24

Oxygen and Carbon Dioxide Transport

LEARNING OBJECTIVES

Upon completion of this chapter, the student should be able to answer the following questions:

1. What are the basic gas diffusion principles and how do they affect O_2 and CO_2 absorption and expiration?
2. What are the chemical transport mechanisms of O_2 and CO_2 in blood?
3. How do the O_2 and CO_2 dissociation curves differ? How does these differences promote tissue O_2 delivery and CO_2 removal?
4. What is the difference between perfusion limitation and diffusion limitation? Why is the diffusion of O_2 and CO_2 considered to be perfusion limited, and why is CO is considered to be diffusion limited?
5. What is meant by a leftward or rightward shift of the oxyhemoglobin dissociation curve?
6. How do the oxyhemoglobin and carboxyhemoglobin dissociation curves differ? What is the clinical significance of the differences?
7. What is the difference between the chloride shift and the Haldane effect on CO_2 transport?

The respiratory and circulatory systems function together to transport oxygen (O_2) from the lungs to the tissues to sustain normal cellular activity and to transport carbon dioxide (CO_2) from the tissues to the lungs for expiration (Fig. 24.1). To enhance uptake and transport of these gases between the lungs and tissues, specialized mechanisms (e.g., binding of O_2 and hemoglobin and HCO_3^- transport of CO_2) have evolved that enable O_2 uptake and CO_2 expiration to occur simultaneously. To understand the mechanisms involved in the transport of these gases, gas diffusion properties, gas transport, and gas delivery mechanisms must be considered.

Gas Diffusion

Gas movement throughout the respiratory system occurs predominantly via diffusion. The respiratory and circulatory systems contain several unique anatomical and physiological features to facilitate gas diffusion: (1) large surface areas for gas exchange (alveolar to pulmonary capillary bed and end organ capillary bed to tissue) with short distances to travel, (2) substantial partial pressure gradient differences, and (3) gases with advantageous diffusion properties. Transport and delivery of O_2 from the lungs to the tissue and vice versa for CO_2 are dependent on basic gas diffusion laws.

Diffusion of Gases From Regions of Higher to Lower Partial Pressure in the Lungs

The process of gas diffusion is passive and similar whether diffusion occurs in a gaseous or liquid state. The rate of diffusion of a gas through a liquid is described by **Graham's law,** which states that the rate is directly proportional to the solubility coefficient of the gas and inversely proportional to the square root of its molecular weight. Calculation of the diffusion properties for O_2 and CO_2 reveals that CO_2 diffuses approximately 20 times faster than O_2. Rates of O_2 diffusion from the lungs into blood and from blood into tissue, and vice versa for CO_2, are predicted by **Fick's law** of gas diffusion (Fig. 24.2). Fick's law states that gas diffusion across a permeable membrane ($\dot{V}$) is proportional to the diffusion coefficient for the gas (D), the surface area of the membrane (A), and the pressure gradient across the membrane ($P_1 - P_2$). It is inversely proportional to the thickness of the membrane (T). The ratio of surface area (A) x diffusion coefficient (D) to membrane thickness (T) (or A•D/T) represents the conductance of a gas from the alveolus to the blood. The diffusing capacity of the lung (D_L) is its conductance (A•D/T) when considered for the entire lung; thus, with Fick's equation, D_L can be calculated as follows:

Equation 24.1

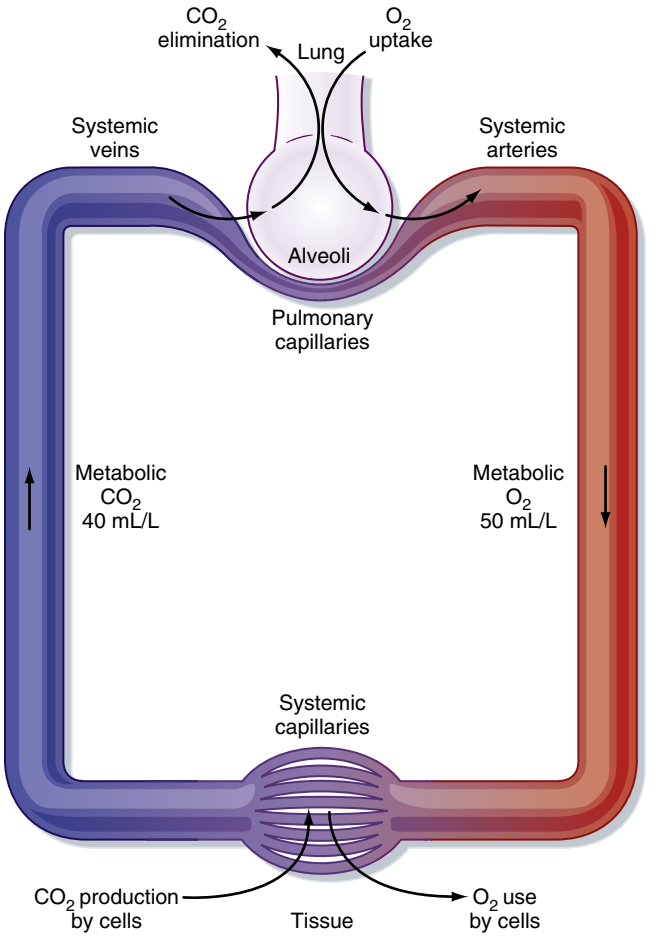
$$\dot{V}_{gas} = A \cdot D \cdot \frac{(P_1 - P_2)}{T}$$

$$\dot{V} = D_L (P_1 - P_2)$$

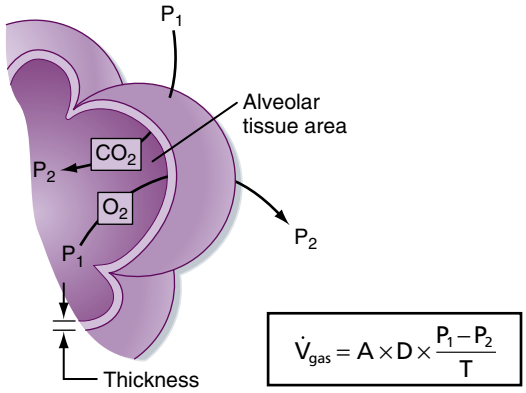
$$D_L = \frac{\dot{V}}{(P_1 - P_2)}$$

where $\dot{V}_{gas}$ = gas diffusion.

