CHAPTER 21

Gas Transfer and Transport

Rodney A. Rhoades, Ph.D.

CHAPTER OUTLINE

KEY CONCEPTS

1. The diffusion of gases follows Fick's law.
2. Pulmonary blood flow limits the transfer of O_2 and CO_2 in the lungs.
3. Diffusing capacity depends on the diffusion properties of the lungs.
4. Most of the oxygen in the blood is carried by hemoglobin.
5. Arterial oxygen saturation is a measure of the percentage of hemoglobin loaded with oxygen.
6. Carbon monoxide has a strong affinity for hemoglobin and decreases the ability of the blood to carry O_2.
7. Most of the CO_2 in the blood is carried in the form of HCO_3^- in the plasma.
8. An alveolar-arterial oxygen ($A\text{-}aO_2$) gradient occurs because of venous admixture.
9. Hypoxemia is an abnormally low P_{O_2} or oxygen content in arterial blood.
10. A low $\dot{V}_A/\dot{Q}$ ratio is the major cause of hypoxemia.

GAS DIFFUSION AND UPTAKE

There are two types of gas movements in the lungs, **bulk flow** and **diffusion**. Gas moves in the airways, from the trachea down to the alveoli, by bulk flow, analogous to water coming out of a faucet, in which all molecules move as a unit. The driving pressure (P) for bulk flow in the airways is barometric pressure (P_B) at the mouth minus alveolar pressure (P_A).

Respiratory Gases Cross the Alveolar-Capillary Membrane by Diffusion

The movement of gases in the alveoli and across the alveolar-capillary membrane is by diffusion in response to partial pressure gradients (see Chapter 2). Recall that partial pressure or gas tension can be determined by measuring barometric pressure and the fractional concentration (F) of the gas (Dalton's law; see Chapter 19). At sea level, P_{O_2} is 160 mm Hg (760 mm Hg × 0.21). F_{O_2} does not change with altitude, which means that the percentage of O_2 in the atmosphere is essentially the same at 30,000 feet (about 9,000 m) as it is as sea level. Therefore, the decreased P_{O_2} at an altitude that makes it difficult to breathe is due to a decrease in the P_B, not to a decrease in F_{O_2} (Fig. 21.1).

Oxygen is taken up by blood in the lungs and is transported to the tissues. **Oxygen uptake** is the transfer of oxygen from the alveolar spaces to the blood in the pulmonary capillaries. Gas uptake is determined by three factors: the diffusion properties of the alveolar-capillary membrane, the partial pressure gradient, and pulmonary capillary blood flow.

The diffusion of gases is a function of the partial pressure difference of the individual gases. For example, oxygen diffuses across the alveolar-capillary membrane because of the difference in P_{O_2} between the alveoli and pulmonary capillaries (Fig. 21.2). The partial pressure difference for oxygen is referred to as the **oxygen diffusion gradient**; in the normal lung, the *initial* oxygen diffusion gradient, P_{AO_2} (102 mm Hg) minus P_{vO_2} (40 mm Hg), is 62 mm Hg. The *initial* diffusion gradient across the alveolar-capillary membrane for carbon dioxide ($P_{vCO_2} - P_{ACO_2}$) is about 6 mm Hg, which is much smaller than that of oxygen.

When gases are exposed to a liquid such as blood plasma, gas molecules move into the liquid and exist in a dissolved state. The dissolved gases also exert a partial pressure. A gas will continue to dissolve in the liquid until the partial pressure of the dissolved gas equals the partial pressure above the liquid. **Henry's law** states that at equilibrium, the amount of gas dissolved in a liquid at a given tempera-

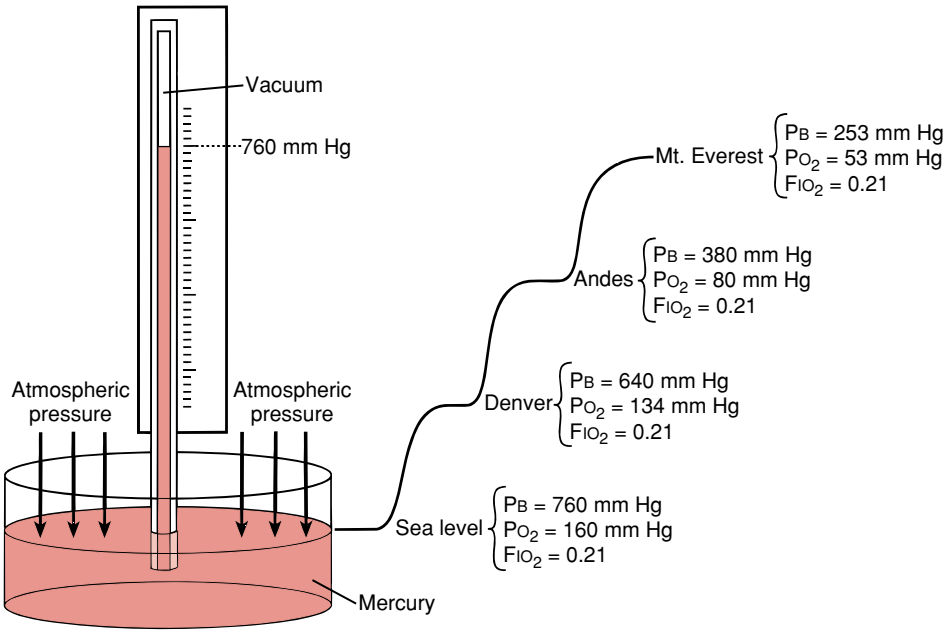

FIGURE 21.1 **Changes in oxygen tension with altitude.** The height of the column of mercury that is supported by air pressure decreases with increasing altitude and is a result of a fall in barometric pressure (P_B). Because the fractional concentration of inspired O_2 (F_{IO_2}) does not change with altitude, the decrease in P_{O_2} with altitude is caused entirely by a decrease in P_B.

ture is directly proportional to the partial pressure and the solubility of the gas. Henry's law only accounts for the gas that is physically dissolved and not for chemically combined gases (e.g., oxygen bound to hemoglobin).

Gas diffusion in the lungs can be described by **Fick's law**, which states that the volume of gas diffusing per minute (gas) across a membrane is directly proportional to the membrane surface area (As), the diffusion coefficient of the gas (D), and the partial pressure difference (ΔP) of the gas and inversely proportional to membrane thickness (T) (Fig. 21.3):

$$\dot{V}gas = \frac{As \times D \times \Delta P}{T} \qquad (1)$$

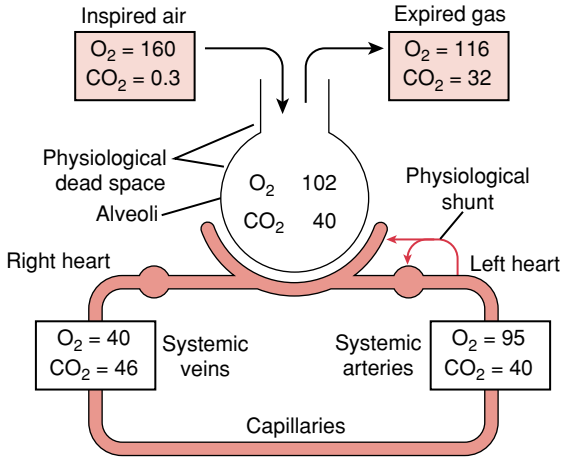

FIGURE 21.2 **Partial pressures of oxygen (P_{O_2}) and carbon dioxide (P_{CO_2}) in the lungs and systemic circulation.**

The diffusion coefficient of a gas is directly proportional to its solubility and inversely related to the square root of its molecular weight (MW):

$$D \propto \frac{\text{solubility}}{(MW)^{1/2}} \qquad (2)$$

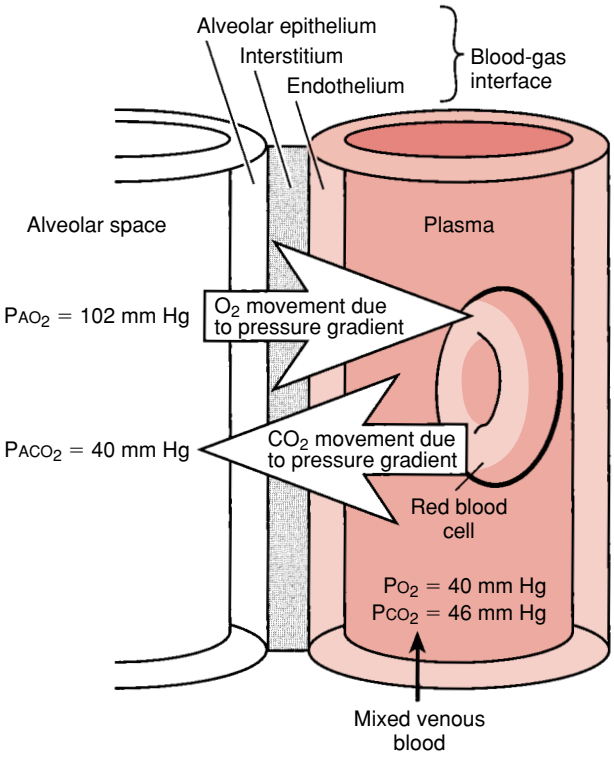

FIGURE 21.3 **Diffusion path of O_2 and CO_2 in the lungs.** Gases move across the blood-gas interface (alveolar-capillary membrane) by diffusion, following Fick's law.

