oxygen.

Clinical Manifestations

Acute respiratory failure is usually manifested by varying degrees of hypoxemia and hypercapnia. There is no absolute definition of the levels of PO_2 and PCO_2 that indicate respiratory failure. Respiratory failure is conventionally defined by an arterial PO_2 of less than 50 mm Hg, an arterial PCO_2 of more than 50 mm Hg, or both when prior blood values have been normal. It is important to emphasize that these cutoff values are not rigid but simply serve as a general guide in combination with history and physical assessment information. The signs and symptoms of acute respiratory failure are those of the underlying disease combined with signs of hypoxemia and hypercapnia/hypoxemia**. Respiratory acidosis** is usually present because the retention of CO_2 results in increased production of acids.

Hypoxemia is accompanied by increased respiratory drive and increased sympathetic tone. Potential signs of hypoxemia include cyanosis, restlessness, confusion, anxiety, delirium, fatigue, tachypnea, hypertension, cardiac arrhythmias, and tremor. The initial cardiovascular effects are tachycardia with increased cardiac output and increased blood pressure. Serious arrhythmias may be triggered. The pulmonary vasculature constricts in response to low alveolar PO_2. If severe, the pulmonary vasoconstriction may result in acute right ventricular failure with manifestations such as jugular vein distention and dependent edema. Profound acute hypoxemia can cause convulsions, retinal hemorrhages, and permanent brain damage. Hypotension and bradycardia often are preterminal events in people with hypoxemic respiratory failure, indicating the failure of compensatory mechanisms.

Many of the adverse consequences of hypercapnia are the result of respiratory acidosis. Direct effects of acidosis include depression of cardiac contractility, decreased respiratory muscle contractility, and arterial vasodilation. Raised levels of PCO_2 greatly increase cerebral blood flow, which may result in headache, increased cerebrospinal fluid pressure, and sometimes papilledema. The headache is due to dilation of the cerebral vessels. Additional indicators of hypercapnia are warm and flushed skin and hyperemic conjunctivae. Hypercapnia has nervous system effects similar to those of an anesthetic—hence the term *carbon dioxide narcosis*. There is progressive somnolence, disorientation, and, if the condition is untreated, coma. Mild to moderate increases in blood pressure are common. Air hunger and rapid breathing occur when alveolar PCO_2 levels rise to

approximately 60 to 75 mm Hg; as PCO_2 levels reach 80 to 100 mm Hg, the person becomes lethargic and sometimes semicomatose.

Treatment

The treatment of the person with acute respiratory failure consists of specific therapy directed toward the underlying disease, respiratory supportive care directed toward maintenance of adequate gas exchange, and general supportive care. A number of treatment modalities are available, including the establishment of an airway and the use of antiinflammatory bronchodilators, mucolytics, and antibiotics for respiratory infections. The main therapeutic goal in acute hypoxemic respiratory failure is to ensure adequate oxygenation of vital organs, which is generally accomplished by mechanical ventilation.

IN SUMMARY

The hallmark of ALI and ARDS is a pronounced inflammatory response that affects the lung and may or may have already resulted in systemic organ failure. In fact, the damage to the lung in ARDS may not be the initial manifestation but part of a multiorgan shutdown due to leaky capillary syndrome. The acute inflammatory response results in damage and dysfunction of the alveolar–capillary membrane of the lung. Classically, there is interstitial edema of lung tissue, an increase in surface tension caused by inactivation of surfactant, collapse of the alveolar structures, a stiff and noncompliant lung that is difficult to inflate, and impaired diffusion of the respiratory gases with severe hypoxia that is totally refractory to oxygen therapy.

Acute respiratory failure is a condition in which the lungs fail to oxygenate the blood adequately (hypoxemic respiratory failure) or prevent undue retention of carbon dioxide (hypercapnic/hypoxemic respiratory failure). The causes of respiratory failure are many. It may arise acutely in people with previously healthy lungs, or it may be superimposed on chronic lung disease. Treatment of acute respiratory failure is directed toward treatment of the underlying disease, maintenance of adequate gas exchange and tissue oxygenation, and general supportive care. When alveolar ventilation is inadequate to maintain PO_2 or PCO_2 levels because of impaired respiratory function or neurologic failure, mechanical ventilation may be necessary. There are multiple problems that can result from the barotraumas caused by the mechanical ventilation to the lung parenchyma. This condition is caused by ventilator-induced lung injury, which needs to be prevented if at all possible. Lung protective strategies are focused on increasing compliance and decreasing shear stresses, which occur with the frequent alveolar collapse secondary to the high pressure needed to ventilate the lungs.

