3rd Edition

HARRISON'S™

PULMONARY AND CRITICAL CARE MEDICINE

JOSEPH LOSCALZO

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3rd Edition

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PULMONARY AND CRITICAL CARE MEDICINE

Derived from Harrison's Principles of Internal Medicine, 19th Edition

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PREFACE

Harrison's Principles of Internal Medicine has been a respected information source for more than 60 years. Over time, the traditional textbook has evolved to meet the needs of internists, family physicians, nurses, and other health care providers. T e growing list of Harrison's products now includes Harrison's for the iPad, Harrison's Manual of Medicine, and Harrison's Online. T is book, Harrison's Pulmonary and Critical Care Medicine, now in its third edition, is a compilation of chapters related to respiratory disorders, respiratory diseases, the general approach to the critically ill patient, common critical illnesses and syndromes, and disorders complicating critical illnesses and their management.

Our readers consistently note the sophistication of the material in the specialty sections of Harrison's. Our goal was to bring this information to our audience in a more compact and usable form. We have also included a Review and Self-Assessment section that includes questions and answers to provoke reflection and to provide additional teaching points.

Pulmonary diseases are major contributors to morbidity and mortality in the general population. Although advances in the diagnosis and treatment of many common pulmonary disorders have improved the lives of patients, these complex illnesses continue to affect a large segment of the global population. T e impact of cigarette smoking cannot be underestimated in this regard, especially given the growing prevalence of tobacco use in the developing world. Pulmonary medicine is, therefore, of critical global importance to the field of internal medicine.

Pulmonary medicine is a growing subspecialty and includes a number of areas of disease focus, including reactive airways diseases, chronic obstructive lung disease, environmental lung diseases, and interstitial lung diseases. Furthermore, pulmonary medicine is linked to the field of critical care medicine, both cognitively and as a standard arm of the pulmonary fellowship training programs at most institutions. T e breadth of knowledge in critical care medicine extends well beyond the respiratory system, of course, and includes selected areas of cardiology, infectious diseases, nephrology, and hematology. Given the complexity of these disciplines and the crucial role of the internist in guiding the management of patients with chronic lung diseases and in helping to guide the management of patients in the intensive care setting, knowledge of the discipline is essential for competency in the field of internal medicine.

T e scientific basis of many pulmonary disorders and intensive care medicine is rapidly expanding. Novel diagnostic and therapeutic approaches, as well as prognostic assessment strategies, populate the published literature with great frequency. Maintaining updated knowledge of these evolving areas is, therefore, essential for the optimal care of patients with lung diseases and critical illness.

In view of the importance of pulmonary and critical care medicine to the field of internal medicine and the speed with which the scientific basis of the discipline is evolving, this sectional was developed. T e purpose of this book is to provide the readers with an overview of the field of pulmonary and critical care medicine. To achieve this end, this sectional comprises the key pulmonary and critical care medicine chapters in Harrison's Principles of Internal Medicine, 19th edition, contributed by leading experts in the fields. T is sectional is designed not only for physicians in training, but also for medical students, practicing clinicians, and other health care professionals who seek to maintain adequately updated knowledge of this rapidly advancing field. T e editors believe that this book will improve the reader's knowledge of the discipline, as well as highlight its importance to the field of internal medicine.

T e first section of the book, "Diagnosis of Respiratory Disorders," provides a systematic overview, beginning with approach to the patient with disease of the respiratory system. T e integration of pathophysiology with clinical management is a hallmark of Harrison's, and can be found throughout each of the subsequent disease-oriented chapters. T e book is divided into five main sections that reflect the scope of pulmonary and critical care medicine: (I) Diagnosis of Respiratory Disorders; (II) Diseases of the Respiratory System; (III) General Approach to the Critically Ill Patient; (IV) Common Critical Illnesses and Syndromes; and (V) Disorders Complicating Critical Illnesses and T eir Management.

Our access to information through web-based journals and databases is remarkably efficient. Although these sources of information are invaluable, the daunting body of data creates an even greater need for synthesis by experts in the field. T us, the preparation of these chapters is a special craf that requires the ability to distill core information from the ever-expanding knowledge base. T e editors are, therefore, indebted to our authors, a group of internationally recognized authorities who are masters at providing a comprehensive overview while being able to distill a topic into a concise and interesting chapter. We are also indebted to our colleagues at McGraw-Hill. Jim Shanahan is a champion for Harrison's and these books were impeccably produced by Kim Davis. We hope you will find this book useful in your effort to achieve continuous learning on behalf of your patients.

Joseph Loscalzo, MD, PhD

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. T e authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. T is recommendation is of particular importance in connection with new or infrequently used drugs.

Review and self-assessment questions and answers were taken from Wiener CM, Brown CD, Houston B (eds). Harrison's Self-Assessment and Board Review, 19th ed. New York, McGraw-Hill, 2017, ISBN 978-1-25-964288-3.

T e global icons call greater attention to key epidemiologic and clinical differences in the practice of medicine throughout the world.

T e genetic icons identify a clinical issue with an explicit genetic relationship.

SECTION I

DIAGNOSIS OF RESPIRATORY DISORDERS

CHAPTER 1

APPROACH TO THE PATIENT WITH DISEASE OF THE RESPIRATORY SYSTEM

Patricia Kritek ■ Augustine Choi

The majority of diseases of the respiratory system fall into one of three major categories: (1) obstructive lung diseases; (2) restrictive disorders; and (3) abnormalities of the vasculature. Obstructive lung diseases are most common and primarily include disorders of the airways, such as asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, and bronchiolitis. Diseases resulting in restrictive pathophysiology include parenchymal lung diseases, abnormalities of the chest wall and pleura, and neuromuscular disease. Disorders of the pulmonary vasculature include pulmonary embolism, pulmonary hypertension, and pulmonary veno-occlusive disease. Although many specific diseases fall into these major categories, both infective and neoplastic processes can affect the respiratory system and result in myriad pathologic findings, including those listed in the three categories above **(Table 1–1)**.

Disorders can also be grouped according to gas exchange abnormalities, including hypoxemic, hypercarbic, or combined impairment. However, many diseases of the lung do not manifest as gas exchange abnormalities.

As with the evaluation of most patients, the approach to a patient with disease of the respiratory system begins with a thorough history and a focused physical examination. Many patients will subsequently undergo pulmonary function testing, chest imaging, blood and sputum analysis, a variety of serologic or microbiologic studies, and diagnostic procedures, such as bronchoscopy. This stepwise approach is discussed in detail next.

HISTORY

Dyspnea and cough

The cardinal symptoms of respiratory disease are dyspnea and cough **(Chaps. 2 and 3)**. Dyspnea has many causes, some of which are not predominantly due to lung pathology. The words a patient uses to describe shortness of breath can suggest certain etiologies for dyspnea. Patients with obstructive lung disease often complain of "chest tightness" or "inability to get a deep breath," whereas patients with congestive heart failure more commonly report "air hunger" or a sense of suffocation.

The tempo of onset and the duration of a patient's dyspnea are likewise helpful in determining the etiology. Acute shortness of breath is usually associated with sudden physiologic changes, such as laryngeal edema, bronchospasm, myocardial infarction, pulmonary embolism, or pneumothorax. Patients with COPD and idiopathic pulmonary fibrosis (IPF) experience a gradual progression of dyspnea on exertion, punctuated by acute exacerbations of shortness of breath. In contrast, most asthmatics have normal breathing the majority of the time with recurrent episodes of dyspnea that are usually associated with specific triggers, such as an upper respiratory tract infection or exposure to allergens.

Specific questioning should focus on factors that incite dyspnea as well as on any intervention that helps resolve the patient's shortness of breath. Asthma is commonly exacerbated by specific triggers, although this can also be true of COPD. Many patients with lung disease report dyspnea on exertion. Determining the

TABLE 1-1

CATEGORIES OF RESPIRATORY DISEASE

CATEGORY	EXAMPLES
Obstructive lung disease	Asthma Chronic obstructive pulmonary disease (COPD) Bronchiectasis Bronchiolitis
Restrictive pathophysiology—parenchymal disease	Idiopathic pulmonary fibrosis (IPF) Asbestosis Desquamative interstitial pneumonitis (DIP) Sarcoidosis
Restrictive pathophysiology—neuromuscular weakness	Amyotrophic lateral sclerosis (ALS) Guillain-Barré syndrome
Restrictive pathophysiology—chest wall/pleural disease	Kyphoscoliosis Ankylosing spondylitis Chronic pleural effusions
Pulmonary vascular disease	Pulmonary embolism Pulmonary arterial hypertension (PAH)
Malignancy	Bronchogenic carcinoma (non-small-cell and small-cell) Metastatic disease
Infectious diseases	Pneumonia Bronchitis Tracheitis

degree of activity that results in shortness of breath gives the clinician a gauge of the patient's degree of disability. Many patients adapt their level of activity to accommodate progressive limitation. For this reason, it is important, particularly in older patients, to delineate the activities in which they engage and how these activities have changed over time. Dyspnea on exertion is often an early symptom of underlying lung or heart disease and warrants a thorough evaluation.

Cough generally indicates disease of the respiratory system. The clinician should inquire about the duration of the cough, whether or not it is associated with sputum production, and any specific triggers that induce it. Acute cough productive of phlegm is often a symptom of infection of the respiratory system, including processes affecting the upper airway (e.g., sinusitis, tracheitis), the lower airways (e.g., bronchitis, bronchiectasis), and the lung parenchyma (e.g., pneumonia). Both the quantity and quality of the sputum, including whether it is blood-streaked or frankly bloody, should be determined. Hemoptysis warrants an evaluation as delineated in **Chap. 3**.

Chronic cough (defined as that persisting for >8 weeks) is commonly associated with obstructive lung diseases, particularly asthma and chronic bronchitis, as well as "nonrespiratory" diseases, such as gastroesophageal reflux and postnasal drip. Diffuse parenchymal lung diseases, including IPF, frequently present as a persistent, nonproductive cough. As with dyspnea, all causes of cough are not respiratory in origin, and assessment should encompass a broad differential, including cardiac and gastrointestinal diseases as well as psychogenic causes.

Additional symptoms

Patients with respiratory disease may report wheezing, which is suggestive of airways disease, particularly asthma. Hemoptysis can be a symptom of a variety of lung diseases, including infections of the respiratory tract, bronchogenic carcinoma, and pulmonary embolism. In addition, chest pain or discomfort is often thought to be respiratory in origin. As the lung parenchyma is not innervated with pain fibers, pain in the chest from respiratory disorders usually results from either diseases of the parietal pleura (e.g., pneumothorax) or pulmonary vascular diseases (e.g., pulmonary hypertension). As many diseases of the lung can result in strain on the right side of the heart, patients may also present with symptoms of cor pulmonale, including abdominal bloating or distention and pedal edema.

Additional history

A thorough social history is an essential component of the evaluation of patients with respiratory disease. All patients should be asked about current or previous cigarette smoking, as this exposure is associated with many diseases of the respiratory system, most notably COPD and bronchogenic lung cancer but also a variety of diffuse parenchymal lung diseases (e.g., desquamative interstitial pneumonitis and pulmonary Langerhans cell histiocytosis). For most disorders, longer duration and greater intensity of exposure to cigarette smoke increases the risk of disease. There is growing evidence that "second-hand smoke" is also a risk factor for respiratory tract pathology; for this reason, patients should be asked about parents, spouses, or housemates who smoke. Possible inhalational exposures should be explored, including those at the work place (e.g., asbestos, wood smoke) and those associated with leisure (e.g., excrement from pet birds) **(Chap. 10)**. Travel predisposes to certain infections of the respiratory tract, most notably the risk of tuberculosis. Potential exposure to fungi found in specific geographic regions or climates (e.g., Histoplasma capsulatum) should be explored.