Therefore, a small molecule or one that is very soluble will diffuse at a fast rate; for example, the diffusion coefficient of carbon dioxide in aqueous solutions is about 20 times greater than that of oxygen because of its higher solubility, even though it is a larger molecule than O_2.

Fick's law states that the rate of gas diffusion is inversely related to membrane thickness. This means that the diffusion of a gas will be halved if membrane thickness is doubled. Fick's law also states that the rate of diffusion is directly proportional to surface area (As). If two lungs have the same oxygen diffusion gradient and membrane thickness but one has twice the alveolar-capillary surface area, the rate of diffusion will differ by 2-fold.

Under steady state conditions, approximately 250 mL of oxygen per minute are transferred to the pulmonary circulation ($\dot{V}O_2$) while 200 mL of carbon dioxide per minute are removed ($\dot{V}CO_2$). The ratio $\dot{V}CO_2/\dot{V}O_2$ is the **respiratory exchange ratio** (R) and, in this case, is 0.8.

Capillary Blood Flow Limits Oxygen Uptake From Alveoli

Pulmonary capillary blood flow has a significant influence on oxygen uptake. The effect of blood flow on oxygen uptake is illustrated in Figure 21.4. The time required for the red cells to move through the capillary, referred to as **transit time**, is approximately 0.75 sec, during which time the gas tension in the blood equilibrates with the alveolar gas tension. Transit time can change dramatically with cardiac output. For example, when cardiac output increases, blood flow through the pulmonary capillaries increases, but transit time decreases (i.e., the time blood is in capillaries is less).

Figure 21.4 illustrates the effect of blood flow on the uptake of three test gases. In the first case, a trace amount of nitrous oxide (laughing gas), a common dental anesthetic, is breathed. Nitrous oxide (N_2O) is chosen because it diffuses across the alveolar-capillary membrane and dissolves in the blood, but does not combine with hemoglobin. The partial pressure in the blood rises rapidly and virtually reaches equilibrium with the partial pressure of N_2O in the alveoli by the time the blood is one tenth of the time in the capillary. At this point, the diffusion gradient for N_2O is zero. Once the pressure gradient becomes zero, no additional N_2O is transferred. The only way the transfer of N_2O can be increased is by increasing blood flow. The amount of N_2O that can be taken up is entirely limited by blood flow, not by diffusion of the gas. Therefore, the net transfer or uptake of N_2O is **perfusion-limited.**

When a trace amount of carbon monoxide (CO) is breathed, the transfer shows a different pattern (see Fig. 21.4). CO readily diffuses across the alveolar-capillary membrane but, unlike N_2O, CO has a strong affinity for hemoglobin. As the red cell moves through the pulmonary capillary, CO rapidly diffuses across the alveolar-capillary membrane into the blood and binds to hemoglobin. When a trace amount of CO is breathed, most is chemically bound in the blood, resulting in low partial pressure (P_{CO}). Consequently, equilibrium for CO across the alveolar-capillary membrane is never reached, and the transfer of CO to the blood is, therefore, **diffusion-limited** and not limited by the blood flow.

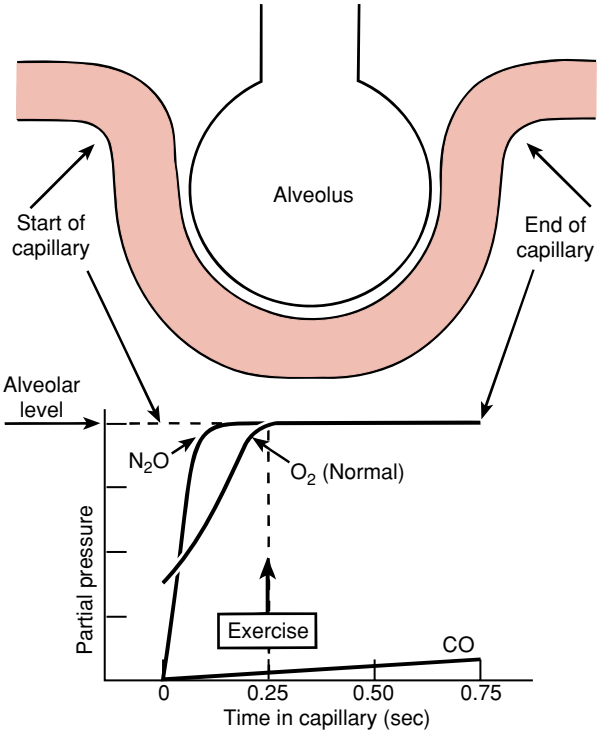

FIGURE 21.4 Uptake of N_2O, O_2, and CO by pulmonary capillary blood. Gas transfer is affected by pulmonary capillary blood flow. The horizontal axis shows time in the capillary. The average transit time it takes blood to pass through the pulmonary capillaries is 0.75 sec. The vertical axis indicates gas tension in the pulmonary capillary blood and the top of the vertical axis indicates gas tension in the alveoli. Individual curves indicates the time it takes for the partial pressure of a specific gas in the pulmonary capillaries to equal the partial pressure in the alveoli. Nitrous oxide (N_2O) is used to illustrate how gas transfer is limited by blood flow; carbon monoxide (CO) illustrates how gas transfer is limited by diffusion. The profile for oxygen is more like that of N_2O, which means oxygen transfer is limited primarily by blood flow. Pulmonary capillary P_{O_2} equilibrates with the alveolar P_{O_2} in about 0.25 second (arrow).

Figure 21.4 shows that the equilibration curve for oxygen lies between the curves for N_2O and CO. Oxygen combines with hemoglobin, but not as readily as CO because it has a lower binding affinity. As blood moves along the pulmonary capillary, the rise in P_{O_2} is much greater than the rise in P_{CO} because of differences in binding affinity. Under resting conditions, the capillary P_{O_2} equilibrates with alveolar P_{O_2} when the blood is about one third of its time in the capillary. Beyond this point, there is no additional transfer of oxygen. Under normal conditions, oxygen transfer is more like that of N_2O and is limited primarily by blood flow in the capillary (perfusion-limited). Hence, an increase in cardiac output will increase oxygen uptake. Not only does cardiac output increase capillary blood flow, but it also increases capillary hydrostatic pressure. The latter increases the surface area for diffusion by opening up more capillary beds by recruitment.

The transit time at rest is normally about 0.75 sec, during which capillary oxygen tension equilibrates with alveo-

lar oxygen tension. Ordinarily this process takes only about one third of the available time, leaving a wide safety margin to ensure that the end-capillary P_{O_2} is equilibrated with alveolar P_{O_2}. With vigorous exercise, the transit time may be reduced to one third of a second (see Fig. 21.4). Thus, with vigorous exercise, there is still time to fully oxygenate the blood. Pulmonary end-capillary P_{O_2} still equals alveolar P_{O_2} and rarely falls with vigorous exercise. In abnormal situations, in which there is a thickening of the alveolar-capillary membrane so that oxygen diffusion is impaired, end-capillary P_{O_2} may not reach equilibrium with alveolar P_{O_2}. In this case, there is measurable difference between alveolar and end-capillary P_{O_2}.

DIFFUSING CAPACITY

In practice, direct measurements of As, T, and D in intact lungs are impossible to make. To circumvent this problem, Fick's law can be rewritten as shown in Figure 21.5, where the three terms are combined as **lung diffusing capacity** (D_L).

Diffusing Capacity Is a Determinant of the Rate of Gas Transfer

The diffusing capacity provides a measure of the rate of gas transfer in the lungs per partial pressure gradient. For example, if 250 mL of O_2 per minute are taken up and the average alveolar-capillary P_{O_2} difference during a normal transit time is 14 mm Hg, then the D_L for oxygen is 18 mL/min per mm Hg. Because the initial alveolar-capillary difference for oxygen cannot be measured and can only be estimated, CO is used to determine the lung diffusing capacity in patients. CO offers several advantages for measuring D_L:

- Its uptake is limited by diffusion and not by blood flow.
- There is essentially no CO in the venous blood.
- The affinity of CO for hemoglobin is 210 times greater than that of oxygen, which causes the partial pressure of carbon monoxide to remain essentially zero in the pulmonary capillaries.