Fick's law of diffusion could be used to assess the diffusion properties of O_2 in the lungs, except that the capillary partial pressure of oxygen cannot be measured. This limitation can be overcome with the use of carbon monoxide (CO) rather than O_2. Because CO has low solubility in the capillary membrane, the rate of CO equilibrium across the capillary is slow, and the partial pressure of CO in capillary blood remains close to 0. In contrast, the solubility of CO



• **Fig. 24.1** Oxygen (O_2) and carbon dioxide (CO_2) transport in arterial and venous blood. Oxygen in arterial blood is transferred from arterial capillaries to tissues. The flow rates for O_2 and CO_2 are shown for 1 L of blood.



• **Fig. 24.2** According to Fick's law, diffusion of a gas across a sheet of tissue ($\dot{V}_{gas}$) is directly related to the surface area *(A)* of the tissue, the diffusion constant *(D)* of the specific gas, and the partial pressure difference ($P_1 - P_2$) of the gas on each side of the tissue, and it is inversely related to tissue thickness *(T)*.

in blood is high. Thus, the only limitation for diffusion of CO is the alveolar-capillary membrane, and thus CO is a useful gas for calculating D_L. The capillary partial pressure (P_2 in Eq. 24.1) is essentially 0 for CO, and therefore D_L can be measured from the diffusion of carbon monoxide ($\dot{V}_{CO}$) and the average partial pressure of CO in the alveolus (P_1); that is,

Equation 24.2

$$\dot{V}_{CO} = D_L CO(P_1 - P_2), \text{or}$$

$$D_L CO = \frac{\dot{V}_{CO}}{(P_1 - P_2)}, \text{ and since } P_2 \text{ is essentially zero,}$$

$$D_L CO = \frac{\dot{V}_{CO}}{(P_1)}$$

where $D_L CO$ = diffusion capacity of the lung for carbon monoxide.

Assessment of $D_L CO$ has become a classic measurement of the diffusion barrier of the alveolar-capillary membrane. It is useful in the differential diagnosis of certain obstructive lung diseases, such as emphysema. Although exposure to high levels of carbon monoxide gas can be toxic, in gas diffusion testing the total CO exposure is negligible.

IN THE CLINIC

A patient with interstitial pulmonary fibrosis (a restrictive lung disease) inhales a single breath of 0.3% CO from residual volume to total lung capacity. He holds his breath for 10 seconds and then exhales. After discarding the exhaled gas from the dead space, a representative sample of alveolar gas from late in exhalation is collected. The average alveolar CO pressure is 0.1 mm Hg, and 0.25 mL of CO has been taken up. The diffusion capacity for CO in this patient is

$$D_L = \frac{\dot{V}_{CO}}{P_{ACO}}$$

$$= 0.25 \text{ mL/10 seconds} \times \frac{60 \text{ seconds/minute}}{0.1 \text{ mm Hg}}$$

$$= 15 \text{ mL/minute/mm Hg}$$

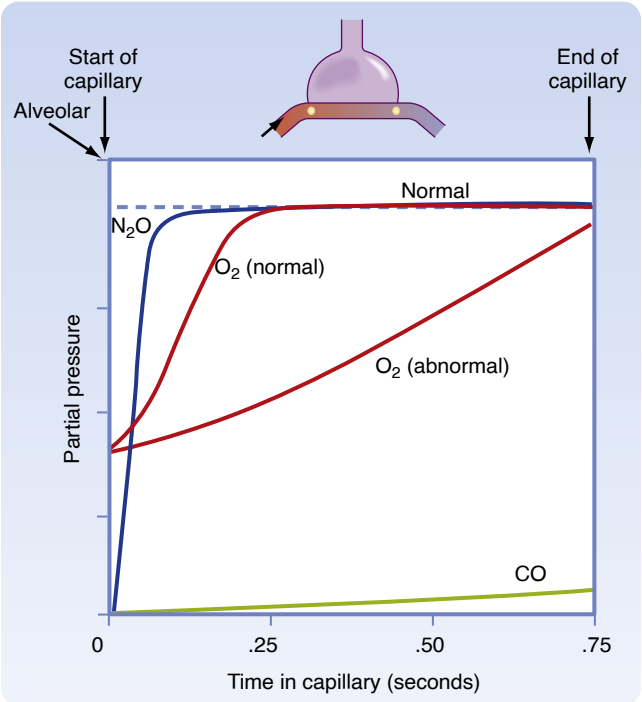
The normal range for $D_L CO$ is 20 to 30 mL/minute/mm Hg. Patients with interstitial pulmonary fibrosis have an initial alveolar inflammatory response with subsequent scar formation within the interstitial space. The inflammation and scar replace the alveoli and decrease the surface area for gas diffusion to occur, which results in decreased $D_L CO$. This is a classic characteristic of certain types of restrictive lung disease.