Associated symptoms of fever and chills should raise the suspicion of infective etiologies, both pulmonary and systemic. A comprehensive review of systems may suggest rheumatologic or autoimmune disease presenting with respiratory tract manifestations. Questions should focus on joint pain or swelling, rashes, dry eyes, dry mouth, or constitutional symptoms. In addition, carcinomas from a variety of primary sources commonly metastasize to the lung and cause respiratory symptoms. Finally, therapy for other conditions, including both irradiation and medications, can result in diseases of the chest.

Physical examination

The clinician's suspicion of respiratory disease often begins with a patient's vital signs. The respiratory rate is often informative, whether elevated (tachypnea) or depressed (hypopnea). In addition, pulse oximetry should be measured, as many patients with respiratory disease have hypoxemia, either at rest or with exertion. The classic structure of the respiratory examination proceeds through inspection, percussion, palpation, and auscultation as described below. Often, however, auscultatory findings will lead the clinician to perform further percussion or palpation in order to clarify these findings.

The first step of the physical examination is inspection. Patients with respiratory disease may be in distress, often using accessory muscles of respiration to breathe. Severe kyphoscoliosis can result in restrictive pathophysiology. Inability to complete a sentence in conversation is generally a sign of severe impairment and should result in an expedited evaluation of the patient.

Percussion of the chest is used to establish diaphragm excursion and lung size. In the setting of decreased breath sounds, percussion is used to distinguish between pleural effusions (dull to percussion) and pneumothorax (hyper-resonant note).

The role of palpation is limited in the respiratory examination. Palpation can demonstrate subcutaneous air in the setting of barotrauma. It can also be used as an adjunctive assessment to determine whether an area of decreased breath sounds is due to consolidation (increased tactile fremitus) or a pleural effusion (decreased tactile fremitus).

The majority of the manifestations of respiratory disease present as abnormalities of auscultation. Wheezes are a manifestation of airway obstruction. While most commonly a sign of asthma, peribronchial edema in the setting of congestive heart failure can also result in diffuse wheezes, as can any other process that causes narrowing of small airways. For this reason, clinicians must take care not to attribute all wheezing to asthma.

Rhonchi are a manifestation of obstruction of medium-sized airways, most often with secretions. In the acute setting, this manifestation may be a sign of viral or bacterial bronchitis. Chronic rhonchi suggest bronchiectasis or COPD. Stridor, a high-pitched, focal inspiratory wheeze, usually heard over the neck, is a manifestation of upper airway obstruction and should prompt expedited evaluation of the patient, as it can precede complete upper airway obstruction and respiratory failure.

Crackles, or rales, are commonly a sign of alveolar disease. A variety of processes that fill the alveoli with fluid may result in crackles. Pneumonia can cause focal crackles. Pulmonary edema is associated with crackles, generally more prominent at the bases. Interestingly, diseases that result in fibrosis of the interstitium (e.g., IPF) also result in crackles often sounding like Velcro being ripped apart. Although some clinicians make a distinction between "wet" and "dry" crackles, this distinction has not been shown to be a reliable way to differentiate among etiologies of respiratory disease.

One way to help distinguish between crackles associated with alveolar fluid and those associated with interstitial fibrosis is to assess for egophony. Egophony is the auscultation of the sound "AH" instead of "EEE" when a patient phonates "EEE." This change in note is due to abnormal sound transmission through consolidated parenchyma and is present in pneumonia but not in IPF. Similarly, areas of alveolar filling have increased whispered pectoriloquy as well as transmission of larger-airway sounds (i.e., bronchial breath sounds in a lung zone where vesicular breath sounds are expected).

The lack or diminution of breath sounds can also help determine the etiology of respiratory disease. Patients with emphysema often have a quiet chest with diffusely decreased breath sounds. A pneumothorax or pleural effusion may present with an area of absent breath sounds.

Other systems

Pedal edema, if symmetric, may suggest cor pulmonale; if asymmetric, it may be due to deep venous thrombosis and associated pulmonary embolism. Jugular venous distention may also be a sign of volume overload associated with right heart failure. Pulsus paradoxus is an ominous sign in a patient with obstructive lung disease, as it is associated with significant negative intrathoracic (pleural) pressures required for ventilation and impending respiratory failure.

As stated earlier, rheumatologic disease may manifest primarily as lung disease. Owing to this association, particular attention should be paid to joint and skin examination. Clubbing can be found in many lung diseases, including cystic fibrosis, IPF, and lung cancer.

Cyanosis is seen in hypoxemic respiratory disorders that result in >5 g of deoxygenated hemoglobin/dL.

DIAGNOSTIC EVALUATION

The sequence of studies is dictated by the clinician's differential diagnosis, as determined by the history and physical examination. Acute respiratory symptoms are often evaluated with multiple tests performed at the same time in order to diagnose any life-threatening diseases rapidly (e.g., pulmonary embolism or multilobar pneumonia). In contrast, chronic dyspnea and cough can be evaluated in a more protracted, stepwise fashion.

Pulmonary function testing

(See also Chap. 6) The initial pulmonary function test obtained is spirometry. This study is an effort-dependent test used to assess for obstructive pathophysiology as seen in asthma, COPD, and bronchiectasis. A diminished-forced expiratory volume in 1 sec (FEV_1)/forced vital capacity (FVC) (often defined as <70% of the predicted value) is diagnostic of obstruction. In addition to measuring FEV_1 and FVC, the clinician should examine the flow-volume loop (which is effort-independent). A plateau of the inspiratory and expiratory curves suggests large-airway obstruction in extrathoracic and intrathoracic locations, respectively.

Spirometry with symmetric decreases in FEV_1 and FVC warrants further testing, including measurement of lung volumes and the diffusion capacity of the lung for carbon monoxide (D_LCO). A total lung capacity <80% of the predicted value for a patient's age, race, sex, and height defines restrictive pathophysiology. Restriction can result from parenchymal disease, neuromuscular weakness, or chest wall or pleural diseases. Restriction with impaired gas exchange, as indicated by a decreased D_LCO, suggests parenchymal lung disease. Additional testing, such as measurements of maximal expiratory pressure and maximal inspiratory pressure, can help diagnose neuromuscular weakness. Normal spirometry, normal lung volumes, and a low D_LCO should prompt further evaluation for pulmonary vascular disease.

Arterial blood gas testing is often helpful in assessing respiratory disease. Hypoxemia, while usually apparent with pulse oximetry, can be further evaluated with the measurement of arterial PO_2 and the calculation of an alveolar gas and arterial blood oxygen tension difference ($[A–a]DO_2$). Patients with diseases that cause ventilation-perfusion mismatch or shunt physiology have an increased $(A–a)DO_2$ at rest. Arterial blood gas testing also allows the measurement of arterial PCO_2. Hypercarbia can accompany severe airway obstruction (e.g., COPD) or progressive restrictive physiology, as in patients with neuromuscular weakness.

Chest imaging

(See Chap. 7) Most patients with disease of the respiratory system undergo imaging of the chest as part of the initial evaluation. Clinicians should generally begin with a plain chest radiograph, preferably posterior-anterior and lateral films. Several findings, including opacities of the parenchyma, blunting of the costophrenic angles, mass lesions, and volume loss, can be very helpful in determining an etiology. However, many diseases of the respiratory system, particularly those of the airways and pulmonary vasculature, are associated with a normal chest radiograph.

CT of the chest is often performed subsequently and allows better delineation of parenchymal processes, pleural disease, masses or nodules, and large airways. If the test includes administration of contrast, the pulmonary vasculature can be assessed with particular utility for determination of pulmonary emboli. Intravenous contrast also allows lymph nodes to be delineated in greater detail.

FURTHER STUDIES

Depending on the clinician's suspicion, a variety of other studies may be done. Concern about large-airway lesions may warrant bronchoscopy. This procedure may also be used to sample the alveolar space with bronchoalveolar lavage or to obtain nonsurgical lung biopsies. Blood testing may include assessment for hypercoagulable states in the setting of pulmonary vascular disease, serologic testing for infectious or rheumatologic disease, or assessment of inflammatory markers or leukocyte counts (e.g., eosinophils). Sputum evaluation for malignant cells or microorganisms may be appropriate. An echocardiogram to assess right- and left-sided heart function is often obtained. Finally, at times, a surgical lung biopsy is needed to diagnose certain diseases of the respiratory system. All of these studies will be guided by the preceding history, physical examination, pulmonary function testing, and chest imaging.

CHAPTER 2

DYSPNEA

Richard M. Schwartzstein

DYSPNEA

The American Thoracic Society defines dyspnea as a "subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors and may induce secondary physiological and behavioral responses." Dyspnea, a symptom, can be perceived only by the person experiencing it and must be distinguished from the signs of increased work of breathing.

MECHANISMS OF DYSPNEA

Respiratory sensations are the consequence of interactions between the efferent, or outgoing, motor output from the brain to the ventilatory muscles (feed-forward) and the afferent, or incoming, sensory input from receptors throughout the body (feedback) as well as the integrative processing of this information that we infer must be occurring in the brain **(Fig. 2-1)**. In contrast to painful sensations, which can often be attributed to the stimulation of a single nerve ending, dyspnea sensations are more commonly viewed as holistic, more akin to hunger or thirst. A given disease state may lead to dyspnea by one or more mechanisms, some of which may be operative under some circumstances (e.g., exercise) but not others (e.g., a change in position).

Motor efferents

Disorders of the ventilatory pump—most commonly, increased airway resistance or stiffness (decreased compliance) of the respiratory system—are associated with increased work of breathing or the sense of an increased effort to breathe. When the muscles are weak or fatigued, greater effort is required, even though the mechanics of the system are normal. The increased neural output from the motor cortex is sensed via a corollary discharge, a neural signal that is sent to the sensory cortex at the same time that motor output is directed to the ventilatory muscles.

Sensory afferents

Chemoreceptors in the carotid bodies and medulla are activated by hypoxemia, acute hypercapnia, and acidemia. Stimulation of these receptors and of others that lead to an increase in ventilation produce a sensation of "air hunger." Mechanoreceptors in the lungs, when stimulated by bronchospasm, lead to a sensation of chest tightness. J-receptors, which are sensitive to interstitial edema, and pulmonary vascular receptors, which are activated by acute changes in pulmonary artery pressure, appear to contribute to air hunger. Hyperinflation is associated with the sensation of increased work of breathing, an inability to get a deep breath, or an unsatisfying breath. Metaboreceptors, which are located in skeletal muscle, are believed to be activated by changes in the local biochemical milieu of the tissue active during exercise and, when stimulated, contribute to breathing discomfort.

Integration: Efferent-reafferent mismatch

A discrepancy or mismatch between the feed-forward message to the ventilatory muscles and the feedback from receptors that monitor the response of the ventilatory pump increases the intensity of dyspnea. This mismatch is particularly important when there is a mechanical derangement of the ventilatory pump, as in asthma or chronic obstructive pulmonary disease (COPD).

