Goodman & Gilman's The Pharmacological Basis of THERAPEUTICS

eleventh edition

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venous blood falls significantly. At the extreme of low $\dot{V}/\dot{Q}$ 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_{O_2} and high $P_{A_{CO_2}}$ as mixed venous blood.

The deleterious effect of $\dot{V}/\dot{Q}$ 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 $P_{A_{O_2}}$ in low $\dot{V}/\dot{Q}$ 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_{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_{O_2}, such as decreased cardiac output or increased oxygen consumption, enhance the hypoxemic effects of $\dot{V}/\dot{Q}$ 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 (cyanide toxicity).

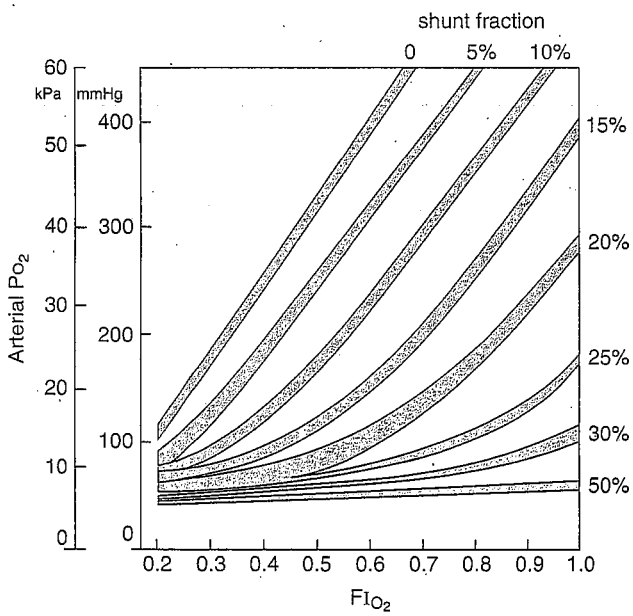

Figure 15–2. *Effect of shunt on arterial oxygenation.* The iso-shunt diagram shows the effect of changing inspired oxygen concentration on arterial oxygenation in the presence of different amounts of pure shunt. As shunt fraction increases, even an inspired oxygen fraction ($F_{I_{O_2}}$) of 1.0 is ineffective at increasing the arterial P_{O_2}. This estimation assumes hemoglobin (Hb) from 10 to 14 g/dl, arterial P_{CO_2} of 3.3 to 5.3 kPa (25 to 40 mmHg), and an arterial–venous (a–v) O_2 content difference of 5 ml/100 ml. Redrawn from Benatar *et al.*, 1973, with permission.

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-1α (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 and energy stores, and anaerobic capacity. Survival times (the 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 of 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_{O_2} of 6.6 kPa (50 mmHg). Dyspnea is not always experienced with simple hypoxia but occurs when the respiratory minute volume approaches half the maximal breathing capacity; this may occur with minimum exertion in patients in whom maximal 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 autoregulatory

gen thus should be used when prolonged therapy (>1 hour) is required. 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 the administration of supplemental oxygen. Furthermore, when supplemental oxygen is administered, desaturation occurs at a later time after airway obstruction or hypoventilation, potentially delaying the detection of these critical events. Therefore, whether or not oxygen is administered to a patient at risk for these problems, it is essential that 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 a manifestation of an underlying disease, and administration of oxygen thus should be viewed as a symptomatic or temporizing therapy. Efforts 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 hypoventilation 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 allowing time for definitive therapy to reverse the primary process. Thus, 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 some 79% of ambient air, it also is the predominant gas in most gas-filled spaces in the body. In certain situations, such as bowel distension from obstruction or ileus, intravascular air embolism, or pneumothorax, it is desirable to reduce the volume of these air-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 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 (Buras, 2000; Shank and Muth, 2000; Myers, 2000). To achieve concentrations of greater than 1 atm, a hyperbaric chamber must be used. These chambers range from small, single-person units to multiroom establishments that may include complex medical equipment. Smaller, one-person chambers typically are pressurized with oxygen, whereas larger ones are pressurized with air, and a patient must wear a mask to receive the oxygen at the increased pressure. The larger chambers are more suitable for critically ill patients who require ventilation, monitoring, and constant attendance. Any chamber must be built to withstand pressures that may range from 200 to 600 kPa (2 to 6 atm), although inhaled oxygen tension that exceeds 300 kPa (3 atm) rarely is used (*see* Oxygen Toxicity, below).

Hyperbaric oxygen therapy has two components: increased hydrostatic pressure and increased oxygen pressure. Both factors are necessary for the treatment of decompression sickness and air embolism. The hydrostatic pressure reduces bubble volume, and the absence of inspired nitrogen increases the gradient for elimination of nitrogen and reduces hypoxia in downstream tissues. Increased oxygen pressure at the tissue level is the primary therapeutic goal for most of the other indications for hyperbaric oxygen. For example, even a small increase in P_{O_2} in previously ischemic areas may enhance the bactericidal activity of leukocytes and increase angiogenesis. Thus, repetitive brief exposures to hyperbaric oxygen are a useful adjunct in the treatment of chronic refractory osteomyelitis, osteoradionecrosis, or crush injury or for the recovery of compromised skin, tissue grafts, or flaps. Furthermore, increased oxygen tension itself can be bacteriostatic; the spread of infection with *Clostridium perfringens* and production of toxin by the bacteria are slowed when oxygen tensions exceed 33 kPa (250 mmHg), justifying the early use of hyperbaric oxygen in clostridial myonecrosis (gas gangrene).

Hyperbaric oxygen also is useful in selected instances of generalized hypoxia. In CO poisoning, hemoglobin (Hb) and myoglobin become unavailable for O_2 binding because of the high affinity of these proteins for CO. This affinity is ~250 times greater than the affinity for O_2; thus, an alveolar concentration of CO = 0.4 mm Hg (1/250th that of alveolar O_2, which is ~100 mm Hg), will compete equally with O_2 for binding sites on Hb. A high P_{O_2} facilitates competition of O_2 for Hb binding sites as CO is exchanged in the alveoli; i.e., the high P_{O_2} increases the probability that O_2 rather than CO will bind to Hb once CO dissociates. In addition, hyperbaric O_2 will increase the availability of dissolved O_2 in the blood (*see* Table 15–1). In a randomized clinical trial (Weaver *et al.*, 2002), hyperbaric oxygen decreased the incidence of long- and short-term neurological sequelae after CO intoxication. The occasional use of hyperbaric oxygen in cyanide poisoning has a similar rationale. Hyperbaric oxygen also may be useful in severe short-term anemia because sufficient oxygen can be dissolved in the plasma at 3 atm to meet metabolic needs. However, such treatment must be limited because oxygen toxicity depends on increased P_{O_2}, not on the oxygen content of the blood.

Hyperbaric oxygen therapy has been used in such diverse conditions as multiple sclerosis, traumatic spinal cord injury, cerebrovascular accidents, bone grafts and fractures, and leprosy; however, data from well-controlled clinical trials are not sufficient to justify these uses.

Oxygen Toxicity

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 (Carraway and Piantadosi, 1999) that attack and damage lipids, proteins, and other macromolecules, especially those in biological mem-