Oxygen and Carbon Dioxide Exchange in the Lung Is Perfusion Limited

Different gases have different solubility factors. Gases that are insoluble in blood (i.e., anesthetic gases such as nitrous oxide and ether) do not chemically combine with proteins in blood and equilibrate rapidly between alveolar gas and blood. The equilibration occurs in less time than the 0.75 to 1.0 seconds that the red blood cell spends in the capillary bed (the capillary transit time). The diffusion of insoluble gases between alveolar gas and blood is considered **perfusion limited** because the partial pressure of gas in the blood

leaving the capillary has reached equilibrium with alveolar gas and is limited only by the amount of blood perfusing the alveolus. In contrast, a gas that is **diffusion limited,** such as CO, has low solubility in the alveolar-capillary membrane but high solubility in blood because of its high affinity for **hemoglobin** (Hgb). These features prevent the equilibration of CO between alveolar gas and blood during the red blood cell transit time.

The high affinity of CO for Hgb enables large amounts of CO to be taken up in blood with little or no appreciable increase in its partial pressure. Gases that are chemically bound to Hgb do not exert a partial pressure in blood. Like CO, both CO_2 and O_2 have relatively low solubility in the alveolar-capillary membrane but high solubility in blood because of their ability to bind to Hgb. However, their rate of equilibration is sufficiently rapid for complete equilibration to occur during the transit time of the red blood cell within the capillary. Equilibration for O_2 and CO_2 usually occurs within 0.25 seconds. Thus, O_2 and CO_2 transfer is normally perfusion limited. The partial pressure of a gas that is diffusion limited (i.e., CO) does not reach equilibrium with the alveolar pressure over the time that it spends in the capillary (Fig. 24.3). Although CO_2 has a greater rate of diffusion in blood than O_2 does, it has a lower membrane-blood solubility ratio and consequently takes approximately the same amount of time to reach equilibration in blood.



• **Fig. 24.3** Uptake of nitrous oxide (N_2O), carbon monoxide (CO), and O_2 in blood in relation to their partial pressures and the transit time of the red blood cell in the capillary. For gases that are perfusion limited (N_2O and O_2), their partial pressures have equilibrated with alveolar pressure before exiting the capillary. In contrast, the partial pressure of CO, a gas that is diffusion limited, does not reach equilibrium with alveolar pressure. In rare conditions, O_2 uptake can become diffusion limited.

Diffusion limitation for O_2 and CO_2 would occur if red blood cells spent less than 0.25 seconds in the capillary bed. This is occasionally the case in very fit athletes during vigorous exercise and in healthy subjects who exercise at high altitude.

Oxygen Transport

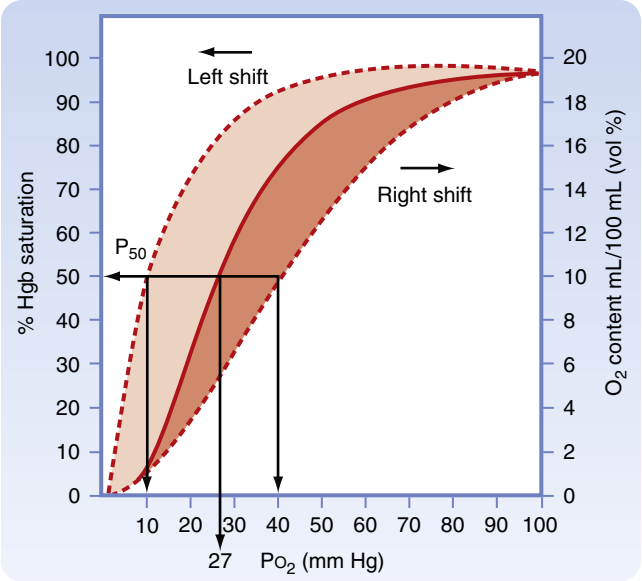
Oxygen is carried in blood in two forms: O_2 dissolved in plasma and O_2 bound to Hgb. The dissolved form is measured clinically in an arterial blood gas sample as the partial pressure of arterial oxygen (Pao_2). Only a small percentage of O_2 in blood is in the dissolved form, and its contribution to O_2 transport under normal conditions is almost negligible. However, dissolved O_2 can become a significant factor in conditions of severe hypoxemia. Binding of O_2 to Hgb to form **oxyhemoglobin** within red blood cells is the primary transport mechanism of O_2. Hgb not bound to O_2 is referred to as *deoxyhemoglobin* or *reduced Hgb.* The O_2-carrying capacity of blood is enhanced about 65 times by its ability to bind to Hgb.

Hemoglobin

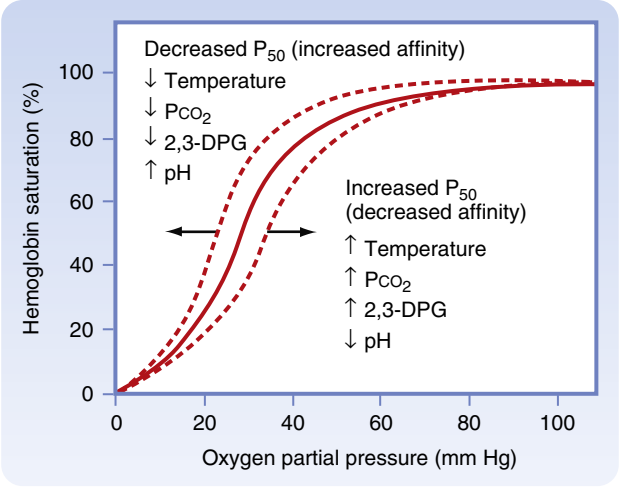
Hgb is the major transport molecule for O_2. The Hgb molecule is a protein with two major components: four nonprotein heme groups, each containing iron in the reduced ferric (Fe^{+++}) form, which is the site of O_2 binding; and a globin portion consisting of four polypeptide chains. Normal adults have two α-globin chains and two β-globin chains (HgbA), whereas children younger than 6 months of age have predominantly fetal Hgb (HgbF), which consists of two α chains and two γ chains. This difference in the structure of HgbF increases its affinity for O_2 and aids in the transport of O_2 across the placenta. In addition, HgbF is not inhibited by 2,3-diphosphoglycerate (2,3-DPG), a product of glycolysis; thus O_2 uptake is further enhanced.