Contribution of emotional or affective factors to dyspnea

Acute anxiety or fear may increase the severity of dyspnea either by altering the interpretation of sensory data or by leading to patterns of breathing that heighten

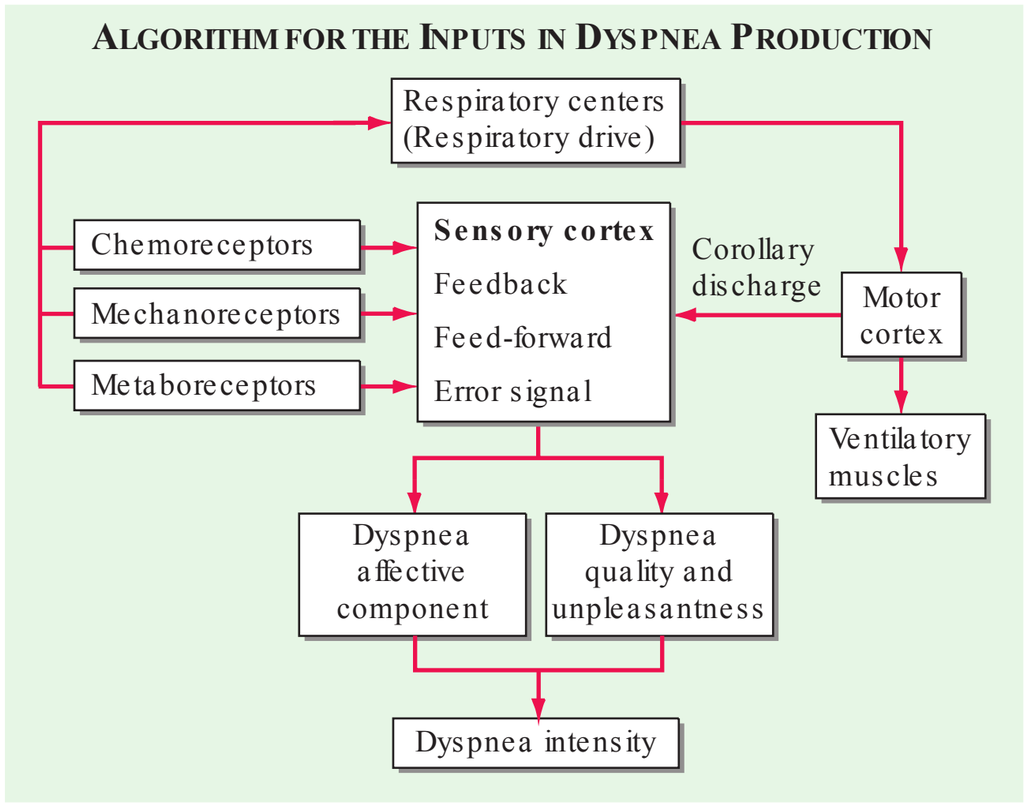

FIGURE 2-1

Hypothetical model for integration of sensory inputs in the production of dyspnea. Afferent information from the receptors throughout the respiratory system projects directly to the sensory cortex to contribute to primary qualitative sensory experiences and to provide feedback on the action of the ventilatory pump. Afferents also project to the areas of the brain responsible for control of ventilation. The motor cortex, responding to input from the control centers, sends neural messages to the ventilatory muscles and a corollary discharge to the sensory cortex (feed-forward with respect to the instructions sent to the muscles). If the feed-forward and feedback messages do not match, an error signal is generated and the intensity of dyspnea increases. An increasing body of data supports the contribution of affective inputs to the ultimate perception of unpleasant respiratory sensations. (Adapted from MA Gillette, RM Schwartzstein, in SH Ahmedzai, MF Muer [eds]. Supportive Care in Respiratory Disease. Oxford, UK, Oxford University Press, 2005.)

TABLE 2-1

ASSOCIATION OF QUALITATIVE DESCRIPTORS, CLINICAL CHARACTERISTICS, AND PATHOPHYSIOLOGIC MECHANISMS OF SHORTNESS OF BREATH

DESCRIPTOR	CLINICAL EXAMPLES	PATHOPHYSIOLOGY
Chest tightness or constriction	Asthma, CHF	Bronchoconstriction, interstitial edema
Increased work or effort of breathing	COPD, asthma, neuromuscular disease, chest wall restriction	Airway obstruction, neuromuscular disease
"Air hunger," need to breathe, urge to breathe	CHF, PE, COPD, asthma, pulmonary fibrosis	Increased drive to breathe
Inability to get a deep breath, unsatisfying breath	Moderate to severe asthma and COPD, pulmonary fibrosis, chest wall disease	Hyperinflation and restricted tidal volume
Heavy breathing, rapid breathing, breathing more	Sedentary status in healthy individual or patient with cardiopulmonary disease	Deconditioning

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PE, pulmonary embolism.

physiologic abnormalities in the respiratory system. In patients with expiratory flow limitation, for example, the increased respiratory rate that accompanies acute anxiety leads to hyperinflation, increased work and effort of breathing, and the sense of an unsatisfying breath.

ASSESSING DYSPNEA

Quality of sensation

Like pain assessment, dyspnea assessment begins with a determination of the quality of the patient's discomfort **(Table 2-1)**. Dyspnea questionnaires or lists of phrases commonly used by patients assist those who have difficulty describing their breathing sensations.

Sensory intensity

A modified Borg scale or visual analogue scale can be utilized to measure dyspnea at rest, immediately following exercise, or on recall of a reproducible physical task, such as climbing the stairs at home. An alternative approach is to gain a sense of the patient's disability by inquiring about what activities are possible. These methods indirectly assess dyspnea and may be affected by nonrespiratory factors, such as leg arthritis or weakness. The Baseline Dyspnea Index and the Chronic Respiratory Disease Questionnaire are commonly used tools for this purpose.

Affective dimension

For a sensation to be reported as a symptom, it must be perceived as unpleasant and interpreted as abnormal. Laboratory studies have demonstrated that air hunger evokes a stronger affective response than does increased effort or work of breathing. Some therapies for dyspnea, such as pulmonary rehabilitation, may reduce breathing discomfort, in part, by altering this dimension.

DIFFERENTIAL DIAGNOSIS

Dyspnea most often results from deviations from normal function in the cardiovascular and respiratory systems. These deviations produce breathlessness as a consequence of increased drive to breathe; increased effort or work of breathing; and/or stimulation of

receptors in the heart, lungs, or vascular system. Most diseases of the respiratory system are associated with alterations in the mechanical properties of the lungs and/or chest wall, and some stimulate pulmonary receptors. In contrast, disorders of the cardiovascular system more commonly lead to dyspnea by causing gas-exchange abnormalities or stimulating pulmonary and/or vascular receptors **(Table 2-2)**.

Respiratory system dyspnea

Diseases of the airways

Asthma and COPD, the most common obstructive lung diseases, are characterized by expiratory airflow obstruction, which typically leads to dynamic hyperinflation of the lungs and chest wall. Patients with moderate to severe disease have both increased resistive and elastic loads (a term that relates to the stiffness of the system) on the ventilatory muscles and experience increased work of breathing. Patients with acute bronchoconstriction also report a sense of tightness, which can exist even when lung function is still within the normal range. T ese patients are commonly tachypneic; this condition leads to hyperinflation and reduced respiratory system compliance and also limits tidal volume. Both the chest tightness and the tachypnea are probably due to stimulation of pulmonary receptors. Both asthma and COPD may lead to hypoxemia and hypercapnia from ventilation-perfusion (V̇/Q) mismatch (and diffusion limitation during exercise with emphysema); hypoxemia is much more common than hypercapnia as a consequence of the different ways in which oxygen and carbon dioxide bind to hemoglobin.

Diseases of the chest wall

Conditions that stiffen the chest wall, such as kyphoscoliosis, or that weaken ventilatory muscles, such as myasthenia gravis or the Guillain-Barré syndrome, are also associated with an increased effort to breathe. Large pleural effusions may contribute to dyspnea, both by increasing the work of breathing and by stimulating pulmonary receptors if there is associated atelectasis.

Diseases of the lung parenchyma

Interstitial lung diseases, which may arise from infections, occupational exposures, or autoimmune disorders, are associated with increased stiffness (decreased compliance) of the lungs and increased work of breathing. In addition, V̇/Q mismatch and the destruction and/or thickening of the alveolar-capillary interface may lead to hypoxemia and an increased drive to breathe. Stimulation of pulmonary receptors may further enhance the hyperventilation characteristic of mild to moderate interstitial disease.

Cardiovascular system dyspnea

Diseases of the left heart

Diseases of the myocardium resulting from coronary artery disease and nonischemic cardiomyopathies cause a greater left-ventricular end-diastolic volume and an elevation of the left-ventricular end-diastolic as well as pulmonary capillary pressures. T ese elevated pressures lead to interstitial edema and stimulation of pulmonary receptors, thereby causing dyspnea; hypoxemia due to V̇/Q mismatch may also contribute to breathlessness. Diastolic dysfunction, characterized by a very stiff left

TABLE 2-2

MECHANISMS OF DYSPNEA IN COMMON DISEASES

DISEASE	WORK OF BREATHING	DRIVE TO BREATHE	HYPOXEMIA[a]	ACUTE HYPERCAPNIA[a]	STIMULATION OF PULMONARY RECEPTORS	STIMULATION OF VASCULAR RECEPTORS	METABORECEPTORS
COPD	•		•	•			
Asthma	•	•	•	•	•		
ILD	•	•	•	•	•		
PVD		•	•			•	
CPE	•	•	•		•	•	•
NCPE	•	•	•		•		
Anemia							•
Decon-ditioning							•

[a]Hypoxemia and hypercapnia are not always present in these conditions. When hypoxemia is present, dyspnea usually persists, albeit at a reduced intensity, with correction of hypoxemia by the administration of supplemental oxygen.

Abbreviations: COPD, chronic obstructive pulmonary disease; CPE, cardiogenic pulmonary edema; ILD, interstitial lung disease; NCPE, noncardiogenic pulmonary edema; PVD, pulmonary vascular disease.

ventricle, may lead to severe dyspnea with relatively mild degrees of physical activity, particularly if it is associated with mitral regurgitation.

Diseases of the pulmonary vasculature

Pulmonary thromboembolic disease and primary diseases of the pulmonary circulation (primary pulmonary hypertension, pulmonary vasculitis) cause dyspnea via increased pulmonary-artery pressure and stimulation of pulmonary receptors. Hyperventilation is common, and hypoxemia may be present. However, in most cases, use of supplemental oxygen has only a minimal impact on the severity of dyspnea and hyperventilation.

Diseases of the pericardium

Constrictive pericarditis and cardiac tamponade are both associated with increased intracardiac and pulmonary vascular pressures, which are the likely cause of dyspnea in these conditions. To the extent that cardiac output is limited (at rest or with exercise) metaboreceptors may be stimulated if cardiac output is compromised to the degree that lactic acidosis develops; chemoreceptors will also be activated.

Dyspnea with normal respiratory and cardiovascular systems

Mild to moderate anemia is associated with breathing discomfort during exercise. T is symptom is thought to be related to stimulation of metaboreceptors; oxygen saturation is normal in patients with anemia. T e breathlessness associated with obesity is probably due to multiple mechanisms, including high cardiac output and impaired ventilatory pump function (decreased compliance of the chest wall). Cardiovascular deconditioning (poor fitness) is characterized by the early development of anaerobic metabolism and the stimulation of chemoreceptors and metaboreceptors. Dyspnea that is medically unexplained has been associated with increased sensitivity to the unpleasantness of acute hypercapnia.

APPROACH TO THE PATIENT: Dyspnea

DYSPNEA HISTORY T e patient should be asked to describe in his/her own words what the discomfort feels like as well as the effect of position, infections, and environmental stimuli on the dyspnea (see **Fig. 2-2**). Orthopnea is a common indicator of congestive heart failure (CHF), mechanical impairment of the diaphragm associated with obesity, or asthma triggered by esophageal reflux. Nocturnal dyspnea suggests CHF or asthma. Acute, intermittent episodes of dyspnea are more likely to reflect episodes of myocardial ischemia, bronchospasm, or pulmonary embolism, while chronic persistent dyspnea is typical of COPD, interstitial lung disease, and chronic thromboembolic disease. Information on risk factors for occupational lung disease and for coronary artery disease should be elicited. Left atrial myxoma or hepatopulmonary syndrome should be considered when the patient complains of platypnea—i.e., dyspnea in the upright position with relief in the supine position.

