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■ ■DIAGNOSTIC STUDIES Laboratory studies for initial evaluation should include a complete blood count, coagulation studies, basic metabolic panel, and urinalysis (to evaluate for pulmonary-renal disease). The absence of anemia in lifethreatening hemoptysis is not uncommon, as asphyxiation can occur without large blood volume loss. Infectious workup (including bacterial sputum culture, acid-fast bacillus culture, and respiratory viral panel) and serologic workup (including antinuclear antibody, antineutrophilic cytoplasmic antibody, and anti-GBM) can be obtained if indicated.

Imaging of the chest is essential. While a chest radiograph is often first obtained, aside from large masses, it often does not localize the site and can be normal. In most patients without risk factors for malignancy or other abnormalities in the initial evaluation and with a normal chest radiograph, treating for bronchitis and ensuring close follow-up is a reasonable strategy, with further diagnostic workup. PART 2 Cardinal Manifestations and Presentation of Diseases In contrast, patients with risk factors for malignancy (i.e., age >40, especially those with risk factors for malignancy or significant hemoptysis) should have a chest computed tomography (CT). A chest CT identifies the site and cause of hemoptysis in the majority of patients. A CT angiogram can be considered to identify a source for possible embolization if needed. A diagnostic bronchoscopy can be a complementary study performed to evaluate for subtle mucosal lesions that are often missed on CT scans, perform interventions as per below, or localize the general location and laterality of bleeding. This is best performed during an acute episode of hemoptysis to increase the yield. ■ ■INTERVENTIONS When the amount of hemoptysis is life-threatening, there are three simultaneous goals: first, protect the nonbleeding lung; second, locate the site of bleeding; and third, control the bleeding. Protecting the airway and nonbleeding lung is paramount in the management of life-threatening hemoptysis because asphyxiation can happen quickly. If the side of bleeding is known, the patient should be positioned with the bleeding side down to use gravitational advantage to keep blood out of the nonbleeding lung. A strong cough reflex can often be highly effective at clearing clot from the airway, but intubation is sometimes necessary if the patient cannot protect their airway. Intubation with a large endotracheal tube (size 8.5) is preferred to allow for suctioning and interventions. If needed, this can be advanced into the mainstem airway of the nonbleeding lung for isolation. Double-lumen endotracheal tubes can also be used, but the lumen of each is often too small for suctioning and therapeutic interventions. Imaging obtained during initial evaluation can indicate the source of the bleeding. Flexible bronchoscopy during active bleeding is most useful. Even if a bleeding lesion is not identified, flexible bronchoscopy can help identify a side and lobe. Finally, proceeding directly to CT angiography is also a reasonable strategy given that it has both diag

nostic and therapeutic capabilities. Controlling the bleeding during an episode of life-threatening hemoptysis can be accomplished in one of three ways: from the airway lumen, from the involved blood vessel, or by surgical resection of both airway and vessel involved. Any known bleeding diathesis should be corrected first. As above, bronchoscopic measures can often be diagnostic, but also therapeutic if the bleeding is from a central airway lesion. Initially, a flexible bronchoscope can be used to help stabilize a patient via suctioning clot and insertion of a balloon catheter or bronchial blocker to occlude the involved airway. Additionally, instillation of iced saline or epinephrine can help temporize bleeding. Tranexamic acid (TXA), an antifibrinolytic agent (500 mg/5 mL), can be instilled during bronchoscopy or administered via nebulizer. Rigid bronchoscopy, done by an interventional pulmonologist or thoracic surgeon, allows therapeutic interventions of bleeding airway lesions such as argon plasma coagulation and cautery, which can be definitive. However, because most life-threatening cases of hemoptysis arise from the bronchial circulation, bronchial artery embolization is the procedure of choice for control of the bleeding. It is generally successful in the short term, with >80% success rate at controlling bleeding immediately, although bleeding can recur if the underlying disease (e.g., a mycetoma) is not treated. Surgical resection has a high mortality rate (up to

15–40%) and should not be pursued unless initial measures have failed and bleeding is ongoing. Ideal candidates for surgery have localized disease but otherwise normal lung parenchyma. Acknowledgment Anna K. Brady and Patricia A. Kritek contributed to this chapter in the 20th edition and some material from that chapter has been retained here. ■ ■ FURTHER READING Bellam BL et al: Efficacy of tranexamic acid in haemoptysis: A randomized, controlled pilot study. *Pulm Pharmacol Ther* 40:80, 2016. Davidson K, Shojaee S: Managing massive hemoptysis. *Chest* 157:77, 2020. Flume PA et al: CF pulmonary guidelines. *Pulmonary complications: Hemoptysis and pneumothorax*. *Am J Respir Crit Care Med* 182:298, 2010. Layden JE et al: Pulmonary illness related to e-cigarette use in Illinois and Wisconsin—final report. *N Engl J Med* 382:903, 2020. Lim RK et al: Evaluating hemoptysis hospitalizations among patients with bronchiectasis in the United States: A population-based cohort study. *BMC Pulm Med* 21:392, 2021. Mondoni M et al: Observational, multicentre study on the epidemiology of haemoptysis. *Eur Resp J* 51:1701813, 2018. Mondoni M et al: Bronchoscopy to assess patients with hemoptysis: Which is the optimal timing? *BMC Pulm Med* 19:36, 2019. Joseph Loscalzo