Binding of O_2 to Hgb alters the ability of Hgb to absorb light. This effect of O_2 on Hgb is responsible for the change in color between oxygenated arterial blood (bright red) and deoxygenated venous blood (dark red-bluish). Binding and dissociation of O_2 with Hgb occur in milliseconds, thus facilitating O_2 transport because red blood cells spend only 0.75 seconds in the capillaries. There are approximately 280 million Hgb molecules per red blood cell, which provides an efficient mechanism to transport O_2. Myoglobin, a protein in striated muscle similar in structure and function to Hgb, has only one subunit of the Hgb molecule. It aids in the transfer of O_2 from blood to muscle cells and in the storage of O_2, which is especially critical in O_2-deprived conditions.

Abnormalities of the Hgb molecule occur with mutations in the amino acid sequence (i.e., sickle cell disease) or in the spatial arrangement of the globin polypeptide chains and result in abnormal function. Compounds such as CO, nitrites (nitric oxide), and cyanides can oxidize the iron molecule in the heme group and change it from the reduced ferrous state (Fe^{++}) to the ferric state (Fe^{+++}), which reduces the ability of O_2 to bind to Hgb.



• **Fig. 24.4** Oxyhemoglobin dissociation curve showing the relationship between the partial pressure of oxygen (Po_2) in blood and the percentage of hemoglobin (Hgb)-binding sites that are occupied by oxygen molecules (percentage saturation). Adult hemoglobin (HgbA) is about 50% saturated with oxygen at a Po_2 of 27 mm Hg, 90% saturated at 60 mm Hg, and about 98% saturated at 100 mm Hg. The P_{50} is the partial pressure at which Hgb is 50% saturated with O_2. When the O_2 dissociation curve shifts to the right, P_{50} increases. When the curve shifts to the left, P_{50} decreases.



• **Fig. 24.5** Factors that shift the oxyhemoglobin dissociation curve to the *right* (decreased affinity of Hgb for O_2) or to the *left* (increased affinity). *2,3-DPG*, 2,3-Diphosphoglycerate; *Pco_2*, partial pressure of carbon dioxide.

Oxyhemoglobin Dissociation Curve

In the alveoli, the majority of O_2 in plasma quickly diffuses into red blood cells and chemically binds to Hgb. This process is reversible, so that Hgb quickly gives up its O_2 to tissue through passive diffusion (the concentration of O_2 in Hgb decreases). The oxyhemoglobin dissociation curve illustrates the relationship between Po_2 in blood and the number of O_2 molecules bound to Hgb (Fig. 24.4). The S shape of the curve demonstrates the dependence of Hgb saturation on Po_2, especially at partial pressures lower than 60 mm Hg. The clinical significance of the flat portion of the oxyhemoglobin dissociation curve (>60 mm Hg) is that a drop in Po_2 over a wide range of partial pressures (100–60 mm Hg) has a minimal effect on Hgb saturation, which remains at 90% to 100%, a level sufficient for normal O_2 transport and delivery. The clinical significance of the steep portion (<60 mm Hg) of the curve is that a large amount of O_2 is released from Hgb with only a small change in Po_2, which facilitates the release and diffusion of O_2 into tissue. The point on the curve at which Hgb is 50% saturated with O_2 is called the P_{50}, and it is 27 mm Hg in normal adults.

Physiological Factors That Shift the Oxyhemoglobin Dissociation Curve

The oxyhemoglobin dissociation curve can shift in numerous clinical conditions, either to the right or to the left (Fig. 24.5). The curve is shifted to the right when the affinity of Hgb for O_2 decreases, which enhances O_2 dissociation. This results in decreased Hgb binding to O_2 at a given Po_2, which causes the P_{50} to increase. When the affinity of Hgb for O_2 increases, the curve is shifted to the left, which causes the P_{50} to decrease. In this state, O_2 dissociation and delivery

IN THE CLINIC

In the inherited homozygous condition known as *sickle cell disease,* affected individuals have an amino acid substitution (valine for glutamic acid) on the β chain of the Hgb molecule. This creates a sickle cell Hgb (HgbS), which, when not bound to oxygen (deoxyhemoglobin or desaturated Hgb), can transform into a stiff gelatinous material that distorts the normal biconcave shape of the red blood cell to a crescent, or sickle-shaped, form. This change in appearance from spherical to a sickle shape increases the tendency of the red blood cell to form thrombi or clots that obstruct small vessels and creates a clinical condition known as *acute sickle cell episode.* The symptoms of such an episode vary, depending on the site of the obstruction (e.g., in the brain, stroke; in the lungs, pulmonary infarction), and are commonly associated with intense pain. The spleen is a common site of obstruction/infarction, and the ensuing tissue damage compromises the immune capabilities of affected individuals and renders them susceptible to recurrent infections. In the homozygous form, this condition is life-shortening; however, individuals with the heterozygous form are resistant to malaria. Thus, an individual with heterozygous alleles has a survival advantage in regions of the world where malaria is prevalent, which may explain why the sickle cell mutation has been preserved through evolution. The increased affinity of HgbF for O_2 confers advantages to individuals with sickle cell disease in that the cells do not desaturate as much when O_2 is released from Hgb to the tissue and thus are less likely to become deformed in the sickle shape. Sickle cell disease is most prevalent among individuals of African American descent, but it is also observed in Hispanic, Turkish, Asian, and other ethnic groups.

to tissue are inhibited. Shifts to the right or left of the dissociation curve have little effect when they occur at O_2 partial pressures within the normal range (80–100 mm Hg). However, at O_2 partial pressures below 60 mm Hg (steep part of the curve), shifts in the oxyhemoglobin dissociation curve can dramatically influence O_2 transport.