PHYSICAL EXAMINATION T e physical examination should begin during the interview of the patient. Inability of the patient to speak in full sentences before stopping to get a deep breath suggests a condition that leads to stimulation of the controller or impairment of the ventilatory pump with reduced vital capacity. Evidence of increased work of breathing (supraclavicular retractions; use of accessory muscles of ventilation; and the tripod position, characterized by sitting with the hands braced on the knees) is indicative of increased airway resistance or stiffness of the lungs and the chest wall. When measuring the vital signs, the physician should accurately assess the respiratory rate and measure the pulsus paradoxus; if the systolic pressure decreases by >10 mmHg, the presence of COPD, acute asthma, or pericardial disease should be considered. During the general examination, signs of anemia (pale conjunctivae), cyanosis, and cirrhosis (spider angiomata, gynecomastia) should be sought. Examination of the chest should focus on symmetry of movement; percussion (dullness is indicative of pleural effusion; hyperresonance is a sign of emphysema); and auscultation (wheezes, rhonchi, prolonged expiratory phase, and diminished breath sounds are clues to disorders of the airways; rales suggest interstitial edema or fibrosis). T e cardiac examination should focus on signs of elevated right heart pressures (jugular venous distention, edema, accentuated pulmonic component to the second heart sound); left ventricular dysfunction (S3 and S4 gallops); and valvular disease (murmurs). When examining the abdomen with the patient in the supine position, the physician should note whether there is paradoxical movement of the abdomen: inward motion during inspiration is a sign of diaphragmatic weakness, and rounding of the abdomen during exhalation is suggestive of pulmonary edema. Clubbing of the digits may be an indication of interstitial pulmonary fibrosis, and joint swelling or deformation as well as changes consistent with Raynaud's disease may be indicative of a collagen-vascular process that can be associated with pulmonary disease.

Patients with exertional dyspnea should be asked to walk under observation in order to reproduce the symptoms. T e patient should be examined during and at the end of exercise for new findings that were not present at rest and for changes in oxygen saturation.

CHEST IMAGING After the history elicitation and the physical examination, a chest radiograph should be obtained. T e lung volumes should be assessed: hyperinflation indicates

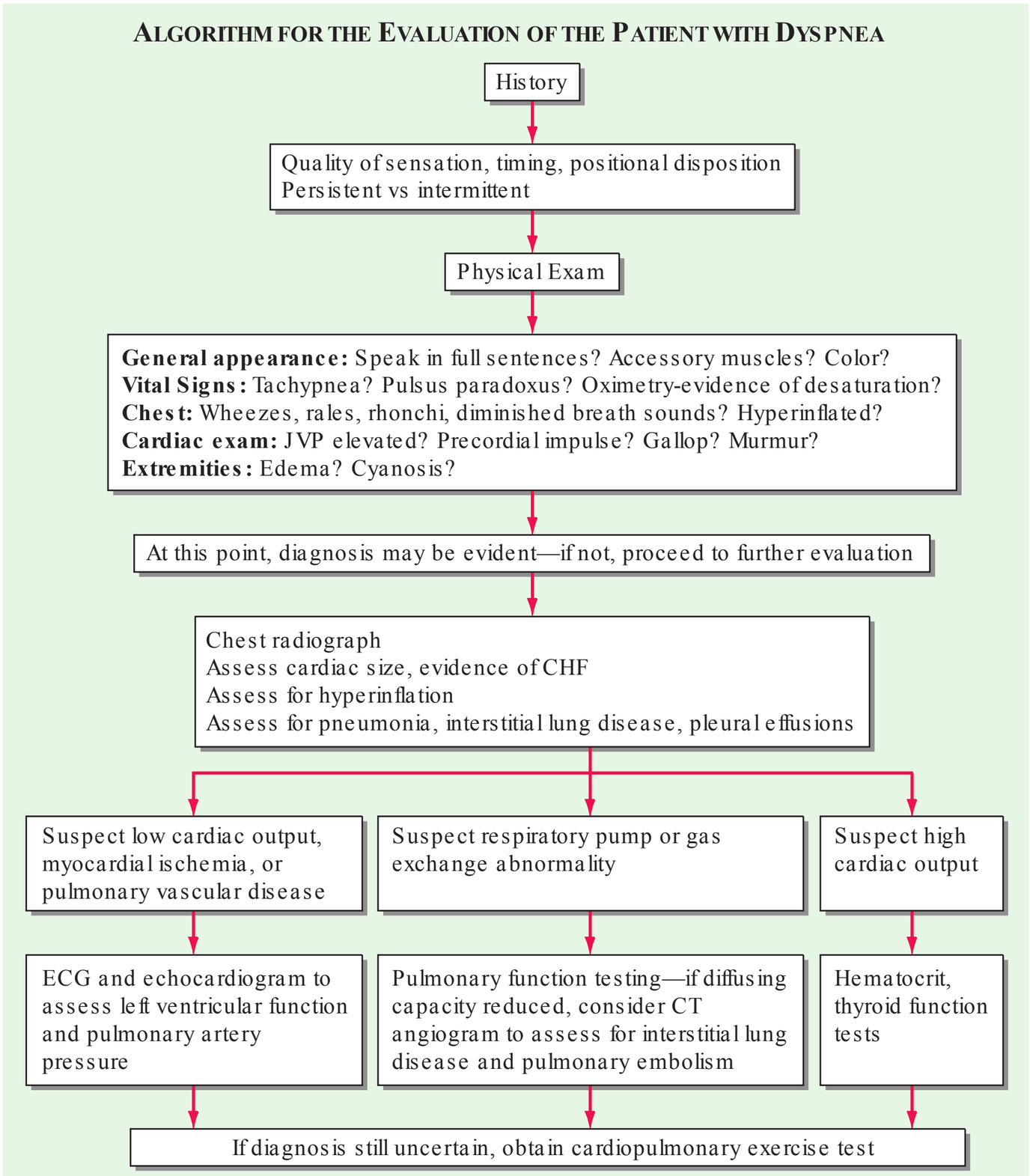

FIGURE 2-2

Algorithm for the evaluation of the patient with dyspnea. JVP, jugular venous pulse; CHF, congestive heart failure; ECG, electrocardiogram; CT, computed tomography. (Adapted from RM Schwartzstein, D Feller-Kopman, in E Braunwald, L Goldman [eds]. Primary Cardiology, 2nd ed. Philadelphia, WB Saunders, 2003.)

obstructive lung disease, whereas low lung volumes suggest interstitial edema or fibrosis, diaphragmatic dysfunction, or impaired chest wall motion. The pulmonary parenchyma should be examined for evidence of interstitial disease and emphysema. Prominent pulmonary vasculature in the upper zones indicates pulmonary venous hypertension, while enlarged central pulmonary arteries suggest pulmonary arterial hypertension. An enlarged cardiac silhouette suggests dilated cardiomyopathy or valvular disease. Bilateral pleural effusions are typical of CHF and some forms of collagen-vascular disease. Unilateral effusions raise the specter of carcinoma and pulmonary embolism but may also occur in heart failure. CT of the chest is generally reserved for further evaluation of the lung parenchyma (interstitial lung disease) and possible pulmonary embolism.

LABORATORY STUDIES Laboratory studies should include electrocardiography to seek evidence of ventricular hypertrophy and prior myocardial infarction. Echocardiography is indicated when systolic dysfunction, pulmonary hypertension, or valvular heart disease is suspected. Bronchoprovocation testing is useful in patients with intermittent symptoms suggestive of asthma but normal physical examination and lung function; up to one-third of patients with the clinical diagnosis of asthma do not have reactive airways disease when formally tested. Measurement of brain natriuretic peptide levels in serum is increasingly used to assess for CHF in patients presenting with acute dyspnea but may be elevated in the presence of right ventricular strain as well.

DISTINGUISHING CARDIOVASCULAR FROM RESPIRATORY SYSTEM DYSPNEA If a patient has evidence of both pulmonary and cardiac disease, a cardiopulmonary exercise test should be carried out to determine which system is responsible for the exercise limitation. If, at peak exercise, the patient achieves predicted maximal ventilation, demonstrates an increase in dead space or hypoxemia, or develops bronchospasm, the respiratory system is probably the cause of the problem.

Alternatively, if the heart rate is >85% of the predicted maximum, if the anaerobic threshold occurs early, if the blood pressure becomes excessively high or decreases during exercise, if the O_2 pulse (O_2 consumption/heart rate, an indicator of stroke volume) falls, or if there are ischemic changes on the electrocardiogram, an abnormality of the cardiovascular system is likely the explanation for the breathing discomfort.

TREATMENT Dyspnea

The first goal is to correct the underlying problem responsible for the symptom. If this is not possible, an effort is made to lessen the intensity of the symptom and its effect on the patient's quality of life. Supplemental O_2 should be administered if the resting O_2 saturation is ≤89% or if the patient's saturation drops to these levels with activity. For patients with COPD, pulmonary rehabilitation programs have demonstrated positive effects on dyspnea, exercise capacity, and rates of hospitalization. Studies of anxiolytics and antidepressants have not documented consistent benefit. Experimental interventions—e.g., cold air on the face, chest wall vibration, and inhaled furosemide—aimed at modulating the afferent information from receptors throughout the respiratory system are being studied. Morphine has been shown to reduce dyspnea out of proportion to the change in ventilation in laboratory models.

PULMONARY EDEMA

MECHANISMS OF FLUID ACCUMULATION

The extent to which fluid accumulates in the interstitium of the lung depends on the balance of hydrostatic and oncotic forces within the pulmonary capillaries and in the surrounding tissue. Hydrostatic pressure favors movement of fluid from the capillary into the interstitium. The oncotic pressure, which is determined by the protein concentration in the blood, favors movement of fluid into the vessel. Levels of albumin, the primary protein in the plasma, may be low in conditions such as cirrhosis and nephrotic syndrome. While hypoalbuminemia favors movement of fluid into the tissue for any given hydrostatic pressure in the capillary, it is usually not sufficient by itself to cause interstitial edema. In a healthy individual, the tight junctions of the capillary endothelium are impermeable to proteins, and the lymphatics in the tissue carry away the small amounts of protein that may leak out; together, these factors result in an oncotic force that maintains fluid in the capillary. Disruption of the endothelial barrier, however, allows protein to escape the capillary bed and enhances the movement of fluid into the tissue of the lung.

CARDIOGENIC PULMONARY EDEMA

(See also Chap. 32) Cardiac abnormalities that lead to an increase in pulmonary venous pressure shift the balance of forces between the capillary and the interstitium. Hydrostatic pressure is increased and fluid exits the capillary at an increased rate, resulting in interstitial and, in more severe cases, alveolar edema. The development of pleural effusions may further compromise respiratory system function and contribute to breathing discomfort.

Early signs of pulmonary edema include exertional dyspnea and orthopnea. Chest radiographs show peribronchial thickening, prominent vascular markings in the upper lung zones, and Kerley B lines. As the pulmonary edema worsens, alveoli fill with fluid; the chest radiograph shows patchy alveolar filling, typically in a perihilar distribution, which then progresses to diffuse alveolar infiltrates. Increasing airway edema is associated with rhonchi and wheezes.

NONCARDIOGENIC PULMONARY EDEMA

In noncardiogenic pulmonary edema, lung water increases due to damage of the pulmonary capillary lining with consequent leakage of proteins and other macromolecules into the tissue; fluid follows the protein as oncotic forces are shifted from the vessel to the surrounding lung tissue. This process is associated with dysfunction of the surfactant lining the alveoli, increased surface forces, and a propensity for the alveoli to collapse at low lung volumes. Physiologically, noncardiogenic pulmonary edema is characterized by intrapulmonary shunt with hypoxemia and decreased pulmonary compliance leading to lower functional residual capacity. On pathologic examination, hyaline membranes are evident in the alveoli, and inflammation leading to pulmonary fibrosis may be seen. Clinically, the picture ranges from mild dyspnea to respiratory failure. Auscultation of the lungs may be relatively normal despite chest radiographs that show diffuse alveolar infiltrates. CT scans demonstrate that the distribution of alveolar edema is more heterogeneous than was once thought. Although normal intracardiac pressures are considered by many to be part of the definition of noncardiogenic pulmonary edema, the pathology of the process, as described above, is distinctly different, and a combination of cardiogenic and noncardiogenic pulmonary edema is observed in some patients.