To measure the diffusing capacity in a patient with CO, the equation is

$$D_L = \frac{\dot{V}_{CO}}{Paco} \quad (3)$$

where $\dot{V}_{CO}$ equals CO uptake in mL/min and P_{ACO} equals alveolar partial pressure of CO.

The most common technique for making this measurement is called the **single-breath test.** The patient inhales a single breath of a dilute mixture of CO and holds his or her breath for about 10 sec. By determining the percentage of CO in the alveolar gas at the beginning and the end of 10 sec and by measuring lung volume, one can calculate $\dot{V}_{CO}$. The single-breath test is very reliable. The normal resting value for $D_{L_{CO}}$ depends on age, sex, and body size. $D_{L_{CO}}$ ranges from 20 to 30 mL/min per mm Hg and decreases with pulmonary edema or a loss of alveolar membrane (e.g., emphysema).

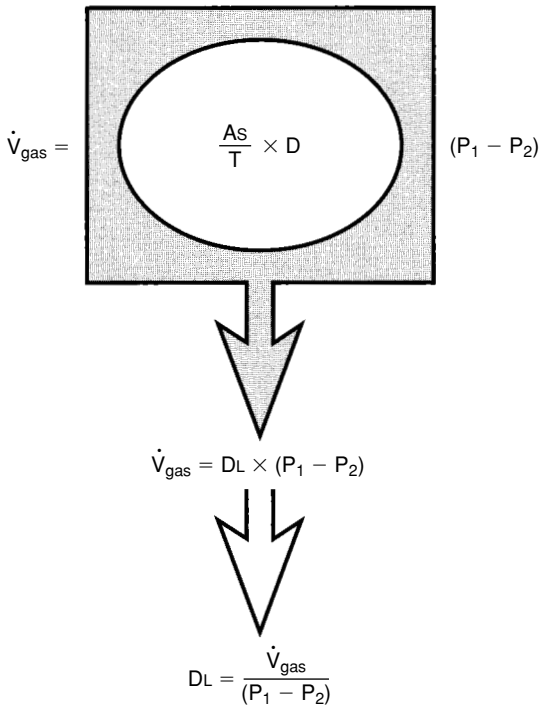

FIGURE 21.5 **Lung diffusing capacity.** Membrane surface area (As), gas diffusion coefficient (D), and membrane thickness (T) affect gas diffusion in the lungs. These properties are combined into one term, lung diffusing capacity (D_L), which can be measured in a human subject. D_L is equal to the volume of gas transferred/min (gas) divided by the mean partial pressure gradient for the gas.

Hemoglobin and Capillary Blood Volume Affect Lung Diffusing Capacity

Diffusing capacity does not depend solely on the diffusion properties of the lungs; it is also affected by blood hematocrit and pulmonary capillary blood volume. Both the hematocrit and capillary blood volume affect D_L in the same direction (i.e., a decrease in either the hematocrit or capillary blood volume will lower the diffusing capacity in otherwise normal lungs). For example, if two individuals have the same the pulmonary diffusion properties but one is anemic (reduced hematocrit), the anemic individual will have a decreased lung diffusing capacity. An abnormally low cardiac output lowers the pulmonary capillary blood volume, which decreases the alveolar capillary surface area and will, in turn, decrease the diffusing capacity in otherwise normal lungs.

GAS TRANSPORT BY THE BLOOD

The transport of O_2 and CO_2 by the blood, often referred to as **gas transport**, is an important step in the overall gas exchange process and is one of the important functions of the systemic circulation.

Oxygen Is Transported in Two Forms

Oxygen is transported to the tissues in two forms: combined with hemoglobin (Hb) in the red cell or physically

dissolved in the blood. Approximately 98% of the oxygen is carried by hemoglobin and the remaining 2% is carried in the physically dissolved form. The amount of physically dissolved oxygen in the blood can be calculated from the following equation:

$$\text{Dissolved } O_2 \text{ (mL/dL)} = 0.003 \text{ (mL/dL per mm Hg)} \times Pa_{O_2} \text{ (mm Hg)} \quad (4)$$

If Pa_{O_2} equals 100 mm Hg, then dissolved O_2 = 0.3 mL/dL.

Binding Affinity of Hemoglobin for Oxygen. The hemoglobin molecule consists of four oxygen-binding heme sites and a globular protein chain. When hemoglobin binds with oxygen, it is called **oxyhemoglobin** (HbO_2). The hemoglobin that does not bind with O_2 is called **deoxyhemoglobin** (Hb). Each gram of hemoglobin can bind with 1.34 mL of oxygen. Oxygen binds rapidly and reversibly to hemoglobin: $O_2 + Hb \rightleftharpoons HbO_2$. The amount of oxyhemoglobin is a function of the partial pressure of oxygen in the blood. In the pulmonary capillaries, where P_{O_2} is high, the reaction is shifted to the right to form oxyhemoglobin. In tissue capillaries, where P_{O_2} is low, the reaction is shifted to the left; oxygen is unloaded from hemoglobin and becomes available to the cells. The maximum amount of oxygen that can be carried by hemoglobin is called the **oxygen carrying capacity**—about 20 mL O_2/dL blood in a healthy young adult. This value is calculated assuming a normal hemoglobin concentration of 15 g Hb/dL of blood (1.34 mL O_2 /g Hb × 15 g Hb/dL blood = 20.1 mL O_2/dL blood).

Oxygen content is the amount of oxygen actually bound to hemoglobin (whereas capacity is the amount that can potentially be bound). The **percentage saturation of oxygen** (S_{O_2}) is calculated from the ratio of oxyhemoglobin content over capacity:

$$S_{O_2} = \frac{Hb\ O_2 \text{ content}}{Hb\ O_2 \text{ capacity}} \times 100 \quad (5)$$

Thus, the oxygen saturation is the ratio of the quantity of oxygen *actually bound* to the quantity that can be *potentially bound*. For example, if oxygen content is 16 mL O_2/dL blood and oxygen capacity is 20 mL O_2/dL blood, then the blood is 80% saturated. Arterial blood saturation (Sa_{O_2}) is normally about 98%.

Blood P_{O_2}, O_2 saturation, and oxygen content are three closely related indices of oxygen transport. The relationship between P_{O_2}, oxygen saturation, and oxygen content is illustrated by the **oxyhemoglobin equilibrium curve**, an S-shaped curve over a range of arterial oxygen tensions from 0 to 100 mm Hg (Fig. 21.6). The shape of the curve results because the hemoglobin affinity for oxygen increases progressively as blood P_{O_2} increases.

The shape of the oxyhemoglobin equilibrium curve reflects several important physiological advantages. The plateau region of the curve is the **loading phase**, in which oxygen is loaded onto hemoglobin to form oxyhemoglobin in the pulmonary capillaries. The plateau region illustrates how oxygen saturation and content remain fairly constant despite wide fluctuations in alveolar P_{O_2}. For example, if P_{AO_2} were to rise from 100 to 120 mm Hg, hemoglobin would become only slightly more saturated (97 to 98%). For this reason, oxygen content cannot be raised appreciably by hyperventilation. The steep **unloading phase** of the curve allows large quantities of oxygen to be released or unloaded from hemoglobin in the tissue capillaries where a lower capillary P_{O_2} prevails. The S-shaped oxyhemoglobin equilibrium curve enables oxygen to saturate hemoglobin under high partial pressures in the lungs and to give up large amounts of oxygen with small changes in P_{O_2} at the tissue level.

A change in the binding affinity of hemoglobin for O_2 shifts the oxyhemoglobin-equilibrium curve to the right or left of normal (Fig. 21.7). The $\mathbf{P_{50}}$—the P_{O_2} at which 50% of the hemoglobin is saturated—provides a functional way to assess the binding affinity of hemoglobin for oxygen. The normal P_{50} for arterial blood is 26 to 28 mm Hg. A high P_{50} signifies a decrease in hemoglobin's affinity for oxygen and results in a rightward shift in the oxyhemoglobin equilibrium curve, whereas a low P_{50} signifies the opposite and shifts the curve to the left. A shift in the P_{50} in either direction has the greatest effect on the steep phase and only a small effect on the loading of oxygen in the normal lung, because loading occurs at the plateau.