Hydrogen Ion Concentration and Carbon Dioxide

Changes in blood hydrogen ion concentration (pH) shift the oxyhemoglobin dissociation curve. An increase in CO_2 production by tissue and its release into blood results in the generation of hydrogen ions (H^+) and a decrease in pH. This shifts the dissociation curve to the right, which has a beneficial effect by aiding in the release of O_2 from Hgb for diffusion into metabolically active tissues. The shift to the right in the dissociation curve is due to the decrease in pH and to a direct effect of CO_2 on Hgb. Conversely, as blood passes through the lungs, CO_2 is exhaled, which results in an increase in pH, which in turn causes the oxyhemoglobin dissociation curve to shift to the left. This effect of CO_2 on the affinity of Hgb for O_2 is known as the **Bohr effect,** and it serves to enhance O_2 uptake in the lungs and delivery of O_2 to tissues. An increase in body temperature, as occurs during exercise, shifts the oxyhemoglobin dissociation curve to the right and enables more O_2 to be released to tissues, where it is needed in response to increased metabolic demand. During cold weather, a decrease in body temperature, especially in the extremities (lips, fingers, toes, and ears), shifts the O_2 dissociation curve to the left (higher Hgb affinity). In this instance, Pao_2 may be normal, but release of O_2 in these extremities is not facilitated.

2,3-Diphosphoglycerate

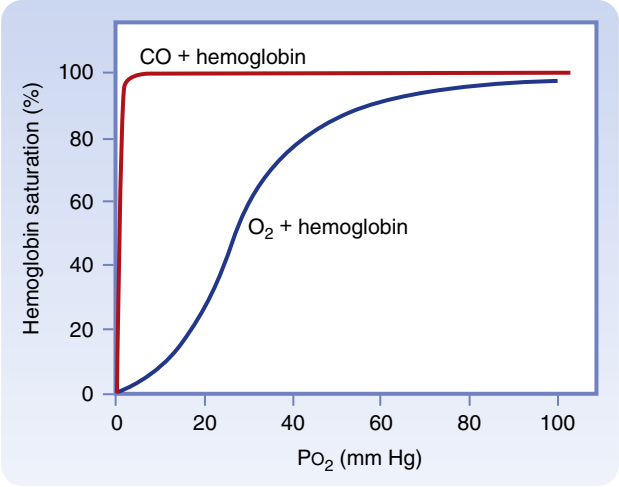
Mature red blood cells do not have mitochondria, and therefore they depend on anaerobic glycolysis. Large quantities of a metabolic intermediary, 2,3-DPG, are formed in red blood cells during glycolysis, and the affinity of Hgb for O_2 decreases as 2,3-DPG levels increase. Thus, the oxyhemoglobin dissociation curve shifts to the right. Although the binding sites of 2,3-DPG and O_2 differ on the Hgb molecule, binding of 2,3-DPG creates an allosteric effect that inhibits the binding of O_2. Conditions that increase 2,3-DPG include hypoxia, decreased Hgb, and increased pH. Decreased levels of 2,3-DPG are observed in stored blood samples and thus may present a problem to transfusion recipients because of the greater affinity of Hgb for O_2, which inhibits the unloading of O_2 to tissues.

Fetal Hemoglobin (HgbF)

As discussed previously, HgbF has a greater affinity for O_2 than does adult Hgb, and the oxyhemoglobin dissociation curve thus shifts to the left.

Carbon Monoxide

CO binds to the heme group of the Hgb molecule at the same site as O_2 and forms **carboxyhemoglobin** (HgbCO). A major difference between the ability of CO and that of O_2 to bind to Hgb is illustrated by a comparison of the oxyhemoglobin and carboxyhemoglobin dissociation curves. The affinity of CO for Hgb is about 200 times greater than that for O_2 for Hgb (Fig. 24.6). Thus, small amounts of CO can greatly influence the binding of O_2 to Hgb. In the presence of CO, the affinity of Hgb for O_2 is enhanced. This causes the dissociation curve to shift to the left, which further prevents the unloading and delivery of O_2 to tissues. As the P_{CO} of blood approaches 1.0 mm Hg, all of the Hgb binding sites are occupied by CO, and Hgb is unable to bind to O_2. This situation is not compatible with life and is the cause of death in cases of CO poisoning. In healthy individuals, HgbCO occupies about 1% to 2% of the Hgb-binding sites; however, in cigarette smokers and in individuals who reside in high-density urban traffic areas, occupation of Hgb-binding sites can be increased to 10%. Levels above 5% to 7% are considered hazardous. Potential sources of CO include smoke from a burning building, exposure to indoor heating systems with faulty ventilation, use of gas or charcoal grills in poorly ventilated environments, and use of gasoline-powered engines (including car engines) in closed spaces. Treatment of individuals with high levels of CO consists of removing the individual from the source of CO, and then administering high concentrations of O_2 to displace CO from Hgb. Increasing the ambient pressure above atmospheric pressure through the use of a barometric chamber substantially increases O_2 tension. This promotes the dissociation of CO from Hgb.



• **Fig. 24.6** The oxyhemoglobin and carboxyhemoglobin dissociation curves clearly illustrate the increased affinity that carbon monoxide (CO) has for Hgb, in comparison with O_2.