It is useful to categorize the causes of noncardiogenic pulmonary edema in terms of whether the injury to the lung is likely to result from direct, indirect, or

pulmonary vascular causes **(Table 2-3)**. Direct injuries are mediated via the airways (e.g., aspiration) or as the consequence of blunt chest trauma. Indirect injury is the consequence of mediators that reach the lung via the bloodstream. T e third category includes conditions that may result from acute changes in pulmonary vascular pressures, possibly due to sudden autonomic discharge (in the case of neurogenic and high-altitude pulmonary edema) or sudden swings of pleural pressure as well as transient damage to the pulmonary capillaries (in the case of reexpansion pulmonary edema).

TABLE 2-3

COMMON CAUSES OF NONCARDIOGENIC PULMONARY EDEMA
Direct Injury to Lung
Chest trauma, pulmonary contusion
Aspiration
Smoke inhalation
Pneumonia
Oxygen toxicity
Pulmonary embolism, reperfusion
Hematogenous Injury to Lung
Sepsis
Pancreatitis
Nonthoracic trauma
Leukoagglutination reactions
Multiple transfusions
Intravenous drug use (e.g., heroin)
Cardiopulmonary bypass
Possible Lung Injury Plus Elevated Hydrostatic Pressures
High-altitude pulmonary edema
Neurogenic pulmonary edema
Reexpansion pulmonary edema

DISTINGUISHING CARDIOGENIC FROM NONCARDIOGENIC PULMONARY EDEMA

T e history is essential for assessing the likelihood of underlying cardiac disease as well as for identification of one of the conditions associated with noncardiogenic pulmonary edema. T e physical examination in cardiogenic pulmonary edema is notable for evidence of increased intracardiac pressures (S3 gallop, elevated jugular venous pulse, peripheral edema) and rales and/or wheezes on auscultation of the chest. In contrast, the physical examination in noncardiogenic pulmonary edema is dominated by the findings of the precipitating condition; pulmonary findings may be relatively normal in the early stages. T e chest radiograph in cardiogenic pulmonary edema typically shows an enlarged cardiac silhouette, vascular redistribution, interstitial thickening, and perihilar alveolar infiltrates; pleural effusions are common. In noncardiogenic pulmonary edema, heart size is normal, alveolar infiltrates are distributed more uniformly throughout the lungs, and pleural effusions are uncommon. Finally, the hypoxemia of cardiogenic pulmonary edema is due largely to V̇/Q̇ to mismatch and responds to the administration of supplemental oxygen. In contrast, hypoxemia in noncardiogenic pulmonary edema is due primarily to intrapulmonary shunting and typically persists despite high concentrations of inhaled oxygen.

CHAPTER 3

COUGH AND HEMOPTYSIS

Patricia A. Kritek ■ Christopher H. Fanta

COUGH

Cough performs an essential protective function for human airways and lungs. Without an effective cough reflex, we are at risk for retained airway secretions and aspirated material predisposing to infection, atelectasis, and respiratory compromise. At the other extreme, excessive coughing can be exhausting; can be complicated by emesis, syncope, muscular pain, or rib fractures; and can aggravate abdominal or inguinal hernias and urinary incontinence. Cough is often a clue to the presence of respiratory disease. In many instances, cough is an expected and accepted manifestation of disease, as in acute respiratory tract infection. However, persistent cough in the absence of other respiratory symptoms commonly causes patients to seek medical attention.

COUGH MECHANISM

Spontaneous cough is triggered by stimulation of sensory nerve endings that are thought to be primarily rapidly adapting receptors and C fibers. Both chemical (e.g., capsaicin) and mechanical (e.g., particulates in air pollution) stimuli may initiate the cough reflex. A cationic ion channel—the type 1 vanilloid receptor—found on rapidly adapting receptors and C fibers is the receptor for capsaicin, and its expression is increased in patients with chronic cough. Afferent nerve endings richly innervate the pharynx, larynx, and airways to the level of the terminal bronchioles and extend into the lung parenchyma. T ey may also be located in the external auditory meatus (the auricular branch of the vagus nerve, or the Arnold nerve) and in the esophagus. Sensory signals travel via the vagus and superior laryngeal nerves to a region of the brainstem in the nucleus tractus solitarius vaguely identified as the "cough center." T e cough reflex involves a highly orchestrated series of involuntary muscular actions, with the potential for input from cortical pathways as well. T e vocal cords adduct, leading to transient upper-airway occlusion. Expiratory muscles contract, generating positive intrathoracic pressures as high as 300 mmHg. With sudden release of the laryngeal contraction, rapid expiratory flows are generated, exceeding the normal "envelope" of maximal expiratory flow seen on the flow-volume curve **(Fig. 3-1)**. Bronchial smooth-muscle contraction together with dynamic compression of airways narrows airway lumens and maximizes the velocity of exhalation. T e kinetic energy available to dislodge mucus from the inside of airway walls is directly proportional to the square of the velocity of expiratory airflow. A deep breath preceding a cough optimizes the function of the expiratory muscles; a series of repetitive coughs at successively lower lung volumes sweeps the point of maximal expiratory velocity progressively further into the lung periphery.

IMPAIRED COUGH

Weak or ineffective cough compromises the ability to clear lower respiratory tract infections, predisposing to more serious infections and their sequelae. Weakness, paralysis, or pain of the expiratory (abdominal and intercostal) muscles is foremost on the list of causes of impaired cough **(Table 3-1)**. Cough strength is generally assessed qualitatively; peak expiratory flow or maximal expiratory pressure at the mouth can be used as a surrogate marker for cough strength. A variety of assistive devices and techniques have been developed to improve cough strength, running the gamut from simple (splinting of the abdominal muscles with a tightly-held pillow to reduce postoperative pain while coughing) to complex (a mechanical cough-assist device supplied via face mask or tracheal tube that applies a cycle of positive pressure followed rapidly by negative pressure). Cough may fail to clear secretions despite a preserved ability to generate normal

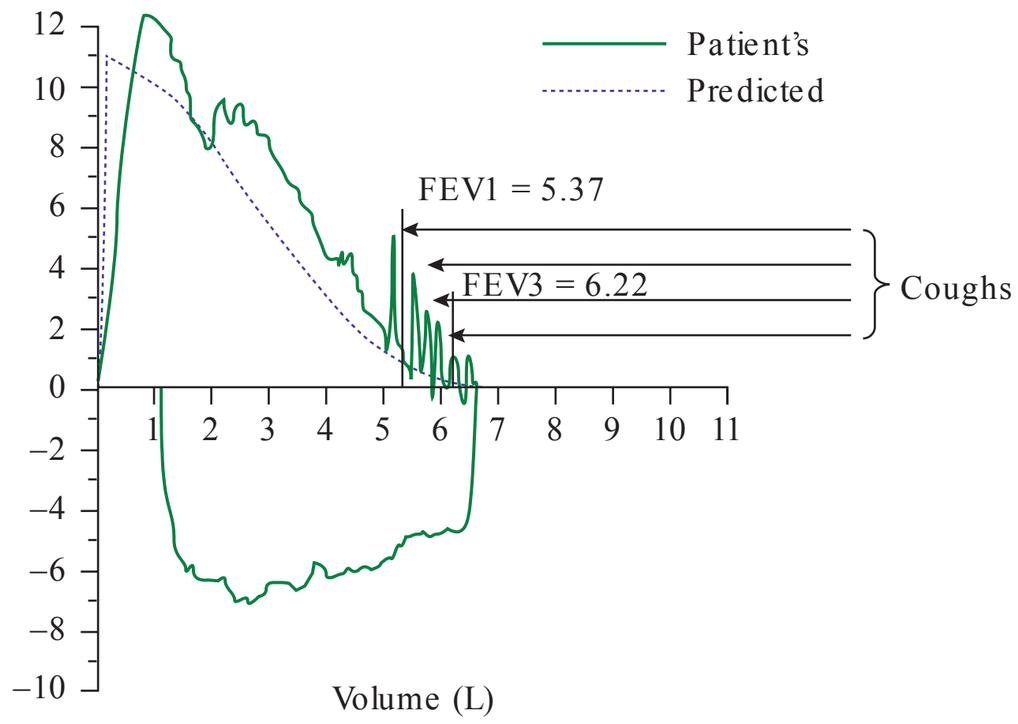

FIGURE 3-1
Flow-volume curve shows spikes of high expiratory fow achieved with cough. FEV_1, forced expiratory volume in 1 s.

expiratory velocities; such failure may be due to either abnormal airway secretions (e.g., bronchiectasis due to cystic fibrosis) or structural abnormalities of the airways (e.g., tracheomalacia with expiratory collapse during cough).

SYMPTOMATIC COUGH

T e cough of chronic bronchitis in long-term cigarette smokers rarely leads the patient to seek medical advice. It lasts for only seconds to a few minutes, is productive of benign-appearing mucoid sputum, and generally does not cause discomfort. Cough may occur in the context of other respiratory symptoms that together point to a diagnosis; for example, cough accompanied by wheezing, shortness of breath, and chest tightness after exposure to a cat or other sources of allergens suggests asthma. At times, however, cough is the dominant or sole symptom of disease, and it may be of suf cient duration and severity that relief is sought. T e duration of cough is a clue to its etiology. Acute cough (<3 weeks) is most commonly due to a respiratory tract infection, aspiration, or inhalation of noxious chemicals or smoke. Subacute cough (3–8 weeks in duration) is a common residuum of tracheobronchitis, as in pertussis or "postviral tussive syndrome." Chronic cough (>8 weeks) may be caused by a wide variety of cardiopulmonary diseases, including those of inflammatory, infectious, neoplastic, and cardiovascular etiologies. When initial assessment with chest examination and radiography is normal, cough-variant asthma, gastroesophageal reflux, nasopharyngeal drainage, and medications (angiotensin-converting enzyme [ACE] inhibitors) are the most common causes of chronic cough.

TABLE 3-1

CAUSES OF IMPAIRED COUGH
Decreased expiratory-muscle strength
Decreased inspiratory-muscle strength
Chest wall deformity
Impaired glottic closure or tracheostomy
Tracheomalacia
Abnormal airway secretions
Central respiratory depression (e.g., anesthesia, sedation, or coma)

ASSESSMENT OF CHRONIC COUGH

Details as to the sound, the time of occurrence during the day, and the pattern of coughing infrequently provide useful etiologic clues. Regardless of cause, cough often worsens upon first lying down at night, with talking, or with the hyperpnea of exercise; it frequently improves with sleep. An exception may involve the cough that occurs only with certain allergic exposures or exercise in cold air, as in asthma. Useful historical questions include what circumstances surround the onset of cough, what makes the cough better or worse, and whether or not the cough produces sputum.

T e physical examination seeks clues suggesting the presence of cardiopulmonary disease, including findings such as wheezing or crackles on chest examination. Examination of the auditory canals and tympanic membranes (for irritation of the latter resulting in stimulation of Arnold's nerve), the nasal passageways (for rhinitis or polyps), and the nails (for clubbing) may also provide etiologic clues. Because cough can be a manifestation of a systemic disease such as sarcoidosis or vasculitis, a thorough general examination is equally important.