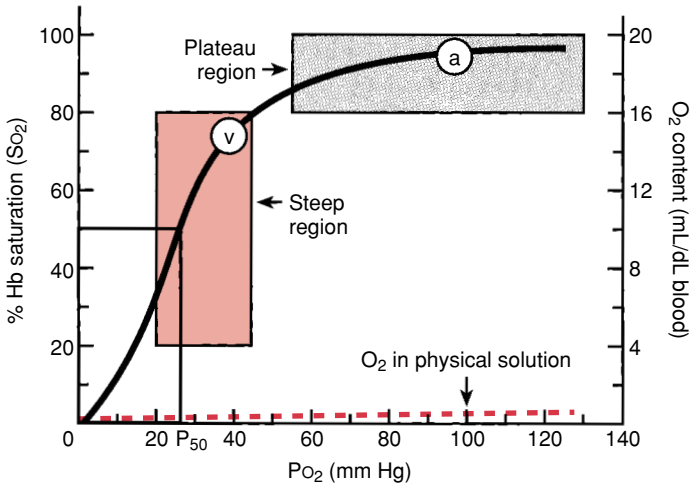

FIGURE 21.6 **An oxyhemoglobin equilibrium curve.** The oxygen saturation (left vertical axis) or oxygen content (right vertical axis) is plotted against partial pressure of oxygen (horizontal axis) to generate an oxyhemoglobin equilibrium curve. The curve is S-shaped and can be divided into a plateau region and a steep region. The dashed line indicates amount of oxygen dissolved in the plasma. a = arterial; v = venous; S_{O_2} = oxygen saturation; and P_{50} = partial pressure of O_2 required to saturate 50% of the hemoglobin with oxygen.

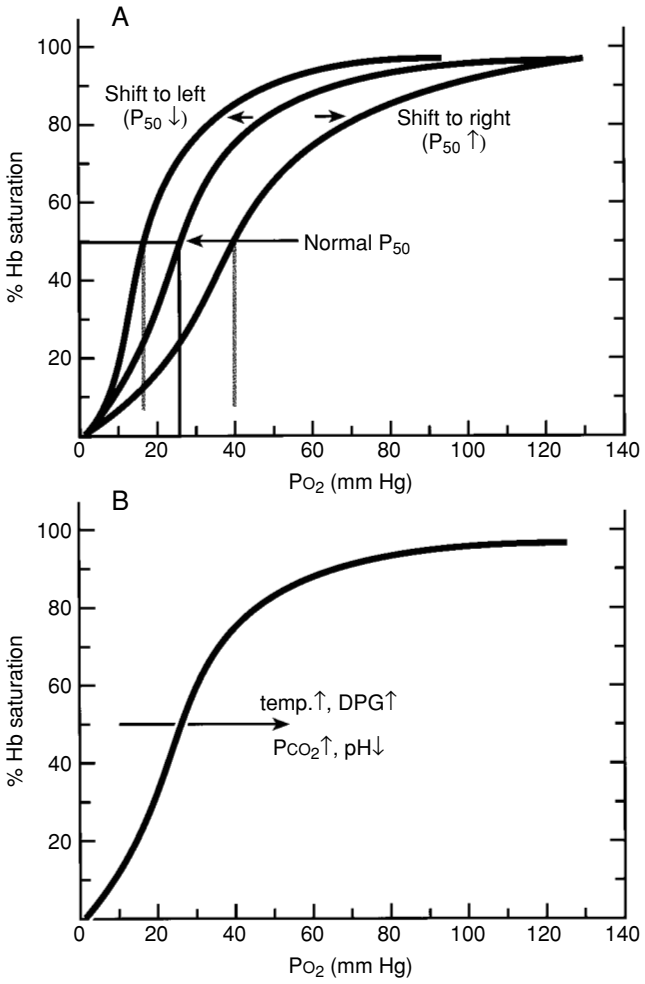

FIGURE 21.7 **Hemoglobin (Hb) binding affinity for O_2.** **A,** A shift in the oxyhemoglobin equilibrium curve affects the P_{50}. **B,** An increase in temperature, $[H^+]$, or arterial P_{CO_2} causes a rightward shift of the oxyhemoglobin equilibrium curve. A P_{50} increase indicates that binding affinity for oxygen decreases, which favors the unloading of O_2 from Hb at the tissue level. An increase in red cell levels of 2,3-diphosphoglycerate (DPG) will also shift the curve to the right. The increase in DPG occurs with hypoxemic conditions.

Effect of Blood Chemistry on Hemoglobin Binding Affinity.

Several factors affect the binding affinity of hemoglobin for O_2, including temperature, arterial carbon dioxide tension, and arterial pH. A rise in P_{CO_2}, a fall in pH, and a rise in temperature all shift the curve to the right (see Fig. 21.7). The effect of carbon dioxide and hydrogen ions on the affinity of hemoglobin for oxygen is known as the **Bohr effect.** A shift of the oxyhemoglobin equilibrium curve to the right is physiologically advantageous at the tissue level because the affinity is lowered (increased P_{50}). A rightward shift enhances the unloading of oxygen for a given P_{O_2} in the tissue, and a leftward shift increases the affinity of hemoglobin for oxygen, thereby, lowering the ability to release oxygen to the tissues. A simple way to remember the functional importance of these shifts is that an exercising muscle is warm and acidic and produces large amounts of carbon dioxide (high P_{CO_2}), all of which favor the unloading of more oxygen to metabolically active muscles.

Red blood cells contain 2,3-diphosphoglycerate (2,3-DPG), an organic phosphate compound that also can affect affinity of hemoglobin for oxygen. In red cells, 2,3-DPG levels are much higher than in other cells because erythrocytes lack mitochondria. An increase in 2,3-DPG facilitates unloading of oxygen from the red cell at the tissue level (shifts the curve to the right). An increase in red cell 2,3-DPG occurs with exercise and with hypoxia (e.g., high altitude, chronic lung disease).

Oxygen content, rather than P_{O_2} or Sa_{O_2}, is what keeps us alive and serves as a better gauge for oxygenation. For example, an individual can have a normal arterial P_{O_2} and Sa_{O_2} but reduced oxygen content. This situation is seen in patients who have anemia (a decreased number of circulating red cells). A patient with anemia who has a hemoglobin concentration half of normal (7.5 g/dL instead of 15 g/dL) will have a normal arterial P_{O_2} and Sa_{O_2}, but oxygen content will be reduced to half of normal. A patient with anemia has a normal Sa_{O_2} because that content and capacity are proportionally reduced. The usual oxyhemoglobin equilibrium curve does not show changes in blood oxygen content, since the vertical axis is saturation. If the vertical axis is changed to oxygen content (mL O_2/dL blood), then changes in content are seen (Fig. 21.8). The shape of the oxyhemoglobin equilibrium curve does not change, but the curve moves down to reflect the reduction in oxygen content. A good analogy for comparing an anemic patient with a normal patient is a bicycle tire and a truck tire: both can have the same air pressure, but the amount of air each tire holds is different.

Effect of Carbon Monoxide.

Carbon monoxide interferes with oxygen transport by competing for the same binding sites on hemoglobin. Carbon monoxide binds to hemoglobin to form **carboxyhemoglobin** (HbCO). The reaction

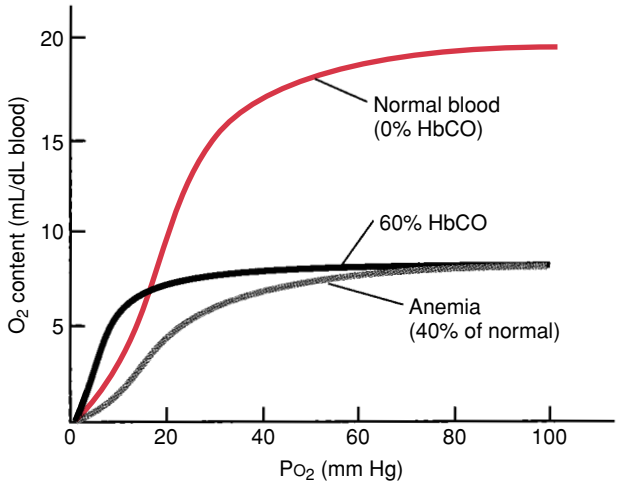

FIGURE 21.8 **Effect of blood hematocrit and CO on the oxyhemoglobin equilibrium curve.** Severe anemia can lower the O_2 content to 40% of normal. The blood O_2 content of an individual exposed to CO is shown for comparison. When the blood is 60% saturated with carbon monoxide (HbCO), O_2 content is reduced to about 8 mL/dL of blood. Note the leftward shift of the oxyhemoglobin equilibrium curve when CO binds with hemoglobin.

(Hb + CO ≔ HbCO) is reversible and is a function of P_{CO}. This means that breathing higher concentrations of CO will favor the reaction to the right. Breathing fresh air will favor the reaction to the left, which will cause CO to be released from the hemoglobin. A striking feature of CO is a binding affinity about 210 times that of oxygen. Consequently, CO will bind with the same amount of hemoglobin as oxygen at a partial pressure 210 times lower than that of oxygen. For example, breathing normal air (21% O_2) contaminated with 0.1% CO would cause half of the hemoglobin to be saturated with CO and half with O_2. With the high affinity of hemoglobin for CO, breathing a small amount CO can result in the formation of large amounts of HbCO. Arterial P_{O_2} in the plasma will still be normal because the oxygen diffusion gradient has not changed. However, oxygen content will be greatly reduced because oxygen cannot bind to hemoglobin. This is seen in Figure 21.8, which shows the effect of CO on the oxyhemoglobin equilibrium curve. When the blood is 60% saturated with CO (carboxyhemoglobin) the oxygen content is reduced to less than 10 mL/dL. The presence of CO also shifts the curve to the left, making it more difficult to unload or release oxygen to the tissues.