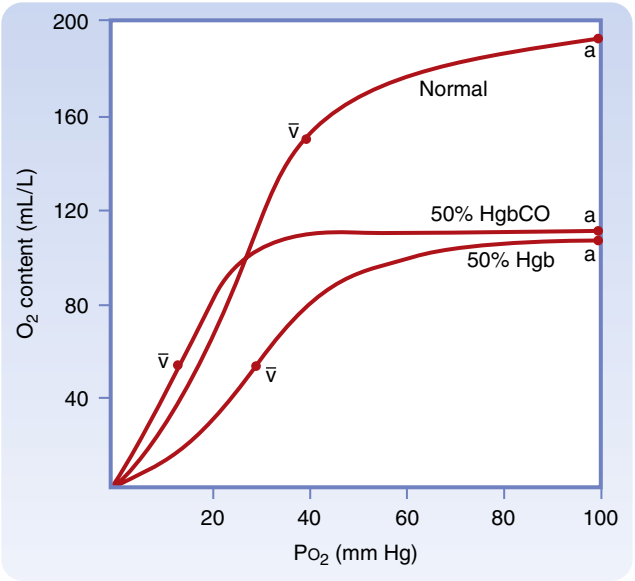
Another gas, nitric oxide, has great affinity (200,000 times greater than O_2) for Hgb, and it binds irreversibly to Hgb at the same site that O_2 does. Endothelial cells synthesize nitric oxide, which has potent vasodilation properties. Thus, nitric oxide is used therapeutically as an inhalant in patients with pulmonary hypertension to reduce pulmonary arterial pressure. Although nitric oxide poisoning is not common, the clinician should be cautious when administering nitric oxide therapy for long periods. Nitric oxide can

oxidize the iron molecule in the heme group, changing it from the reduced ferrous state (Fe^{++}) to the oxidized ferric state (Fe^{+++}). This converts hemoglobin to methemoglobin, which reduces its ability to release oxygen. Methemoglobinemia can be detected by CO-oximetry or by arterial blood gas analysis.

Oxygen Saturation, Content, and Delivery

Each Hgb molecule can bind up to four O_2 atoms, and each gram of Hgb can bind up to 1.34 mL of O_2. The term **O_2 saturation** (SO_2) refers to the amount of O_2 bound to Hgb in relation to the maximal amount of O_2 (100% O_2 capacity) that can bind Hgb. At 100% O_2 capacity, the heme groups of the Hgb molecules are fully saturated with O_2, and at 75% O_2 capacity, three of the four heme groups are occupied. Binding of O_2 to each heme group increases the affinity of the Hgb molecule to bind additional O_2. The O_2 content in blood is the sum of the O_2 bound to Hgb and the dissolved O_2. Oxygen content is decreased in the presence of increased CO_2 and CO and in individuals with anemia (Fig. 24.7).

Oxygen delivery from the lungs to tissues is dependent on several factors, including cardiac output, the Hgb content of blood, and the ability of the lung to oxygenate the blood. Not all of the O_2 carried in blood is unloaded at the tissue level. The actual O_2 extracted from blood by the tissue is the difference between the arterial O_2 content and the venous O_2 content, multiplied by cardiac output. Under normal conditions, Hgb leaves the tissue 75% saturated with O_2, and only about 25% is actually used by tissues. Hypothermia, relaxation of skeletal muscles, and an increase in cardiac output reduce O_2 extraction. Conversely, a decrease in cardiac output, anemia, hyperthermia, and exercise increase O_2 extraction.



• **Fig. 24.7** A comparison of O_2 content curves under three conditions shows why carboxyhemoglobin *(HgbCO)* dramatically reduces the O_2 transport system. Fifty percent HgbCO represents the binding of half the circulating Hgb with carbon monoxide (CO). The 50% hemoglobin and 50% HgbCO curves show the same decreased O_2 content in arterial blood. However, CO has a profound effect in lowering venous partial pressure of oxygen. The arterial *(a)* and mixed venous ($\bar{V}$) points of constant cardiac output are indicated.

Tissue hypoxia is a condition in which O_2 available to cells is insufficient for maintaining adequate aerobic metabolism. Thus, anaerobic metabolism is stimulated and results in the increases in levels of lactate and H^+ and the subsequent formation of lactic acid. The net result can lead to a significant decrease in blood pH. In cases of severe hypoxia, the extremities, toes, and fingertips may appear blue-gray **(cyanotic)** because of lack of O_2 and increased deoxyhemoglobin levels. There are four major types of tissue hypoxia (hypoxic hypoxia, circulatory hypoxia, anemic hypoxia, histotoxic hypoxia), discussed in detail in Chapter 23.

Erythropoiesis

Tissue oxygenation depends on the concentration of Hgb and thus on the number of red blood cells available in the circulation. Red blood cell production **(erythropoiesis)** in the bone marrow is controlled by the hormone **erythropoietin,** which is synthesized in the kidneys by cortical interstitial cells. Although Hgb levels are normally very stable, decreased O_2 delivery, low Hgb concentration, and low Pao_2 stimulate the secretion of erythropoietin. This increases the production of red blood cells. Chronic renal disease damages the cortical interstitial cells and thereby suppresses their ability to synthesize erythropoietin. This causes anemia, along with decreased Hgb because of the lack of erythropoietin. Erythropoietin replacement therapy using epoetin alfa or darbepoetin alfa effectively increases red blood cell production.

Carbon Dioxide Transport

Glucose Metabolism and Carbon Dioxide Production

CO_2 is produced at a rate of approximately 200 mL/minute under healthy conditions, and typically 80 molecules of CO_2 are expired by the lung for every 100 molecules of O_2 that enter the capillary bed. The ratio of expired CO_2 to O_2 uptake is referred to as the **respiratory exchange ratio** and, under normal conditions, is 0.8 (80 molecules of CO_2 to 100 molecules of O_2). This ratio is similar at the tissue to blood compartment, where it is referred to as the **respiratory quotient.**

The body has enhanced storage capabilities for CO_2, in comparison with O_2, and hence Pao_2 is much more sensitive to changes in ventilation than is $Paco_2$. Whereas Pao_2 is dependent on several factors, in addition to alveolar ventilation, arterial $Paco_2$ is solely dependent on alveolar ventilation and CO_2 production. There is an inverse relationship between alveolar ventilation and $Paco_2$.