In virtually all instances, evaluation of chronic cough merits a chest radiograph. T e list of diseases that can cause persistent cough without other symptoms and without detectable abnormalities on physical examination is long. It includes serious illnesses such as sarcoidosis or Hodgkin's disease in young adults, lung cancer in older patients, and (worldwide) pulmonary tuberculosis. An abnormal chest film prompts an evaluation aimed at explaining the cough. In a patient with chronic productive cough, examination of expectorated sputum is warranted. Purulent-appearing sputum should be sent for routine bacterial culture and, in certain circumstances, mycobacterial culture as well. Cytologic examination of mucoid sputum may be useful to assess for malignancy and to distinguish neutrophilic from eosinophilic bronchitis. Expectoration of blood—whether streaks of blood, blood mixed with airway secretions, or pure blood—deserves a special approach to assessment and management (see "Hemoptysis," below).

CHRONIC COUGH WITH A NORMAL CHEST RADIOGRAPH

It is commonly held that (alone or in combination) the use of an ACE inhibitor; postnasal drainage; gastroesophageal reflux; and asthma account for more than 90% of cases of chronic cough with a normal or noncontributory chest radiograph. However, clinical experience does not support this contention, and strict adherence to this concept discourages the search for alternative explanations by both clinicians and researchers. ACE inhibitor–induced cough occurs in 5–30% of patients taking these agents and is not dose dependent. ACE metabolizes bradykinin and other tachykinins, such as substance P. T e mechanism of ACE inhibitor–associated cough may involve sensitization of sensory nerve endings due to accumulation of bradykinin. In support of this hypothesis, polymorphisms in the neurokinin-2 receptor gene are associated with ACE inhibitor–induced cough. Any patient with chronic unexplained cough who is taking an ACE inhibitor should have a trial period off the medication, regardless of the timing of the onset of cough relative to the initiation of ACE inhibitor therapy. In most instances, a safe alternative is available; angiotensin-receptor blockers do not cause cough. Failure to observe a decrease in cough after 1 month off medication argues strongly against this etiology. Postnasal drainage of any etiology can cause cough as a response to stimulation of sensory receptors of the cough-reflex pathway in the hypopharynx or aspiration of draining secretions into the trachea. Clues suggesting this etiology include postnasal drip, frequent throat clearing, and sneezing and rhinorrhea. On speculum examination of the nose, excess mucoid or purulent secretions, inflamed and edematous nasal mucosa, and/or polyps may be seen; in addition, secretions or a cobblestoned appearance of the mucosa along the posterior pharyngeal wall may be noted. Unfortunately, there is no means by which to quantitate postnasal drainage. In many instances, this diagnosis must rely on subjective information provided by the patient. T is assessment must also be counterbalanced by the fact that many people who have chronic postnasal drainage do not experience cough.

Linking gastroesophageal reflux to chronic cough poses similar challenges. It is thought that reflux of gastric contents into the lower esophagus may trigger cough via reflex pathways initiated in the esophageal mucosa. Reflux to the level of the pharynx (laryngopharyngeal reflux), with consequent aspiration of gastric contents, causes a chemical bronchitis and possibly pneumonitis that can elicit cough for days afterward. Retrosternal burning after meals or on recumbency, frequent eructation, hoarseness, and throat pain may be indicative of gastroesophageal reflux. Nevertheless, reflux may also elicit minimal or no symptoms. Glottic inflammation detected on laryngoscopy may be a manifestation of recurrent reflux to the level of the throat, but it is a nonspecific finding. Quantification of the frequency and level of reflux requires a somewhat invasive procedure to measure esophageal pH directly (either nasopharyngeal placement of a catheter with a pH probe into the esophagus for 24 h or endoscopic placement of a radiotransmitter capsule into the esophagus). T e precise interpretation of test results that permits an etiologic linking of reflux events and cough remains debated. Again, assigning the cause of cough to gastroesophageal reflux must be weighed against the observation that many people with symptomatic reflux do not experience chronic cough.

Cough alone as a manifestation of asthma is common among children but not among adults. Cough due to asthma in the absence of wheezing, shortness of breath, and chest tightness is referred to as "cough-variant asthma." A history suggestive of cough-variant asthma ties the onset of cough to exposure to typical triggers for asthma and the resolution of cough to discontinuation of exposure. Objective testing can establish the diagnosis of asthma (airflow obstruction on spirometry that varies over time or reverses in response to a bronchodilator) or exclude it with certainty (a negative response to a bronchoprovocation challenge—e.g., with methacholine). In a patient capable of taking reliable measurements, home expiratory peak flow monitoring can be a cost-effective method to support or discount a diagnosis of asthma.

Chronic eosinophilic bronchitis causes chronic cough with a normal chest radiograph. T is condition is characterized by sputum eosinophilia in excess of 3% without airflow obstruction or bronchial hyperresponsiveness and is successfully treated with inhaled glucocorticoids.

Treatment of chronic cough in a patient with a normal chest radiograph is often empirical and is targeted at the most likely cause(s) of cough as determined by history, physical examination, and possibly pulmonary-function testing. T erapy for postnasal drainage depends on the presumed etiology (infection, allergy, or vasomotor rhinitis) and may include systemic antihistamines; antibiotics; nasal saline irrigation; and nasal pump sprays with glucocorticoids, antihistamines, or anticholinergics. Antacids, histamine type 2 (H2) receptor antagonists, and proton-pump inhibitors are used to neutralize or decrease the production of gastric acid in gastroesophageal reflux disease; dietary changes, elevation of the head and torso during sleep, and medications to improve gastric emptying are additional therapeutic measures. Cough-variant asthma typically

responds well to inhaled glucocorticoids and intermittent use of inhaled β-agonist bronchodilators.

Patients who fail to respond to treatment targeting the common causes of chronic cough or who have had these causes excluded by appropriate diagnostic testing should undergo chest CT. Diseases causing cough that may be missed on chest x-ray include tumors, early interstitial lung disease, bronchiectasis, and atypical mycobacterial pulmonary infection. On the other hand, patients with chronic cough who have normal findings on chest examination, lung function testing, oxygenation assessment, and chest CT can be reassured as to the absence of serious pulmonary pathology.

SYMPTOM-BASED TREATMENT OF COUGH

Chronic idiopathic cough, also called cough hypersensitivity syndrome, is distressingly common. It is often experienced as a tickle or sensitivity in the throat, occurs more often in women, and is typically "dry" or at most productive of scant amounts of mucoid sputum. It can be exhausting, interfere with work, and cause social embarrassment. Once serious underlying cardiopulmonary pathology has been excluded, an attempt at cough suppression is appropriate. Most effective are narcotic cough suppressants, such as codeine or hydrocodone, which are thought to act in the "cough center" in the brainstem. T e tendency of narcotic cough suppressants to cause drowsiness and constipation and their potential for addictive dependence limit their appeal for long-term use. Dextromethorphan is an over-the-counter, centrally acting cough suppressant with fewer side effects and less ef cacy than the narcotic cough suppressants. Dextromethorphan is thought to have a different site of action than narcotic cough suppressants and can be used in combination with them if necessary. Benzonatate is thought to inhibit neural activity of sensory nerves in the cough-reflex pathway. It is generally free of side effects; however, its effectiveness in suppressing cough is variable and unpredictable. Case series have reported benefit from off-label use of gabapentin or amitriptyline for chronic idiopathic cough. Novel cough suppressants without the limitations of currently available agents are greatly needed. Approaches that are being explored include the development of neurokinin receptor antagonists, type 1 vanilloid receptor antagonists, and novel opioid and opioid-like receptor agonists.

HEMOPTYSIS

Hemoptysis, the expectoration of blood from the respiratory tract, can arise at any location from the alveoli to the glottis. It is important to distinguish hemoptysis from epistaxis (bleeding from the nasopharynx) and hematemesis (bleeding from the upper gastrointestinal tract). Hemoptysis can range from the expectoration of blood-tinged sputum to that of life-threatening large volumes of bright red blood. For most patients, any degree of hemoptysis can cause anxiety and often prompts medical evaluation.

While precise epidemiologic data are lacking, the most common etiology of hemoptysis is infection of the medium-sized airways. In the United States, the cause is usually viral or bacterial bronchitis. Hemoptysis can arise in the setting of acute bronchitis or during an exacerbation of chronic bronchitis. Worldwide, the most common cause of hemoptysis is infection with Mycobacterium tuberculosis, presumably because of the high prevalence of tuberculosis and its predilection for cavity formation. While these are the most common causes, the differential diagnosis for hemoptysis is extensive, and a step-wise approach to evaluation is appropriate.

ETIOLOGY

One way to approach the source of hemoptysis is to search systematically for potential sites of bleeding from the alveolus to the mouth. Diffuse bleeding in the alveolar space, often referred to as di*ff*use alveolar hemorrhage (DAH), may present as hemoptysis. Causes of DAH can be inflammatory or noninflammatory. Inflammatory DAH is due to small-vessel vasculitis/capillaritis from a variety of diseases, including granulomatosis with polyangiitis and microscopic polyangiitis. Similarly, systemic autoimmune diseases such as systemic lupus erythematosus can manifest as pulmonary capillaritis. Antibodies to the alveolar basement membrane, as are seen in Goodpasture's disease, can also result in alveolar hemorrhage. In the early period after bone marrow transplantation, patients can develop a form of inflammatory DAH that can be catastrophic and life-threatening. T e exact pathophysiology of this process is not well understood, but DAH should be suspected in patients with sudden-onset dyspnea and hypoxemia in the first 100 days after bone marrow transplantation.

Alveoli can also bleed due to direct inhalational injury, including thermal injury from fires, inhalation of illicit substances (e.g., cocaine), and inhalation of toxic chemicals. If alveoli are irritated from any process, patients with thrombocytopenia, coagulopathy, or antiplatelet or anticoagulant use will be at increased risk of hemoptysis.

Bleeding in hemoptysis most commonly arises from the small- to medium-sized airways. Irritation and injury of the bronchial mucosa can lead to

small-volume bleeding. More significant hemoptysis can result from the proximity of the bronchial artery and vein to the airway, with these vessels and the bronchus running together in what is often referred to as the bronchovascular bundle. In the smaller airways, these blood vessels are close to the airspace, and lesser degrees of inflammation or injury can therefore result in their rupture into the airways. While alveolar hemorrhage arises from capillaries that are part of the low-pressure pulmonary circulation, bronchial bleeding generally originates from bronchial arteries, which are under systemic pressure and thus are predisposed to larger-volume bleeding.

Any infection of the airways can result in hemoptysis, although acute bronchitis is most commonly caused by viral infection. In patients with a history of chronic bronchitis, bacterial superinfection with organisms such as Streptococcus pneumoniae, Haemophilus infuenzae, or Moraxella catarrhalis can also result in hemoptysis. Patients with bronchiectasis (a permanent dilation of the airways with loss of mucosal integrity) are particularly prone to hemoptysis due to chronic inflammation and anatomic abnormalities that bring the bronchial arteries closer to the mucosal surface. One common presentation of patients with advanced cystic fibrosis—the prototypical bronchiectatic lung disease—is hemoptysis, which can be life-threatening.

Pneumonias of any sort can cause hemoptysis. Tuberculous infection, which can lead to bronchiectasis or cavitary pneumonia, is a very common cause of hemoptysis worldwide. Patients may present with a chronic cough productive of blood-streaked sputum or with larger-volume bleeding. Rasmussen's aneurysm (the dilation of a pulmonary artery in a cavity formed by previous tuberculous infection) remains a source of massive, life-threatening hemoptysis in the developing world. Community-acquired pneumonia and lung abscess can also result in bleeding. Once again, if the infection results in cavitation, there is a greater likelihood of bleeding due to erosion into blood vessels. Infections with Staphylococcus aureus and gram-negative rods (e.g., Klebsiella pneumoniae) are especially likely to cause necrotizing lung infections and thus to be associated with hemoptysis.

While not common in North America, pulmonary paragonimiasis (i.e., infection with the lung fluke Paragonimus westermani) often presents as fever, cough, and hemoptysis. T is infection is a public health issue in Southeast Asia and China and is frequently confused with active tuberculosis, in which the clinical picture can be similar. Paragonimiasis should be considered in recent immigrants from endemic areas who have new or recurrent hemoptysis. In addition, pulmonary paragonimiasis has been reported secondary to ingestion of crayfish or small crabs in the United States.