Carbon monoxide is dangerous for several reasons:

- It has a strong binding affinity for hemoglobin.
- As an odorless, colorless, and nonirritating gas, it is virtually undetectable.
- Pa_{O_2} is normal, and there is no feedback mechanism to indicate that oxygen content is low.
- There are no physical signs of hypoxemia (i.e., cyanosis or bluish color around the lips and fingers) because the blood is bright cherry red when CO binds with hemoglobin.

Therefore, a person can be exposed to CO and have oxygen content reduced to a level that becomes lethal, by causing tissue anoxia, without the individual being aware of the danger. The brain is one of the first organs affected by lack of oxygen. CO can alter reaction time, cause blurred vision and, if severe enough, cause unconsciousness.

The best treatment for CO poisoning is breathing 100% oxygen or a mixture of 95% O_2/5% CO_2. Since O_2 and CO compete for the same binding site on the hemoglobin molecule, breathing a high oxygen concentration will drive off the CO and favor the formation of oxyhemoglobin. The addition of 5% carbon dioxide to the inspired gas stimulates ventilation, which lowers the CO and enhances the

CLINICAL FOCUS BOX 21.1

Free Radical-Induced Lung Injury

Although an "oxygen paradox" has long been recognized in biology, only recently has it been well understood: Oxygen is essential for life, but too much oxygen or inappropriate oxygen metabolism can be harmful to both cells and the organism. The synthesis of ATP involves reactions in which molecular oxygen is reduced to form water. This reduction is accomplished by addition of four electrons by the mitochondrial electron transport system. About 98% of the oxygen consumed is reduced to water in the mitochondria. "Leaks" in the mitochondrial electron transport system, however, allow oxygen to accept less than four electrons, forming a free radical.

A **free radical** is any atom, molecule, or group of molecules with an unpaired electron in its outermost orbit. Free radicals include the **superoxide ion** ($O_2{\bullet}^-$) and the **hydroxyl radical** (•OH). The single unpaired electron in the free radical is denoted by a dot. The •OH radical is the most reactive and most damaging to cells. **Hydrogen peroxide** (H_2O_2), while not a free radical, is also reactive to tissues and has the potential to generate the hydroxyl radical (•OH). These three substances are collectively called **reactive oxygen species** (ROS). In addition to free radicals produced by leaks in the mitochondrial transport system, ROS also can be formed by cytochrome P_{450}, in the production of NADPH and in arachidonic acid metabolism. Superoxide ion in the presence of NO will form **peroxynitrite**, another free radical that is also extremely toxic to cells. Under normal conditions, ROS are neutralized by the protective enzymes **superoxide dismutase**, **catalase**, and **peroxidases** and no damage occurs. However, when ROS are greatly increased, they overwhelm the protective enzyme systems and damage cells by oxidizing membrane lipids, cellular proteins, and DNA.

The lungs are a major organ for free radical injury, and the pulmonary vessels are the primary target site. Free radicals damage the pulmonary capillaries, causing them to become leaky, leading to pulmonary edema. In addition to intracellular production, ROS are produced during inflammation and episodes of oxidant exposure (i.e., oxygen therapy or breathing ozone and nitrogen dioxide from polluted air). During the inflammatory response, neutrophils become sequestered and activated; they undergo a respiratory burst (which produces free radicals) and release catalytic enzymes. This release of free radicals and catalytic enzymes functions to kill bacteria, but endothelial cells can become damaged in the process.

Paraquat, an agricultural herbicide, is another source of free radical-induced injury to the lungs. Crop dusters and migrant workers are particularly at risk because of exposure to paraquat through the lungs and skin. Tobacco or marijuana that has been sprayed with paraquat and subsequently smoked can also produce lung injury from ROS.

Ischemia-reperfusion, another cause of free radical-induced injury in the lungs, usually results from a blood clot that gets lodged in the pulmonary circulation. Tissues beyond the clot (or embolus) become ischemic, cellular ATP decreases, and hypoxanthine accumulates. When the clot dissolves, blood flow is reestablished. During the reperfusion phase, hypoxanthine, in the presence of oxygen, is converted to xanthine and then to urate. These reactions, catalyzed by the enzyme **xanthine oxidase** on the pulmonary endothelium, result in the production of superoxide ions. Neutrophils also become sequestered and activated in these vessels during the reperfusion phase. Thus, the pulmonary vasculature and surrounding lung parenchyma become damaged from a double hit of free radicals—those produced from the oxidation of hypoxanthine and those from activated neutrophils.

release of CO from hemoglobin. The loading and unloading of CO from hemoglobin is a function of P_{CO}.

Oxygen is not always beneficial. Oxygen metabolism can produce harmful products that injure tissues (see Clinical Focus Box 21.1).

Carbon Dioxide Is Transported in Three Forms

Figure 21.9 illustrates the processes involved in carbon dioxide transport. Carbon dioxide is carried in the blood in three forms:

- Physically dissolved in the plasma (10%).
- As bicarbonate ions in the plasma and in the red cells (60%).
- As **carbamino proteins** (30%).

The high P_{CO_2} in the tissues drives carbon dioxide into the blood, but only a small amount stays as dissolved CO_2 in the plasma. The bulk of the carbon dioxide diffuses into the red cell, where it forms either carbonic acid (H_2CO_3) or **carbaminohemoglobin.** In the red cell, carbonic acid is formed in the following reaction:

$$CO_2 + H_2O \underset{CA}{\rightleftharpoons} H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \qquad (4)$$

The hydration of CO_2 would take place very slowly if it were not accelerated about 1,000 times in red cells by the enzyme **carbonic anhydrase** (CA). This enzyme is also found in renal tubular cells, gastrointestinal mucosa, muscle, and other tissues, but its activity is highest in red blood cells.

Carbonic acid readily dissociates in red blood cells to form bicarbonate (HCO_3^-) and H^+. HCO_3^- leaves the red blood cells, and chloride diffuses in from the plasma to maintain electrical neutrality (see Fig. 21.9). The chloride movement is known as the **chloride shift** and is facilitated by a **chloride-bicarbonate exchanger** (**anion exchanger**) in the red blood cell membrane. The H^+ cannot readily move out because of the low permeability of the membrane to H^+. Most of the H^+ is buffered by hemoglobin: $H^+ + HbO_2^- \rightleftharpoons HHb + O_2$. As H^+ binds to hemoglobin, it decreases oxygen binding and shifts the oxyhemoglobin equilibrium curve to the right. This promotes the unloading of oxygen from hemoglobin in the tissues and favors the carrying of carbon dioxide. In the pulmonary capillaries, the oxygenation of hemoglobin favors the unloading of carbon dioxide.

Carbaminohemoglobin is formed in red cells from the reaction of carbon dioxide with free amine groups (NH_2) on the hemoglobin molecule:

$$CO_2 + HbNH_2 \rightleftharpoons HbNHCOOH \qquad (6)$$

Deoxygenated hemoglobin can bind much more CO_2 in this way than oxygenated hemoglobin. Although major reactions related to CO_2 transport occur in the red cells, the bulk of the CO_2 is actually carried in the plasma in the form of bicarbonate.

A **carbon dioxide equilibrium curve** can be constructed in a fashion similar to that for oxygen (Fig. 21.10). The carbon dioxide equilibrium curve is nearly a straight-line function of P_{CO_2} in the normal arterial CO_2 range. Note that a higher P_{O_2} will shift the curve downward and to the right. This is known as the **Haldane effect**, and its advantage is that it allows the blood to load more CO_2 in the tissues and unload more CO_2 in the lungs.