GERIATRIC Considerations

- Bronchiectasis, heart problems, and higher mortality rates often occur in older asthmatics due to the additional stress that asthma has on the heart (Kyle & Carman, 2020).
- Bronchospasms associated with cold damp weather alert the older person that symptoms of chronic bronchitis are worsening (Kyle & Carman, 2020).
- The risk of emphysema increases with age, as do mortality rates from the disease. Recurrent lung infections, heart failure, and cardiac arrhythmias are serious complications resulting from emphysema (Kyle & Carman, 2020).
- Carbon dioxide narcosis is associated with aging when oxygen therapy is needed. Close monitoring is necessary during oxygen therapy to identify high amounts of carbon dioxide retention (Kyle & Carman, 2020).

PEDIATRIC Considerations

- ARDS in children can result in residual lung disease in children. Nasal flaring with sternal retractions are common clinical manifestations (Malhotra & Kacmarek, 2021).
- Asthma impacts over 10 million American children prior to age 18 and accounts for over 3 billion dollars in healthcare cost annually (Malhorta & Kacmarek, 2021).
  - The increase in asthma, as well as the severity, is thought to be due to air pollution, more children living in urban areas, and the ability to accurately diagnose the disease.
- CF screening is performed as part of the newborn assessment and is strongly recommended preconception (Malhotra & Kacmarek, 2021).

REVIEW EXERCISES

1. A 30-year-old man is brought to the emergency department with a knife wound to the chest. On visual inspection, asymmetry of chest movement during inspiration, displacement of the trachea, and absence of breath sounds on the side of the wound are noted. His neck veins are distended, and his pulse is rapid and thready. A rapid diagnosis of tension pneumothorax is made.

Continued

   A. *Explain the observed respiratory and cardiovascular function in terms of the impaired lung expansion and the air that has entered the chest as a result of the injury.*
   B. *What type of emergent treatment is necessary to save this man's life?*
2. A 10-year-old boy who is having an acute asthmatic attack is brought to the emergency department by his parents. The boy is observed to be sitting up and struggling to breathe. His breathing is accompanied by use of the accessory muscles, a weak cough, and audible wheezing sounds. His pulse is rapid and weak and both heart and breath sounds are distant on auscultation. His parents relate that his asthma began to worsen after he developed a "cold," and now he does not even get relief from his "albuterol" inhaler.
   A. *Explain the changes in physiologic function underlying this boy's signs and symptoms.*
   B. *The boy is treated with a systemic corticosteroid and inhaled anticholinergic and β2-adrenergic agonist and then transferred to the intensive care unit. Explain the action of each of these medications in terms of relieving this boy's symptoms.*
3. A 62-year-old man with an 8-year history of chronic bronchitis reports to his healthcare provider with complaints of increasing shortness of breath, ankle swelling, and a feeling of fullness in his upper abdomen. The expiratory phase of his respirations is prolonged and expiratory wheezes and crackles are heard on auscultation. His blood pressure is 160/90 mm Hg, his red blood cell count is 6.0×10^6 mL (normal 4.2 to 5.4×10^6μmL), his hematocrit is 65% (normal male value 40% to 50%), his arterial PO_2 is 55 mm Hg, and his O_2 saturation, which is 85% while he is resting, drops to 55% during walking exercise.
   A. *Explain the physiologic mechanisms responsible for his edema, hypertension, and elevated red blood cell count.*
   B. *His arterial PO_2 and O_2 saturation indicate that he is a candidate for continuous low-flow oxygen. Explain the benefits of this treatment in terms of his activity tolerance, blood pressure, and red blood cell count.*
   C. *Explain why the oxygen flow rate for people with COPD is normally titrated to maintain the arterial PO_2 between 60 and 65 mm Hg.*
4. An 18-year-old woman is admitted to the emergency department with a suspected drug overdose. Her respiratory rate is slow (4 to 6 breaths/minute) and shallow. Arterial blood gases reveal a PCO_2 of 80 mm Hg and a PO_2 of 60 mm Hg.
   A. *What is the cause of this woman's high PCO_2 and low PO_2?*
   B. *Hypoventilation almost always causes an increase in PCO_2. Explain.*
   C. *Even though her PO_2 increases to 90 mm Hg with institution of oxygen therapy, her PCO_2 remains elevated. Explain.*
5. A 58-year-old man presents to the emergency department with flulike symptoms, generalized weakness, and shortness of breath. His blood pressure (BP) is 170/90 mm Hg, heart rate (HR) is 90 bpm, respiratory rate (RR) is 28, pulse oximetry (SpO_2) is 91%, and temperature (T) is 101.3°F (38.5°C). He is diagnosed with an unknown viral process and placed in a negative-airflow room on airborne, contact, and droplet precautions. Mechanical ventilation is initiated; however, oxygen saturation levels remain in the low 90s.
   A. *The need for improvements in oxygenation indicates he could benefit from prone ventilation. Explain the benefits of this treatment in terms of oxygen saturation and respiratory effort.*
   B. *With prone ventilation and treatment with corticosteroids, antivirals, and antiinflammatories, his O_2 saturation and PaO_2 increases to within normal levels. Explain the action of each of these medications in terms of improving his symptoms.*

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