Bicarbonate and Carbon Dioxide Transport

In blood, CO_2 is transported in red blood cells primarily as bicarbonate (HCO_3^-) but also as dissolved CO_2 and as carbamino protein complexes (i.e., CO_2 binds to plasma proteins and to Hgb; Fig. 24.8). Once CO_2 diffuses through the tissue and enters plasma, it quickly dissolves. The reaction of CO_2 with H_2O to form carbonic acid (H_2CO_3) is the major mechanism for the generation of HCO_3^- in red blood cells, since H_2CO_3 can dissociate into H^+ and HCO_3^-:

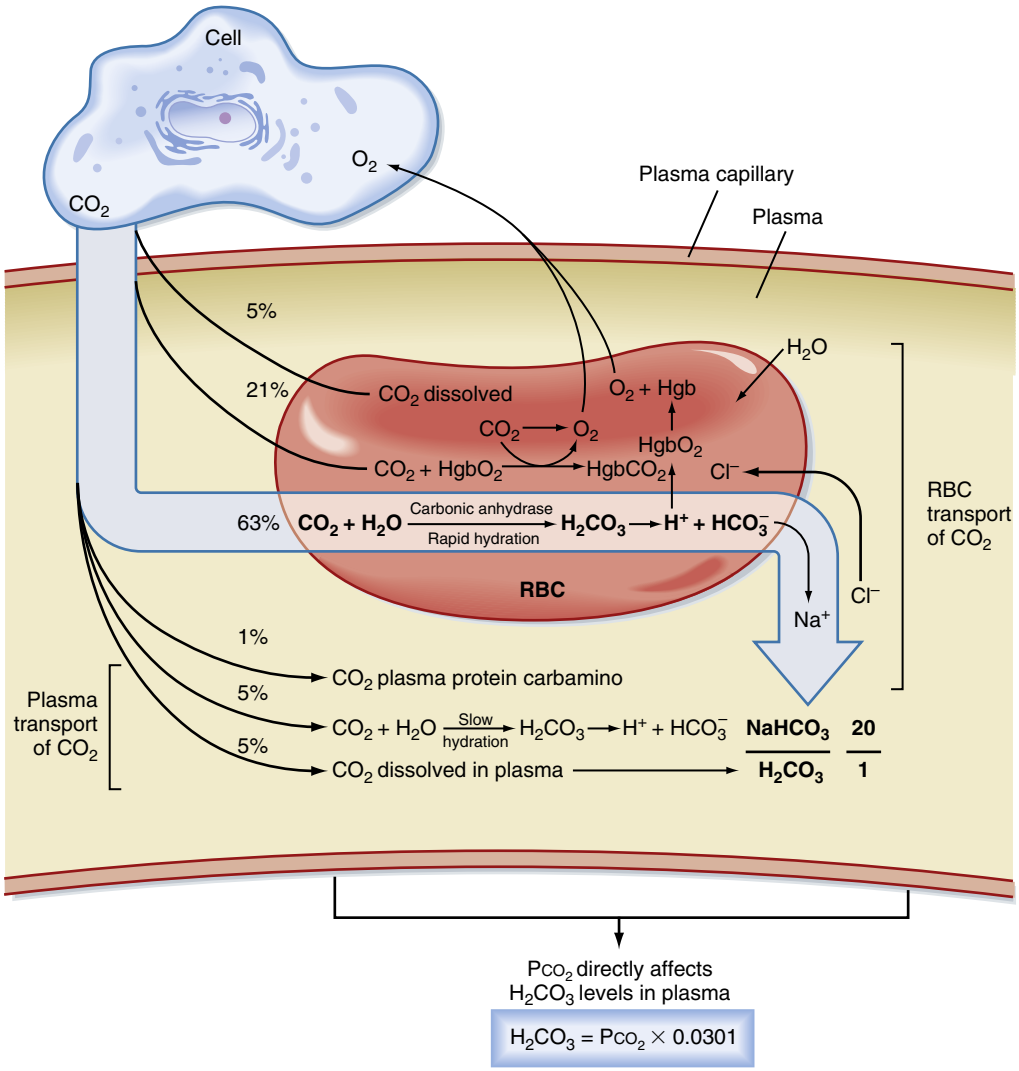
Equation 24.3

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

The reaction normally proceeds quite slowly; however, it is catalyzed within red blood cells by the enzyme **carbonic anhydrase.** The HCO_3^- diffuses out of the red blood cell in exchange for Cl^-, in a process known as the **chloride shift,** which helps the cell maintain its osmotic equilibrium. This chemical reaction (see Fig. 24.8) is reversible and can be shifted to the right to generate more HCO_3^- in response to more CO_2 entering the blood from tissues, or it can be shifted to the left as CO_2 is exhaled in the lungs, which reduces HCO_3^- levels. The free H^+ is quickly buffered within the red blood cell by binding to Hgb. Buffering of H^+ is critical for keeping the reaction moving toward the synthesis of HCO_3; high levels of free H^+ (low pH) cause the reaction to shift to the left.

Regulation of Hydrogen Ion Concentration and Acid-Base Balance

The H^+ concentration (pH) has a dramatic effect on many metabolic processes within cells, and regulation of pH is essential for normal homeostasis. In the clinical setting, blood pH is measured to assess the concentration of H^+. The normal pH range for adults is 7.35 to 7.45 and is maintained



• **Fig. 24.8** Mechanisms of CO_2 transport in blood. The predominant mechanism by which CO_2 is transported from tissue cells to the lung is in the form of bicarbonate anion *(HCO_3^-)*. *H_2CO_3*, Carbonic acid; *HgbO*, oxyhemoglobin; *$NaHCO_3$*, sodium bicarbonate; *RBC*, red blood cell.

by the lungs, kidneys, and chemical buffer systems. In the respiratory system, conversion of CO_2 to HCO_3^-, illustrated as follows, is a major mechanism of buffering and regulating the H^+ concentration (pH):

Equation 24.4

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

(with hydrogen yielding)

$$H^+ + Hgb \rightleftharpoons H \times Hgb$$

As $PAco_2$ changes, so does the concentration of HCO_3^- and H_2CO_3, as well as $Paco_2$.