Other causes of airway irritation resulting in hemoptysis include inhalation of toxic chemicals, thermal injury, and direct trauma from suctioning of the airways (particularly in intubated patients). All of these etiologies should be considered in light of the individual patient's history and exposures.

Perhaps the most feared cause of hemoptysis is bronchogenic lung cancer, although hemoptysis is a presenting symptom in only ~10% of patients. Cancers arising in the proximal airways are much more likely to cause hemoptysis, but any malignancy in the chest can do so. Because both squamous cell carcinomas and small-cell carcinomas are more commonly in or adjacent to the proximal airways, and large at presentation, they are more often a cause of hemoptysis. T ese cancers can present with large-volume and life-threatening hemoptysis because of erosion into the hilar vessels. Carcinoid tumors, which are found almost exclusively as endobronchial lesions with friable mucosa, can also present with hemoptysis.

In addition to cancers arising in the lung, metastatic disease in the pulmonary parenchyma can bleed. Malignancies that commonly metastasize to the lungs include renal cell, breast, colon, testicular, and thyroid cancers as well as melanoma. While hemoptysis is not a common manifestation of pulmonary metastases, the combination of multiple pulmonary nodules and hemoptysis should raise suspicion of this etiology. Finally, disease of the pulmonary vasculature can cause hemoptysis. Perhaps most frequently, congestive heart failure with transmission of elevated left atrial pressures can lead to rupture of small alveolar capillaries. T ese patients rarely present with bright red blood but more commonly have pink, frothy sputum or blood-tinged secretions. Patients with a focal jet of mitral regurgitation can present with an upper-lobe opacity on chest radiography together with hemoptysis. T is finding is thought to be due to focal increases in pulmonary capillary pressure due to the regurgitant jet. Pulmonary arteriovenous malformations are prone to bleeding. Pulmonary embolism can also lead to the development of hemoptysis, which is generally associated with pulmonary infarction. Pulmonary arterial hypertension from other causes rarely results in hemoptysis.

EVALUATION

As with most signs of possible illness, the initial step in the evaluation of hemoptysis is a thorough history and physical examination **(Fig. 3-2)**. As already mentioned, initial questioning should focus on ascertaining

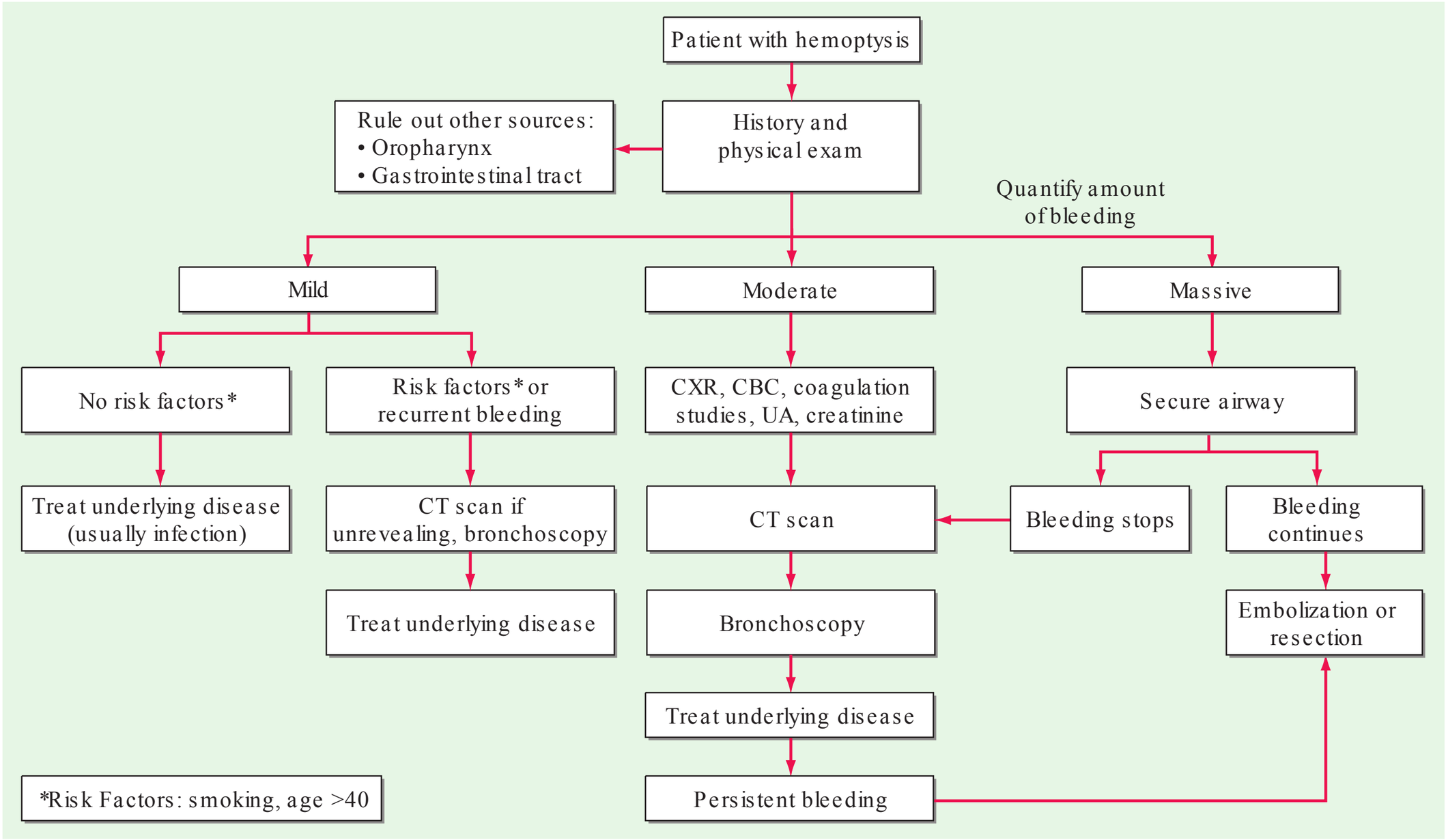

FIGURE 3-2
Decision tree for evaluation of hemoptysis. CBC, complete blood count; CT, computed tomography; CXR, chest x-ray; UA, urinalysis.

whether the bleeding is truly from the respiratory tract and not the nasopharynx or gastrointestinal tract; bleeding from the latter sources requires different approaches to evaluation and treatment.

History and physical examination

The specific characteristics of hemoptysis may be helpful in determining an etiology, such as whether the expectorated material consists of blood-tinged, purulent secretions; pink, frothy sputum; or pure blood. Information on specific triggers of the bleeding (e.g., recent inhalation exposures) as well as any previous episodes of hemoptysis should be elicited during history-taking. Monthly hemoptysis in a woman suggests catamenial hemoptysis from pulmonary endometriosis. Moreover, the volume of blood expectorated is important not only in determining the cause but also in gauging the urgency for further diagnostic and therapeutic maneuvers. Patients rarely exsanguinate from hemoptysis but can effectively "drown" in aspirated blood. Large-volume hemoptysis, referred to as massive hemoptysis, is variably defined as hemoptysis of >200–600 mL in 24 h. Massive hemoptysis should be considered a medical emergency. All patients should be asked about current or former cigarette smoking; this behavior predisposes to chronic bronchitis and increases the likelihood of bronchogenic cancer. Practitioners should inquire about symptoms and signs suggestive of respiratory tract infection (including fever, chills, and dyspnea), recent inhalation exposures, recent use of illicit substances, and risk factors for venous thromboembolism.

A medical history of malignancy or treatment thereof, rheumatologic disease, vascular disease, or underlying lung disease (e.g., bronchiectasis) may be relevant to the cause of hemoptysis. Because many causes of DAH can be part of a pulmonary-renal syndrome, specific inquiry into a history of renal insufficiency is important.

The physical examination begins with an assessment of vital signs and oxygen saturation to gauge whether there is evidence of life-threatening bleeding. Tachycardia, hypotension, and decreased oxygen saturation mandate a more expedited evaluation of hemoptysis. A specific focus on respiratory and cardiac examinations is important; these examinations should include inspection of the nares, auscultation of the lungs and heart, assessment of the lower extremities for symmetric or asymmetric edema, and evaluation for jugular venous distention. Clubbing of the digits may suggest underlying lung diseases such as bronchogenic carcinoma or bronchiectasis, which predispose to hemoptysis. Similarly, mucocutaneous telangiectasias

should raise the specter of pulmonary arterial-venous malformations.

Diagnostic evaluation

For most patients, the next step in evaluation of hemoptysis should be a standard chest radiograph. If a source of bleeding is not identified on plain film, CT of the chest should be performed. CT allows better delineation of bronchiectasis, alveolar filling, cavitary infiltrates, and masses than does chest radiograph. The practitioner should consider a CT protocol to assess for pulmonary embolism if the history or examination suggests venous thromboembolism as a cause of bleeding.

Laboratory studies should include a complete blood count to assess both the hematocrit and the platelet count as well as coagulation studies. Renal function should be evaluated and urinalysis conducted because of the possibility of pulmonary-renal syndromes presenting with hemoptysis. The documentation of acute renal insufficiency or the detection of red blood cells or their casts on urinalysis should elevate suspicion of small-vessel vasculitis, and studies such as antineutrophil cytoplasmic antibody, antiglomerular basement membrane antibody, and antinuclear antibody should be considered. If a patient is producing sputum, Gram's and acid-fast staining as well as culture should be undertaken.

If all of these studies are unrevealing, bronchoscopy should be considered. In any patient with a history of cigarette smoking, airway inspection should be part of the evaluation of new-onset hemoptysis as endobronchial lesions are not reliably visualized on CT.

TREATMENT Hemoptysis

For the most part, the treatment of hemoptysis varies with its etiology. However, large-volume, life-threatening hemoptysis generally requires immediate intervention regardless of the cause. The first step is to establish a patent airway, usually by endotracheal intubation and subsequent mechanical ventilation. As large-volume hemoptysis usually arises from an airway lesion, it is ideal to identify the site of bleeding by either chest imaging or bronchoscopy (more commonly rigid rather than flexible). The goals are then to isolate the bleeding to one lung and not to allow the preserved airspaces in the other lung to be filled with blood so that gas exchange is further impaired. Patients should be placed with the bleeding lung in a dependent position (i.e., bleeding-side down), and, if possible, dual-lumen endotracheal tubes or an airway blocker should be placed in the proximal airway of the bleeding lung. These interventions generally require the assistance of anesthesiologists, interventional pulmonologists, or thoracic surgeons.

If the bleeding does not stop with treatment of the underlying cause and the passage of time, severe hemoptysis from bronchial arteries can be treated with angiographic embolization of the responsible bronchial artery. This intervention should be entertained only in the most severe and life-threatening cases of hemoptysis because of the risk of unintentional spinal-artery embolization and consequent paraplegia. Endobronchial lesions can be treated with a variety of bronchoscopically directed interventions, including cauterization and laser therapy. In extreme circumstances, surgical resection of the affected region of the lung is considered. Most cases of hemoptysis resolve with treatment of the infection or inflammatory process or with removal of the offending stimulus.

CHAPTER 4

HYPOXIA AND CYANOSIS

Joseph Loscalzo

HYPOXIA

T e fundamental purpose of the cardiorespiratory system is to deliver O_2 and nutrients to cells and to remove CO_2 and other metabolic products from them. Proper maintenance of this function depends not only on intact cardiovascular and respiratory systems, but also on an adequate number of red blood cells and hemoglobin and a supply of inspired gas containing adequate O_2.