Important differences are observed between the carbon dioxide and oxygen equilibrium curves (Fig. 21.11). First, one liter of blood can hold much more carbon dioxide than oxygen. Second, the CO_2 equilibrium curve is steeper and more linear, and because of the shape of the CO_2 equilibrium curve, large amounts of CO_2 can be loaded and un-

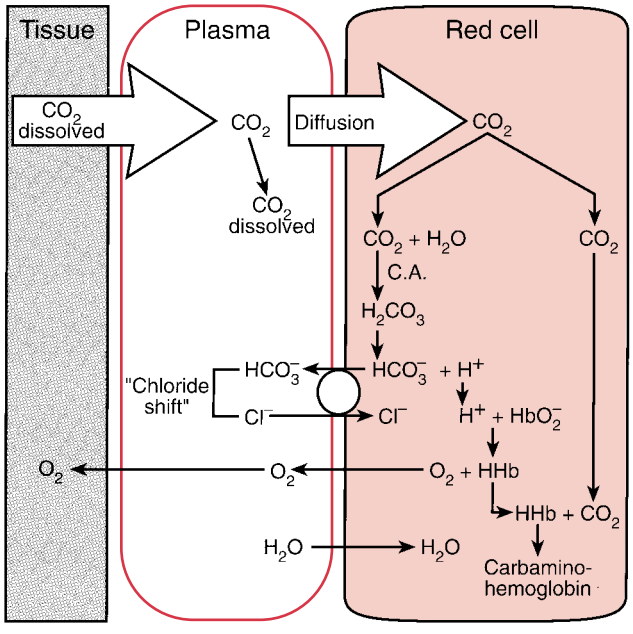

FIGURE 21.9 **Carbon dioxide transport. CO_2 is transported in the blood in three forms: physically dissolved, as HCO_3^-**, and as carbaminohemoglobin in the red cell (see text for details). The uptake of CO_2 favors the release of O_2.

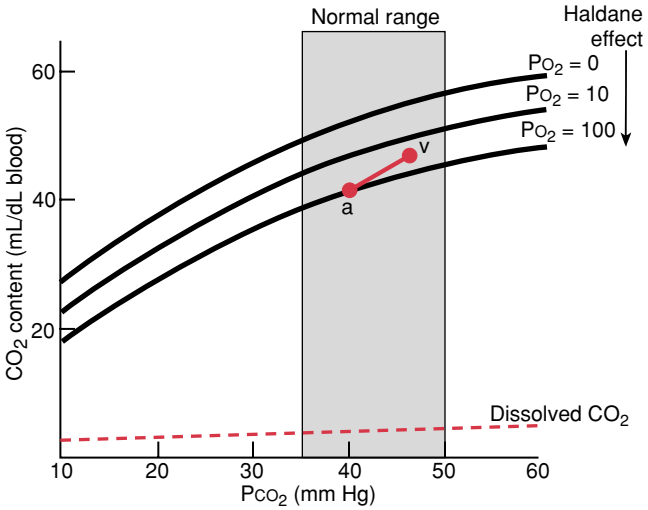

FIGURE 21.10 **Effect of O_2 on the carbon dioxide equilibrium curve.** The carbon dioxide equilibrium curve is relatively linear. An increase in P_{O_2} tension causes a rightward and downward shift of the curve. The P_{O_2} effect on the CO_2 equilibrium curve is known as the Haldane effect. The dashed line indicates the amount dissolved in plasma. a = CO_2 content in arterial blood; v = CO_2 content in mixed venous blood.

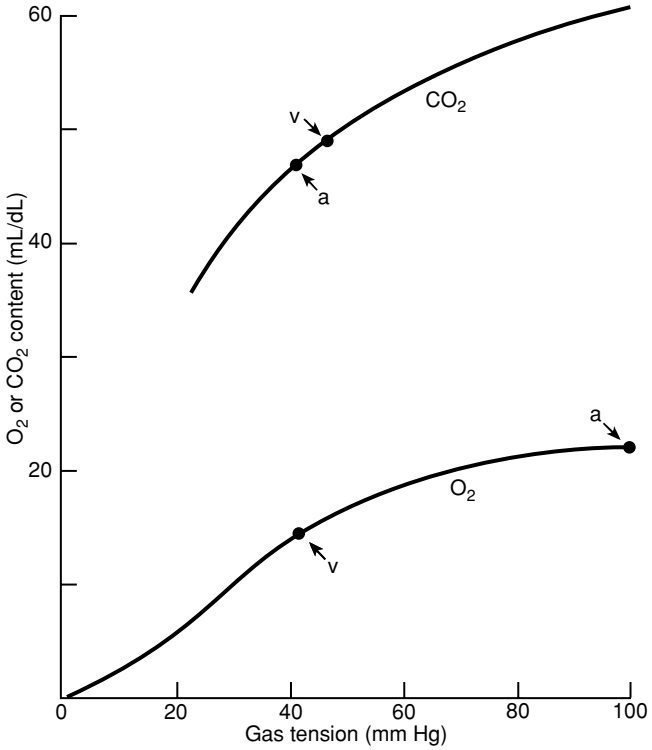

FIGURE 21.11 Comparison of the oxyhemoglobin and CO_2 equilibrium curves. The carrying capacity for CO_2 is much greater than for O_2. The increased steepness and linearity of the CO_2 equilibrium curve allow the lungs to remove large quantities of CO_2 from the blood with a small change in CO_2 tension. a = gas content in arterial blood; v = gas content in mixed venous blood.

loaded from the blood with a small change in P_{CO_2}. This is important not only in gas exchange and transport but also in the regulation of acid-base balance.

RESPIRATORY CAUSES OF HYPOXEMIA

Under normal conditions, hemoglobin is 100% saturated with oxygen when the blood leaves the pulmonary capillaries, and the end-capillary P_{O_2} equals alveolar P_{O_2}. However, the blood that leaves the lungs (via the pulmonary veins) and returns to the left side of the heart has a lower P_{O_2} than pulmonary end-capillary blood. As a result, the systemic arterial blood has an average oxygen tension (Pa_{O_2}) of about 95 mm Hg and is only 98% saturated.

Venous Admixture Causes an Alveolar-Arterial Oxygen Gradient

The difference between alveolar oxygen tension (PA_{O_2}) and arterial oxygen tension (Pa_{O_2}) is the **alveolar-arterial oxygen gradient** or **A-aO_2 gradient** (Fig. 21.12). Because alveolar P_{O_2} is normally 100 to 102 mm Hg and arterial P_{O_2} is 85 to 95 mm Hg, a normal A-aO_2 gradient is 5 to 15 mm Hg. The A-aO_2 gradient is obtained from blood gas measurements and the alveolar gas equation to determine PA_{O_2}.

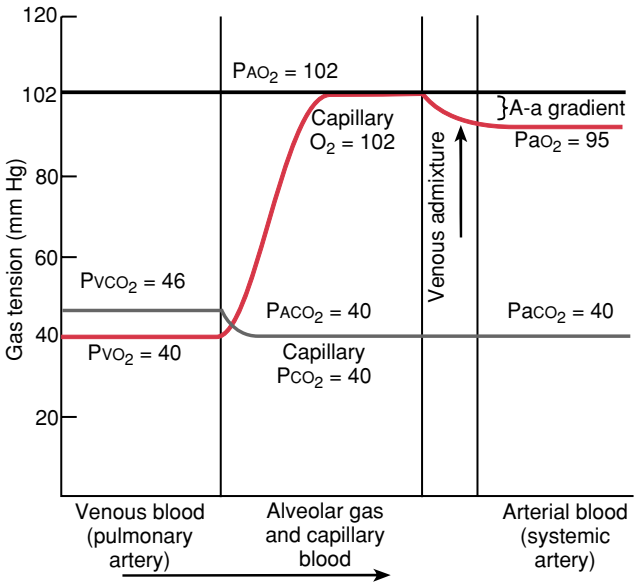

FIGURE 21.12 The alveolar-arterial oxygen gradient. The diagram shows O_2 and CO_2 tensions in blood in the pulmonary artery, pulmonary capillaries, and systemic arterial blood. The P_{O_2} leaving the pulmonary capillary has equilibrated with alveolar P_{O_2}. However, systemic arterial P_{O_2} is below alveolar P_{O_2}. Venous admixture results in the alveolar-arterial (A-a) oxygen gradient.

Recall from Chapter 19 that the simplified equation is $PA_{O_2} = FI_{O_2} \times (P_B - 47) - 1.2 \times PA_{O_2}$.

The A-aO_2 gradient arises in the normal individual because of venous admixture as a result of a shunt (e.g., bronchial circulation) and regional variations of the $\dot{V}/\dot{Q}$ ratio. Approximately half of the normal A-aO_2 gradient is caused by the bronchial circulation and half due to regional variations of the $\dot{V}/\dot{Q}$ ratio. In some pathophysiological disorders, the A-aO_2 gradient can be greatly increased. A value greater than 15 mm Hg is considered abnormal and usually leads to low oxygen in the blood or hypoxemia. The normal ranges of blood gases are shown in Table 21.1. Values for Pa_{O_2} below 85 mm Hg indicate hypoxemia. A Pa_{CO_2} less than 35 mm Hg is called **hypocapnia**; and a Pa_{CO_2} greater than 48 mm Hg is called **hypercapnia**. A pH value for arterial blood less than 7.35 or greater than 7.45 is called **acidemia** or **alkalemia**, respectively.

TABLE 21.1 Arterial Blood Gases

	Normal Range[a]
Pa_{O_2}	85–95 mm Hg
Pa_{CO_2}	35–48 mm Hg
Sa_{O_2}	94–98%
pH	7.35–7.45
HCO_3^-	23–28 mEq/L

[a] Normal range at sea level.