The **Henderson-Hasselbalch** equation is used to calculate how changes in CO_2 and HCO_3^- affect pH:

Equation 24.5

$$pH = pK' + \frac{\log [HCO_3^-]}{\alpha Pco_2}$$

where α = solubility (0.03 at 37°C) and the pK′ is 6.1. Thus

Equation 24.6

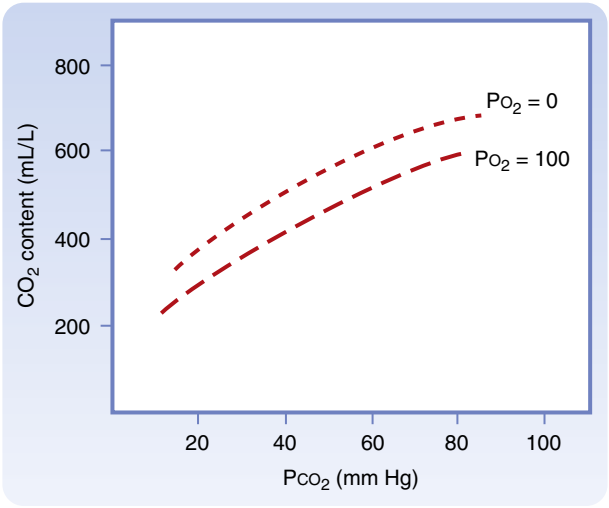
$$pH = 6.1 + \frac{\log [HCO_3^-]}{0.03 \times Pco_2}$$

In these equations, the amount of CO_2 is determined from the Pco_2 and its solubility (α) in solution. For plasma at 37°C, α has a value of 0.03. Also, pK′ is the negative logarithm of the overall dissociation constant for the reaction and has a logarithmic value of 6.1 for plasma at 37°C.

Acute hyperventilation secondary to exercise or anxiety reduces Pco_2 and thereby causes an increase in pH (respiratory alkalosis, see Eq. 24.6). Conversely, if Pco_2 increases because of hypoventilation secondary to an overdose of a respiratory depressant, the pH decreases (respiratory acidosis). Acid-base imbalances are also caused by metabolic disorders such as metabolic acidosis (e.g., lactic acidosis, ketoacidosis, and renal failure) and metabolic alkalosis (e.g., hypokalemia, hypochloremia, vomiting, use of bicarbonate containing antacids, hyperaldosteronism, and rarely administration of high doses of steroids).

Carbon Dioxide Dissociation Curve

In contrast to O_2, the dissociation curve for CO_2 in blood is linear and directly related to Pco_2 (Fig. 24.9). The degree of Hgb saturation with O_2 has a major effect on the CO_2 dissociation curve. Although O_2 and CO_2 bind to Hgb at different sites, deoxygenated Hgb has greater affinity for CO_2 than oxygenated Hgb. Thus, deoxygenated blood (venous blood) freely takes up and transports more CO_2 than oxygenated arterial blood does. The deoxygenated Hgb more readily forms carbamino compounds and also more readily binds free H^+ released during the formation of HCO_3^-. The effect of changes in oxyhemoglobin saturation on the relationship of CO_2 content to Pco_2 is referred to as the **Haldane effect** and is reversed in the lungs when O_2 is transported from the alveoli to red blood cells. This effect is illustrated by a shift to the left in the CO_2 dissociation curve in venous blood in comparison with arterial blood.



• **Fig. 24.9** Equilibrium curves for CO_2 in arterial and venous blood. Venous blood can transport more CO_2 than arterial blood can at any given Pco_2. In comparison with the $HgbO_2$ equilibrium curve, the CO_2 curves are essentially straight lines between a Pco_2 of 20 and a Pco_2 of 80 mm Hg. *Long dashes* represent the arterial equilibrium curve; *short dashes* represent the venous equilibrium curve.

Key Points

1. Gases (nitrous oxide, ether, helium) that have a rapid rate of air-to-blood equilibration are perfusion limited. Gases (CO) that have a slow air-to-blood equilibration rate are diffusion limited. Under normal conditions, O_2 and CO_2 exchanges are perfusion limited but can be diffusion limited in advanced disease states.
2. The major transport mechanism of O_2 in blood is within the red blood cell bound to Hgb, and for CO_2 it is within red blood cells in the form of HCO_3^-.
3. The reversible reaction of CO_2 with H_2O to form H_2CO_3, with its subsequent dissociation to HCO_3^- and H^+, is catalyzed by the enzyme carbonic anhydrase within red blood cells and is the major mechanism for generation of HCO_3^-.
4. The O_2 dissociation curve is S shaped. In the plateau area (>60 mm Hg), increasing or decreasing Po_2 has only a minimal effect on Hgb saturation from 100% to 90%. This ensures adequate Hgb saturation over a large range of Po_2 values.

5. The CO_2 dissociation curve is linear and directly related to Pco_2. Pco_2 is solely dependent on CO_2 production and alveolar ventilation.
6. The CO_2 to HCO_3^- pathway plays a critical role in the regulation of H^+ ions and in maintaining acid-base balance in the body.
7. Tissue oxygenation is dependent on Hgb within red blood cells and subsequently the number (and production) of red blood cells, which is controlled by the hormone erythropoietin. Low O_2 delivery, low Hgb concentration, and low Pao_2 stimulate the secretion of erythropoietin in the kidneys.
8. Tissue hypoxia occurs when insufficient amounts of O_2 are supplied to the tissue to conduct normal levels of aerobic metabolism.