RESPONSES TO HYPOXIA

Decreased O_2 availability to cells results in an inhibition of oxidative phosphorylation and increased anaerobic glycolysis. T is switch from aerobic to anaerobic metabolism, the Pasteur effect, maintains some, albeit reduced, adenosine 5′-triphosphate (ATP) production. In severe hypoxia, when ATP production is inadequate to meet the energy requirements of ionic and osmotic equilibrium, cell membrane depolarization leads to uncontrolled Ca^{2+} influx and activation of Ca^{2+}-dependent phospholipases and proteases. T ese events, in turn, cause cell swelling, activation of apoptotic pathways, and, ultimately, cell death.

T e adaptations to hypoxia are mediated, in part, by the upregulation of genes encoding a variety of proteins, including glycolytic enzymes, such as phosphoglycerate kinase and phosphofructokinase, as well as the glucose transporters Glut-1 and Glut-2; and by growth factors, such as vascular endothelial growth factor (VEGF) and erythropoietin, which enhance erythrocyte production. T e hypoxia-induced increase in expression of these key proteins is governed by the hypoxia-sensitive transcription factor, hypoxia-inducible factor-1 (HIF-1).

During hypoxia, systemic arterioles dilate, at least in part, by opening of K_{ATP} channels in vascular smooth-muscle cells due to the hypoxia-induced reduction in ATP concentration. By contrast, in pulmonary vascular smooth-muscle cells, inhibition of K^+ channels causes depolarization which, in turn, activates voltage-gated Ca^{2+} channels raising the cytosolic $[Ca^{2+}]$ and causing smooth-muscle cell contraction. Hypoxia-induced pulmonary arterial constriction shunts blood away from poorly ventilated portions toward better ventilated portions of the lung; however, it also increases pulmonary vascular resistance and right ventricular afterload.

E*ff*ects on the central nervous system

Changes in the central nervous system (CNS), particularly the higher centers, are especially important consequences of hypoxia. Acute hypoxia causes impaired judgment, motor incoordination, and a clinical picture resembling acute alcohol intoxication. High-altitude illness is characterized by headache secondary to cerebral vasodilation, gastrointestinal symptoms, dizziness, insomnia, fatigue, or somnolence. Pulmonary arterial and sometimes venous constriction causes capillary leakage and high-altitude pulmonary edema (HAPE) **(Chap. 2)**, which intensifies hypoxia, further promoting vasoconstriction. Rarely, high-altitude cerebral edema (HACE) develops, which is manifest by severe headache and papilledema and can cause coma. As hypoxia becomes more severe, the regulatory centers of the brainstem are affected, and death usually results from respiratory failure.

E*ff*ects on the cardiovascular system

Acute hypoxia stimulates the chemoreceptor reflex arc to induce venoconstriction and systemic arterial vasodilation. T ese acute changes are accompanied by transiently increased myocardial contractility, which is followed by depressed myocardial contractility with prolonged hypoxia.

CAUSES OF HYPOXIA

Respiratory hypoxia

When hypoxia occurs from respiratory failure, Pao_2 declines, and when respiratory failure is persistent, the hemoglobin-oxygen (Hb-O_2) dissociation curve is displaced to the right, with greater quantities of O_2 released at any level of tissue Po_2. Arterial hypoxemia, i.e., a reduction of O_2 saturation of arterial blood (Sao_2), and consequent cyanosis are likely to be more marked when such depression of Pao_2 results from pulmonary disease than when the depression occurs as the result of a decline in the fraction of oxygen in inspired air (Fio_2). In this latter situation, $Paco_2$ falls secondary to anoxia-induced hyperventilation and the Hb-O_2 dissociation curve is displaced to the left, limiting the decline in Sao_2 at any level of Pao_2.

The most common cause of respiratory hypoxia is ventilation-perfusion mismatch resulting from perfusion of poorly ventilated alveoli. Respiratory hypoxemia may also be caused by hypoventilation, in which case it is associated with an elevation of $Paco_2$ **(Chap. 5)**. These two forms of respiratory hypoxia are usually correctable by inspiring 100% O_2 for several minutes. A third cause of respiratory hypoxia is shunting of blood across the lung from the pulmonary arterial to the venous bed (intrapulmonary right-to-left shunting) by perfusion of nonventilated portions of the lung, as in pulmonary atelectasis or through pulmonary arteriovenous connections. The low Pao_2 in this situation is only partially corrected by an Fio_2 of 100%.

Hypoxia secondary to high altitude

As one ascends rapidly to 3000 m (~10,000 ft), the reduction of the O_2 content of inspired air (Fio_2) leads to a decrease in alveolar Po_2 to approximately 60 mmHg, and a condition termed high-altitude illness develops (see above). At higher altitudes, arterial saturation declines rapidly and symptoms become more serious; and at 5000 m, unacclimated individuals usually cease to be able to function normally owing to the changes in CNS function described above.

Hypoxia secondary to right-to-left extrapulmonary shunting

From a physiologic viewpoint, this cause of hypoxia resembles intrapulmonary right-to-left shunting but is caused by congenital cardiac malformations, such as tetralogy of Fallot, transposition of the great arteries, and Eisenmenger's syndrome. As in pulmonary right-to-left shunting, the Pao_2 cannot be restored to normal with inspiration of 100% O_2.

Anemic hypoxia

A reduction in hemoglobin concentration of the blood is accompanied by a corresponding decline in the O_2-carrying capacity of the blood. Although the Pao_2 is normal in anemic hypoxia, the absolute quantity of O_2 transported per unit volume of blood is diminished. As the anemic blood passes through the capillaries and the usual quantity of O_2 is removed from it, the Po_2 and saturation in the venous blood decline to a greater extent than normal.

Carbon monoxide (CO) intoxication

Hemoglobin that binds with CO (carboxy-hemoglobin, COHb) is unavailable for O_2 transport. In addition, the presence of COHb shifts the Hb-O_2 dissociation curve to the left so that O_2 is unloaded only at lower tensions, further contributing to tissue hypoxia.

Circulatory hypoxia

As in anemic hypoxia, the Pao_2 is usually normal, but venous and tissue Po_2 values are reduced as a consequence of reduced tissue perfusion and greater tissue O_2 extraction. This pathophysiology leads to an increased arterial-mixed venous O_2 difference (a-v-O_2 difference), or gradient. Generalized circulatory hypoxia occurs in heart failure and in most forms of shock **(Chap. 29)**.

Specific organ hypoxia

Localized circulatory hypoxia may occur as a result of decreased perfusion secondary to arterial obstruction, as in localized atherosclerosis in any vascular bed, or as a consequence of vasoconstriction, as observed in Raynaud's phenomenon. Localized hypoxia may also result from venous obstruction and the resultant expansion of interstitial fluid causing arteriolar compression and, thereby, reduction of arterial inflow. Edema, which increases the distance through which O_2 must diffuse before it reaches cells, can also cause localized hypoxia. In an attempt to maintain adequate perfusion to more vital organs in patients with reduced cardiac output secondary to heart failure or hypovolemic shock, vasoconstriction may reduce perfusion in the limbs and skin, causing hypoxia of these regions.

Increased O_2 requirements

If the O_2 consumption of tissues is elevated without a corresponding increase in perfusion, tissue hypoxia ensues and the Po_2 in venous blood declines.

Ordinarily, the clinical picture of patients with hypoxia due to an elevated metabolic rate, as in fever or thyrotoxicosis, is quite different from that in other types of hypoxia: the skin is warm and flushed owing to increased cutaneous blood flow that dissipates the excessive heat produced, and cyanosis is usually absent.

Exercise is a classic example of increased tissue O_2 requirements. T ese increased demands are normally met by several mechanisms operating simultaneously: (1) increase in the cardiac output and ventilation and, thus, O_2 delivery to the tissues; (2) a preferential shift in blood flow to the exercising muscles by changing vascular resistances in the circulatory beds of exercising tissues, directly and/or reflexly; (3) an increase in O_2 extraction from the delivered blood and a widening of the arteriovenous O_2 difference; and (4) a reduction in the pH of the tissues and capillary blood, shifting the Hb-O_2 curve to the right, and unloading more O_2 from hemoglobin. If the capacity of these mechanisms is exceeded, then hypoxia, especially of the exercising muscles, will result.

Improper oxygen utilization

Cyanide and several other similarly acting poisons cause cellular hypoxia. T e tissues are unable to use O_2, and, as a consequence, the venous blood tends to have a high O_2 tension. T is condition has been termed histotoxic hypoxia.

ADAPTATION TO HYPOXIA

An important component of the respiratory response to hypoxia originates in special chemosensitive cells in the carotid and aortic bodies and in the respiratory center in the brainstem. T e stimulation of these cells by hypoxia increases ventilation, with a loss of CO_2, and can lead to respiratory alkalosis. When combined with the metabolic acidosis resulting from the production of lactic acid, the serum bicarbonate level declines **(Chap. 40)**.

With the reduction of Pao_2, cerebrovascular resistance decreases and cerebral blood flow increases in an attempt to maintain O_2 delivery to the brain. However, when the reduction of Pao_2 is accompanied by hyperventilation and a reduction of $Paco_2$, cerebrovascular resistance rises, cerebral blood flow falls, and tissue hypoxia intensifies.

T e diffuse, systemic vasodilation that occurs in generalized hypoxia increases the cardiac output. In patients with underlying heart disease, the requirements of peripheral tissues for an increase of cardiac output with hypoxia may precipitate congestive heart failure. In patients with ischemic heart disease, a reduced Pao_2 may intensify myocardial ischemia and further impair left ventricular function.

One of the important compensatory mechanisms for chronic hypoxia is an increase in the hemoglobin concentration and in the number of red blood cells in the circulating blood, i.e., the development of polycythemia secondary to erythropoietin production. In persons with chronic hypoxemia secondary to prolonged residence at a high altitude (>13,000 ft, 4200 m), a condition termed chronic mountain sickness develops. T is disorder is characterized by a blunted respiratory drive, reduced ventilation, erythrocytosis, cyanosis, weakness, right ventricular enlargement secondary to pulmonary hypertension, and even stupor.

CYANOSIS

Cyanosis refers to a bluish color of the skin and mucous membranes resulting from an increased quantity of reduced hemoglobin (i.e., deoxygenated hemoglobin) or of hemoglobin derivatives (e.g., methemoglobin or sulfhemoglobin) in the small blood vessels of those tissues. It is usually most marked in the lips, nail beds, ears, and malar eminences. Cyanosis, especially if developed recently, is more commonly detected by a family member than the patient. T e florid skin characteristic of polycythemia vera must be distinguished from the true cyanosis discussed here. A cherry-colored flush, rather than cyanosis, is caused by COHb.

T e degree of cyanosis is modified by the color of the cutaneous pigment and the thickness of the skin, as well as by the state of the cutaneous capillaries. T e accurate clinical detection of the presence and degree of cyanosis is dif cult, as proved by oximetric studies. In some instances, central cyanosis can be detected reliably when the Sao_2 has fallen to 85%; in others, particularly in dark-skinned persons, it may not be detected until it has declined to 75%. In the latter case, examination of the mucous membranes in the oral cavity and the conjunctivae rather than examination of the skin is more helpful in the detection of cyanosis.

T e increase in the quantity of reduced hemoglobin in the mucocutaneous vessels that produces cyanosis may be brought about either by an increase in the quantity of venous blood as a result of dilation of the venules (including precapillary venules) or by a reduction in the Sao_2 in the capillary blood. In general, cyanosis becomes apparent when the concentration of reduced hemoglobin in capillary blood exceeds 40 g/L (4 g/dL).

It is the absolute, rather than the relative, quantity of reduced hemoglobin that is important in producing cyanosis. T us, in a patient with severe anemia, the relative quantity of reduced hemoglobin in the venous blood may be very large when considered in relation to the total quantity of hemoglobin in the blood. However,