Respiratory Dysfunction Is the Major Cause of Hypoxemia

The causes of hypoxemia are classified as respiratory and nonrespiratory (Table 21.2). Respiratory dysfunction is by far the most common cause of hypoxemia in adults. Nonrespiratory causes include anemia, carbon monoxide poisoning, and a decreased inspired oxygen tension (as occurs at high altitude) (see Clinical Focus Box 21.2).

Regional Hypoventilation. The respiratory causes of hypoxemia are listed in order of frequency in Table 21.2. **Regional hypoventilation** is by far the most common cause of hypoxemia (about 90% of cases) and reflects a local $\dot{V}_A/\dot{Q}$ imbalance stemming from a partially obstructed airway. A fraction of the blood that passes through the lungs

TABLE 21.2 Pathophysiological Causes of Hypoxemia

Causes	Effect on A-aO_2 Gradient
Respiratory	
Regional low $\dot{V}_A/\dot{Q}$ ratio	Increased
Anatomic shunt	Increased
Generalized hypoventilation	Normal
Diffusion block	Increased
Nonrespiratory	
Intracardiac right-to-left shunt	Increased
Decreased P_{IO_2}, low P_B, low F_{IO_2}	Normal
Reduced oxygen content (anemia and CO poisoning)	Normal

CLINICAL FOCUS BOX 21.2

Anemia

Anemia, an abnormally low hematocrit or hemoglobin concentration, is by far the most common disorder affecting erythrocytes. The different causes of anemia can be grouped into three categories: decreased erythropoiesis by bone marrow, blood loss, and increased rate of red cell destruction (hemolytic anemia).

Several mechanisms lead to decreased production of red cells by the bone marrow, including aplastic anemia, malignant neoplasms, chronic renal disease, defective DNA synthesis, defective hemoglobin synthesis, and chronic liver disease. **Aplastic anemia** is the result of stem cell destruction in the bone marrow, which leads to decreased production of white cells, platelets, and erythrocytes. Malignant neoplasms (e.g., leukemia) cause an overproduction of immature red cells. Patients with chronic renal disease have a decreased production of erythropoietin, with a concomitant decrease in red cell production.

Patients with defective DNA synthesis have **megaloblastic anemia**, a condition in which red cell maturation in the bone marrow is abnormal; this may result from vitamin B_{12} or folic acid deficiency. These cofactors are essential for DNA synthesis. Vitamin B_{12} is present in high concentration in liver and, to some degree, in most meat, but it is absent in plants. Vitamin B_{12} deficiency is rare except in strict vegetarians. Folic acid is widely distributed in leafy vegetables; folic acid deficiency commonly occurs where malnutrition is prevalent. Pernicious anemia is a form of megaloblastic anemia resulting from vitamin B_{12} deficiency. Most commonly in adults over 60, it results not from deficient dietary intake but from a decreased vitamin B_{12} absorption by the small intestine. Pernicious anemia is linked to an autoimmune disease in which there is immunological destruction of the intestinal mucosa, particularly the gastric mucosa.

Iron-deficiency anemia is the most common cause of anemia worldwide. Although it occurs in both developed and undeveloped countries, the causes are different. In developed countries, the cause is usually due to pregnancy or chronic blood loss due to gastrointestinal ulcers or neoplasms. In undeveloped countries, hookworm infections account for most cases of iron-deficiency anemia.

Acute or chronic blood loss is another cause of anemia. With hemorrhage, red cells are lost and the hypovolemia causes the kidneys to retain water and electrolytes as a compensation. Retention of water and electrolytes restores the blood volume, but the concomitant dilution of the blood causes a further decrease in the red cell count, hemoglobin concentration, and hematocrit. Chronic bleeding is compensated by erythroid hyperplasia, which eventually depletes iron stores. Thus, chronic blood loss results in iron-deficiency anemia.

The last category, increased rate of red cell destruction, includes the Rh factor and sickle-cell anemia. The Rhesus (Rh) blood group antigens are involved in maintaining erythrocyte structure. Patients who lack Rh antigens (Rh null) have severe deformation of the red cells.

Sickle-cell anemia, associated with the abnormal hemoglobin HbS gene, is common in Africa, India, and among African Americans but rare in the Caucasian and Asian populations. In the sickle-cell trait, which occurs in about 9% of African Americans, one abnormal gene is present. A single point mutation occurs in the hemoglobin molecule, causing the normal glutamic acid at position 6 of the beta chain to be replaced with valine, resulting in HbS. The amino acid substitution is on the surface, resulting in a tendency for the hemoglobin molecule to crystallize with anoxia. However, heterozygous individuals have no symptoms, and oxygen transport by fetal (HbF) and adult hemoglobin (HbA) is normal. Sickle-cell trait (i.e., heterozygous individuals) offers protection against malaria, and this selective advantage is thought to have favored the persistence of the HbS gene, especially in regions where malaria is common. Sickle-cell disease represents the homozygous condition (S/S) and occurs in about 0.2% of African Americans. The onset of sickle-cell anemia occurs in infancy as HbS replaces HbF; death often occurs early in adult life. Patients with sickle-cell anemia have >80% HbS in their blood with a decrease or an absence of normal HbA.

Whatever the cause of anemia, the pathophysiological effect is the same—hypoxemia. Symptoms include pallor of the lips and skin, weakness, fatigue, lethargy, dizziness, and fainting. If the anemia is severe, myocardial hypoxia can lead to angina pain.

does not get fully oxygenated, resulting in an increase in venous admixture. Only a small amount of venous admixture is required to lower systemic arterial P_{O_2}, due to the nature of the oxyhemoglobin equilibrium curve. This can be seen from Figure 21.13, which depicts oxygen content from three groups of alveoli with low, normal, and high $\dot{V}_A/\dot{Q}$ ratios. The oxygen content of the blood leaving these alveoli is 16.0, 19.5, and 20.0 mL/dL of blood, respectively. As Figure 21.13 shows, a low $\dot{V}_A/\dot{Q}$ ratio is far more serious because it has the greatest effect on lowering both the P_{O_2} and the O_2 content because of the nonlinear shape of the oxyhemoglobin equilibrium curve. Patients who have an abnormally low $\dot{V}_A/\dot{Q}$ ratio have a high A-a_{O_2} gradient, low P_{O_2}, and low O_2 content, but usually a normal or slightly elevated Pa_{CO_2}. Pa_{CO_2} does not change much because the CO_2 equilibrium curve is nearly linear, which allows excess CO_2 to be removed from the blood by the lungs.

Another cause for a regionally low $\dot{V}_A/\dot{Q}$ ratio is a large blood clot that occludes a major artery in the lungs. When a major pulmonary artery becomes occluded, a greater portion of the cardiac output is redirected to another part of the lungs, resulting in overperfusion with respect to alveolar ventilation. This causes a regionally low $\dot{V}_A/\dot{Q}$ ratio, and leads to an increase in venous admixture.

Shunts. The next most common cause of hypoxemia is a shunt, either a right-to-left anatomic shunt or an absolute intrapulmonary shunt. The latter occurs when an airway is totally obstructed by a foreign object (such as a peanut) or by tumors. Patients with hypoxemia stemming from a shunt also have a high A-a_{O_2} gradient, low P_{O_2}, and low O_2 content, and a normal or slightly elevated Pa_{CO_2}. A test that is often used to distinguish between an abnormally low $\dot{V}_A/\dot{Q}$ ratio and a shunt is to have the patient breathe 100% O_2 for 15 minutes. If the Pa_{O_2} is >150 mm Hg, the cause is a low $\dot{V}_A/\dot{Q}$ ratio. If the patient's Pa_{O_2} is <150 mm Hg, the cause of hypoxemia is a shunt. The principle for using 100% O_2 is illustrated in Figure 21.14. The patient with regional hypoventilation who breathes 100% O_2 compensates for the low $\dot{V}_A/\dot{Q}$ ratio, and because all of the blood leaving the pulmonary capillaries is now fully saturated, the venous admixture is eliminated. However, the low arterial P_{O_2} does not get corrected by breathing 100% O_2 in a patient with a shunt because the enriched oxygen mixture never comes into contact with the shunted blood.

