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The Pharmacological Basis of
THERAPEUTICS

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venous blood falls significantly. At the extreme of low V/Q ratios, there is no ventilation to a perfused region, and a pure shunt results; thus the blood leaving the region has the same low \( P_{\text{O}_2} \) and high \( P_{\text{CO}_2} \) as mixed venous blood.

The deleterious effect of V/Q mismatch on arterial oxygenation is a direct result of the asymmetry of the oxyhemoglobin dissociation curve. Adding supplemental oxygen generally will make up for the fall in \( P_{\text{O}_2} \) in low V/Q units and thereby improve arterial oxygenation. However, since there is no ventilation to units with pure shunt, supplemental oxygen will not be effective in reversing hypoxemia from this cause. Because of the steep oxyhemoglobin dissociation curve at low \( P_{\text{O}_2} \), even moderate amounts of pure shunt will cause significant hypoxemia despite oxygen therapy (Figure 15-2). For the same reason, factors that decrease mixed venous \( P_{\text{O}_2} \), such as decreased cardiac output or increased oxygen consumption, enhance the hypoxic effects of V/Q mismatch and shunt.

**Nonpulmonary Causes of Hypoxia.** In addition to failure of the respiratory system to oxygenate the blood adequately, a number of other factors can contribute to hypoxia at the tissue level. These may be divided into categories of oxygen delivery and oxygen utilization. Oxygen delivery decreases globally when cardiac output falls or locally when regional blood flow is compromised, such as from a vascular occlusion (e.g., stenosis, thrombosis, or microvascular occlusion) or increased downstream pressure (e.g., compartment syndrome, venous stasis, or venous hypertension). Decreased oxygen-carrying capacity of the blood likewise will reduce oxygen delivery, such as occurs with anemia, carbon monoxide poisoning, or hemoglobinopathy. Finally, hypoxia may occur when transport of oxygen from the capillaries to the tissues is decreased (edema) or utilization of the oxygen by the cells is impaired (cytotoxicity).

**Effects of Hypoxia.** There has been a considerable increase in our understanding of the cellular and biochemical changes that occur after acute and chronic hypoxia. Regardless of the cause, hypoxia produces a marked alteration in gene expression, mediated in part by hypoxia-inducible factor-1 \( \alpha \) (Semenza, 2003). Ultimately, hypoxia results in the cessation of aerobic metabolism, exhaustion of high-energy intracellular stores, cellular dysfunction, and death. The time course of cellular demise depends on the tissue’s relative metabolic requirements, oxygen energy stores, and anaerobic capacity. Survival times (time from the onset of circulatory arrest to significant organ dysfunction) range from 1 minute in the cerebral cortex to around 5 minutes in the heart and 10 minutes in the kidneys and liver, with the potential for some degree of recovery if reperfused. Revival times (the duration hypoxia beyond which recovery is no longer possible) are approximately four to five times longer. Less severe degrees of hypoxia have progressive physiological effects on different organ systems (Nunn, 2000b).

**Respiratory System.** Hypoxia stimulates the carotid and aortic baroreceptors to cause increases in both the rate and depth of ventilation. Minute volume almost doubles when normal individuals inspire gas with a \( P_{\text{O}_2} \) of 6.6 kPa (50 mmHg). Dyspnea is not always experienced with simple hypoxia but occurs when the respiratory minute volume approximates half the maximal breathing capacity; this may occur with minimum exertion in patients with minimal breathing capacity is reduced by lung disease. In general, little warning precedes the loss of consciousness resulting from hypoxia.

**Cardiovascular System.** Hypoxia causes reflex activation of the sympathetic nervous system via both autonomic and humoral mechanisms, resulting in tachycardia and increased cardiac output. Peripheral vascular resistance however, decreases primarily via local autoregulation.
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gases should be used when prolonged therapy (>1 hour) is needed. Finally, any oxygen-enriched atmosphere constitutes a fire hazard, and appropriate precautions must be taken both in the operating room and for patients on oxygen at home.

It is important to realize that hypoxemia still can occur despite administration of supplemental oxygen. Furthermore, when supplemental oxygen is administered, desaturation occurs at a later time after airway obstruction or hyperventilation, potentially delaying the treatment of these critical events. Therefore, whether or not oxygen administered to a patient at risk for these problems, it is essential to both oxygen saturation and adequacy of ventilation be assessed frequently.

Therapeutic Uses of Oxygen

Correction of Hypoxia. As stated earlier, the primary therapeutic use of oxygen is to correct hypoxia. However, hypoxia is most commonly the result of an underlying disease, and administration of oxygen should be viewed as a symptomatic or temporizing therapy. Oxygen must be directed at correcting the cause of the hypoxia. For example, airway obstruction is unlikely to respond to an increase in inspired oxygen tension without relief of the obstruction. More important, while hypoxemia owing to hyperventilation after a narcotic overdose can be improved with supplemental oxygen administration, the patient remains at risk for respiratory failure if ventilation is not increased through stimulation, narcotic reversal, or mechanical ventilation. The hypoxia that results from most pulmonary diseases can be alleviated at least partially by administration of oxygen, thereby providing time for definitive therapy to reverse the primary process. This administration of oxygen is a basic and important treatment to be used in all forms of hypoxia, with the understanding that the response will vary in a way that generally is predictable from knowledge of the underlying pathophysiological processes.

Reduction of Partial Pressure of an Inert Gas. Since nitrogen constitutes 79% of ambient air, it is also the predominant gas in gas-filled spaces in the body. In certain situations, such as with air embolization from obstruction or ileus, in vivo air embolization, it is desirable to reduce the volume of these gas-filled spaces. Since nitrogen is relatively insoluble, inhalation of high concentrations of oxygen (and thus low concentrations of nitrogen) rapidly lowers the total-body partial pressure of nitrogen and provides a substantial gradient for the removal of nitrogen from gas spaces. Administration of oxygen for air embolism is additionally beneficial because it also helps to relieve the localized hypoxia distal to the embolic vascular obstruction. In the case of decompression sickness, or bends, lowering of inert gas tension in blood and tissues by oxygen inhalation prior to or during a barometric decompression can reduce the degree of supersaturation that occurs after decompression so that bubbles do not form. If bubbles do form in either the tissues or the vasculature, administration of oxygen is based on the same rationale as that described for gas embolism.

Hyperbaric Oxygen Therapy. Oxygen is administered at greater than atmospheric pressure for a number of conditions when 100% oxygen at 1 atm is insufficient. In extreme cases when supplemental oxygen is insufficient, even higher pressures are required to avoid compromising venous oxygenation. For this purpose, an oxygen-enriched atmosphere constitutes a fire hazard, and appropriate precautions must be taken both in the operating room and for patients on oxygen at home.

In general, these conditions are associated with acute and chronic hypoxia that is unresponsive to traditional therapy. Oxygen is used in cellular energy production and is crucial for cellular metabolism. However, oxygen also may have deleterious actions at the cellular level. Oxygen toxicity probably results from increased production of hydrogen peroxide and reactive agents such as superoxide anion, singlet oxygen, and hydroxyl radicals (Carravay and Piantadosi, 1999) that attack and damage lipids, proteins, and other macromolecules, especially those in biological mem-