Hypoxia and Cyanosis HYPOXIA The fundamental purpose of the cardiorespiratory system is to deliver O₂ and nutrients to cells and to remove CO₂ 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 O₂. ■ ■ RESPONSES TO HYPOXIA Decreased O₂ availability to cells typically results in an inhibition of oxidative phosphorylation and increased anaerobic glycolysis. This switch from aerobic to anaerobic metabolism, the Pasteur effect, reduces the yield of adenosine 5'-triphosphate (ATP) produced per mole of glucose. In severe hypoxia, when ATP production is inadequate to meet the energy requirements of ionic and osmotic equilibrium, cell membrane depolarization leads to uncontrolled Ca²⁺ influx and activation of Ca²⁺-dependent phospholipases and proteases. These events, in turn, cause cell swelling, activation of apoptotic pathways, and, ultimately, cell death. The 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. The hypoxia-induced increase in expression of these and other key proteins is largely 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 KATP 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 Ca²⁺ channels, raising the cytosolic [Ca²⁺] 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 (i.e., improves ventilation-perfusion mismatch); however, it also increases pulmonary vascular resistance and right ventricular afterload. Effects on the Central Nervous System Changes in the central nervous system (CNS) function, 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. 39), 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. Effects on the Cardiovascular System Acute hypoxia stimulates the chemoreceptor reflex arc to induce vasoconstriction and systemic arterial vasodilation. These 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, Pao₂ declines, and when respiratory failure is persistent, the hemoglobin-oxygen (Hb-O₂) dissociation curve (see Fig. 103-2) is displaced to the right, with greater quantities of O₂ released at any level of tissue Po₂. Arterial hypoxemia, that is, a reduction of O₂ saturation of arterial blood (Sao₂), and consequent cyanosis are likely to be more marked when such depression of Pao₂ results from pulmonary disease than when the depression occurs as the result of a decline in the fraction of oxygen in inspired air (Fio₂). In this latter situation, Paco₂ falls secondary to anoxia-induced hyperventilation and the Hb-O₂ dissociation curve is displaced to the left, limiting the decline in Sao₂ at any level of Pao₂. 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 Paco₂ (Chap. 296). These two forms of respiratory hypoxia are usually correctable by inspiring 100% O₂ 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 Pao₂ in this situation is only partially corrected by an Fio₂ of 100%. Hypoxia Secondary to High Altitude As one ascends rapidly to 3000 m (~10,000 ft), the reduction of the O₂ content of inspired air (Fio₂) leads to a decrease in alveolar Po₂ to ~60 mmHg, and a condition termed high-altitude illness develops (see above). At higher altitudes, arterial saturation declines rapidly and symptoms become more severe; 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, atrial or ventricular septal defect, patent ductus arteriosus, and Eisenmenger's syndrome (Chap. 280). As in pulmonary right-to-left shunting, the P_{aO_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 P_{aO_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 P_{o_2} and saturation in the venous blood decline to a greater extent than normal.

Carbon Monoxide (CO) Intoxication (See also Chap. 476) Hemoglobin that binds 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 (see Fig. 103-2) so that O_2 is unloaded only at lower tensions, further contributing to tissue hypoxia.

Hypoxia and Cyanosis CHAPTER 42 Circulatory Hypoxia As in anemic hypoxia, the P_{aO_2} is usually normal, but venous and tissue P_{o_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 (Chap. 264) and in most forms of shock (Chap. 314). 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 (Chap. 292). 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 P_{o_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. These increased demands are normally met by several mechanisms operating simultaneously: (1) an 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 (see Fig. 103-2) and thereby 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 (Chap. 470) and several other similarly acting poisons cause cellular hypoxia by impairing electron transport in mitochondria, thereby limiting oxidative phosphorylation and ATP production. The

tissues are unable to use O₂, and as a consequence, the venous blood tends to have a high O₂ tension. This 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. The stimulation of these cells by hypoxia increases ventilation, with a loss of CO₂, 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. 58).

With the reduction of Pao₂, cerebrovascular resistance decreases and cerebral blood flow increases in an attempt to maintain O₂ delivery to the brain. However, when the reduction of Pao₂ is accompanied by hyperventilation and a reduction of Paco₂, cerebrovascular resistance rises, cerebral blood flow falls, and tissue hypoxia intensifies.

