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.

49 Hypoxia and Cyanosis

Joseph Loscalzo

HYPOXIA

The 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. This 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. 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 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.

Effects 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. 47e), 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 venoconstriction 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, Pao_2 declines, and when respiratory failure is persistent, the hemoglobin-oxygen (Hb-O_2) dissociation curve (see Fig. 127-2) 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. 306e). These two forms of respiratory hypoxia are usually correctable by