The 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 Pao₂ 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, that is, the development of polycythemia induced by erythropoietin production (Chap. 108). 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. This disorder is characterized by a blunted respiratory drive, reduced ventilation, erythrocytosis, cyanosis, weakness, right ventricular enlargement secondary to pulmonary hypertension, and even stupor. PART 2 Cardinal Manifestations and Presentation of Diseases 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., met hemoglobin 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. A cherry-colored flush, rather than cyanosis, is caused by COHb (Chap. 470). The 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. The accurate clinical detection of the presence and degree of cyanosis is difficult, as proved by oximetric studies. In some instances, central cyanosis can be detected reliably when the Sao₂ 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. The 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 Sao₂ 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. Thus, 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, since the concentration of the latter is markedly reduced, the absolute quantity of reduced hemoglobin may still be low, and

therefore, patients with severe anemia and even marked arterial desaturation may not display cyanosis. Conversely, the higher the total hemoglobin content, the greater is the tendency toward cyanosis; thus, patients with marked polycythemia tend to be cyanotic at higher levels of SaO_2 than patients with normal hematocrit values. Likewise, local passive congestion, which causes an increase in the total quantity of reduced hemoglobin in the vessels in a given area, may cause cyanosis. Cyanosis is also observed when nonfunctional hemoglobin, such as methemoglobin (consequential or acquired) or sulfhemoglobin (Chap. 103), is present in blood. Cyanosis may be subdivided into central and peripheral types. In central cyanosis, the SaO_2 is reduced or an abnormal hemoglobin derivative is present, and the mucous membranes and skin are both affected. Peripheral cyanosis is due to a slowing of blood flow and abnormally great extraction of O_2 from normally saturated arterial blood; it results

from vasoconstriction and diminished peripheral blood flow, such as occurs in cold exposure, shock, congestive failure, and peripheral vascular disease. Often in these conditions, the mucous membranes of the oral cavity, including the sublingual mucosa, may be spared. Clinical differentiation between central and peripheral cyanosis may not always be straightforward, and in conditions such as cardiogenic shock with pulmonary edema, there may be a mixture of both types. ■ ■ DIFFERENTIAL DIAGNOSIS Central Cyanosis (Table 42-1) Decreased SaO_2 results from a marked reduction in the Pao_2 . This reduction may be brought about by a decline in the Fio_2 without sufficient compensatory alveolar hyperventilation to maintain alveolar PO_2 . Cyanosis usually becomes manifest in an ascent to an altitude of 4000 m (13,000 ft). Seriously impaired pulmonary function, through perfusion of unventilated or poorly ventilated areas of the lung or alveolar hypoventilation, is a common cause of central cyanosis (Chap. 296). This condition may occur acutely, as in extensive pneumonia or pulmonary edema, or chronically, with chronic pulmonary diseases (e.g., emphysema). In the latter situation, secondary polycythemia is generally present and clubbing of the fingers (see below) may occur. Another cause of reduced SaO_2 is shunting of systemic venous blood into the arterial circuit. Certain forms of congenital heart disease are associated with cyanosis on this basis (see above and Chap. 280). Pulmonary arteriovenous fistulae may be congenital or acquired, solitary or multiple, and microscopic or massive. The severity of cyanosis produced by these fistulae depends on their size and number. They occur with some frequency in hereditary hemorrhagic telangiectasia. SaO_2 reduction and cyanosis may also occur in some patients with cirrhosis, presumably as a consequence of pulmonary arteriovenous fistulae or portal vein–pulmonary vein anastomoses. In patients with cardiac or pulmonary right-to-left shunts, the presence and severity of cyanosis depend on the size of the shunt relative to the systemic flow and on the Hb- O_2 saturation of the venous blood. With increased extraction of O_2 from the blood by the exercising muscles, the venous blood returning to the right side of the heart is more unsaturated than at rest, and shunting of this blood intensifies the cyanosis. Secondary polycythemia occurs frequently in patients in this setting and contributes to the cyanosis. TABLE 42-1 Causes of Cyanosis Central Cyanosis Decreased arterial oxygen saturation Decreased atmospheric pressure—high altitude Impaired pulmonary function Alveolar hypoventilation Inhomogeneity in pulmonary ventilation and perfusion (perfusion of hypoventilated alveoli) Impaired oxygen diffusion Anatomic shunts Certain types of congenital heart disease Pulmonary arteriovenous fistulas Multiple small intrapulmonary shunts Hemoglobin with low affinity for oxygen Hemoglobin abnormalities Methemoglobinemia—hereditary, acquired Sulfhemoglobinemia—acquired Carboxyhemoglobinemia (not true cyanosis) Peripheral Cyanosis Reduced cardiac output Cold exposure Redistribution of blood flow from extremities Arterial obstruction Venous obstruction

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