Generalized Hypoventilation. **Generalized hypoventilation**, the third most common cause of hypoxemia, occurs when alveolar ventilation is depressed. This situation can

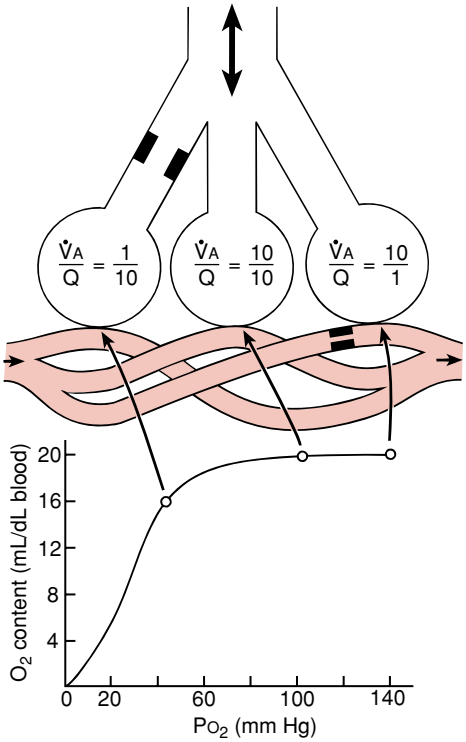

FIGURE 21.13 **Effect of venous admixture on O_2 content.** Because of the S-shaped oxyhemoglobin equilibrium curve, a high $\dot{V}_A/\dot{Q}$ ratio has little effect on arterial O_2 content. However, mixing with blood from a region with a low $\dot{V}_A/\dot{Q}$ ratio can dramatically lower P_{O_2} in blood leaving the lungs.

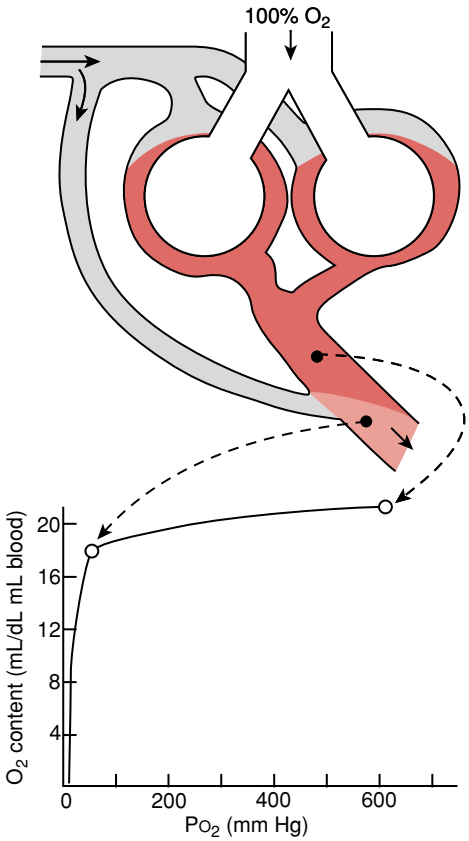

FIGURE 21.14 **Diagnosis of a shunt.** A shunt can be diagnosed by having the subject breathe 100% O_2 for 15 minutes. P_{O_2} in systemic arterial blood in a patient with a shunt does not increase above 150 mm Hg during the 15-minute period. The shunted blood is not exposed to 100% O_2, and the venous admixture reduces arterial P_{O_2}.

arise from a chronic obstructive pulmonary disorder (such as emphysema) or depressed respiration (as a result of a head injury or a drug overdose, for example). Since ventilation is depressed, there is also a significant increase in arterial P_{CO_2} with a concomitant decrease in arterial pH. In generalized hypoventilation, total ventilation is insufficient to maintain normal systemic arterial P_{O_2} and P_{CO_2}. A feature that distinguishes generalized hypoventilation from the other causes of hypoxemia is a normal A-aO_2 gradient, as a result of the alveolar and arterial P_{O_2} being lowered equally. If a patient has a low Pa_{O_2} and a normal A-aO_2 gradient, the cause of hypoxemia is entirely due to generalized hypoventilation. The best corrective measure for generalized hypoventilation is to place the patient on a mechanical ventilator, breathing room air. This treatment will return both arterial P_{O_2} and P_{CO_2} to normal. Administering supplemental oxygen to a patient with generalized hypoventilation will correct hypoxemia but not hypercapnia because ventilation is still depressed.

Diffusion Block. The least common cause of hypoxemia is a **diffusion block.** This condition occurs when the diffusion distance across the alveolar-capillary membrane is increased or the permeability of the alveolar-capillary membrane is decreased. It is characterized by a low Pa_{O_2}, high A-aO_2 gradient, and high Pa_{CO_2}. Pulmonary edema is one of the major causes of diffusion block.

In summary, there are four basic respiratory disturbances that cause hypoxemia. Examining the A-aO_2 gradient or Pa_{CO_2} and/or breathing 100% oxygen distinguishes the four types. For example, if a patient has a low Pa_{O_2}, high Pa_{CO_2}, and normal A-aO_2 gradient, the cause of hypoxemia is generalized hypoventilation. If the Pa_{O_2} is low and the A-aO_2 gradient is high, then the cause can be a shunt, regional low $\dot{V}_A/\dot{Q}$ ratio, or a diffusion block. Breathing 100% O_2 will distinguish between a low $\dot{V}_A/\dot{Q}$ ratio and a shunt. Diffusion impairment is the least likely cause and can be deduced if the other three causes have been eliminated.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the one lettered answer or completion that is BEST in each case.

1. In healthy individuals, the cause of an A-aO_2 gradient is
   (A) Low diffusing capacity for oxygen compared with that for carbon dioxide
   (B) A high $\dot{V}_A/$ ratio in the apex of the lungs
   (C) Overventilation in the base of the lung
   (D) A bronchial circulation shunt
   (E) A right-to-left shunt in the heart
2. Which of the following will *not* cause a low lung diffusing capacity (D_L)?
   (A) Decreased diffusion distance
   (B) Decreased capillary blood volume
   (C) Decreased surface area
   (D) Decreased cardiac output
   (E) Decreased hemoglobin concentration in the blood
3. With respect to oxygen and carbon dioxide transport,
   (A) The slopes of the oxygen and carbon dioxide content curves are similar
   (B) Equal amounts of oxygen and carbon dioxide can be carried in 100 mL of blood
   (C) The presence of carbon dioxide decreases the P_{50} for O_2
   (D) The presence of oxygen lowers carbon dioxide content in the blood
   (E) Most of the O_2 and CO_2 are transported by the red blood cell
4. Which of the following best characterize the blood oxygen of an otherwise healthy person who has lost enough blood to decrease his hemoglobin concentration from the normal 15g/dL of blood to 10 g/dL of blood?

	Pa_{O_2}	Sa_{O_2}	O_2 *content*
(A)	Normal	Normal	Decreased
(B)	Normal	Decreased	Decreased
(C)	Decreased	Decreased	Decreased
(D)	Decreased	Normal	Decreased
(E)	Decreased	Decreased	Normal

5. Which of the following would *not* favor the unloading of oxygen from hemoglobin in tissues?
   (A) Increase in P_{50}
   (B) Increase in tissue pH
   (C) Increase in 2,3-DPG levels
   (D) Increase in tissue P_{CO_2}
   (E) Increase in temperature
6. Which of the following sets of arterial blood gas data is consistent with the presence of an abnormally low $\dot{V}_A/\dot{Q}$ ratio?
   (A) Pa_{O_2} = 130 mm Hg; Pa_{CO_2} = 30 mm Hg
   (B) Pa_{O_2} = 98 mm Hg; Pa_{CO_2} = 40 mm Hg
   (C) Pa_{O_2} = 95 mm Hg; Pa_{CO_2} = 40 mm Hg
   (D) Pa_{O_2} = 60 mm Hg; Pa_{CO_2} = 40 mm Hg
   (E) Pa_{O_2} = 50 mm Hg; Pa_{CO_2} = 30 mm Hg
7. Which of the following ranges of hemoglobin O_2 saturation from systemic venous to systemic arterial blood represents a normal resting condition?
   (A) 25 to 75%
   (B) 40 to 75%
   (C) 40 to 95%
   (D) 60 to 98%
   (E) 75 to 98%
8. A 54-year-old man sustains third-degree burns in a house fire. His respiratory rate is 30/min, Hb = 17 g/dL, arterial P_{O_2} is 95 mm Hg, and arterial O_2 saturation is 50%. The most likely cause of his low oxygen saturation is
   (A) Airway obstruction from smoke inhalation
   (B) Carbon monoxide poisoning
   (C) Pulmonary edema
   (D) Fever
   (E) An abnormally high $\dot{V}_A/$ ratio
9. A patient's Pa_{CO_2} is 68 mm Hg, P_{O_2} is 50 mm Hg, and A-aO_2 gradient is normal. These findings are most consistent with
   (A) A shunt
   (B) A low $\dot{V}_A/\dot{Q}$ ratio
   (C) A diffusion block
   (D) Generalized hypoventilation
   (E) A high $\dot{V}_A/\dot{Q}$ ratio
10. A patient is breathing room air and has Pa_{CO_2} of 45 mm Hg, Pa_{O_2} of 70 mm Hg, pH of 7.30, and Sa_{O_2} of 85%. What is her A-aO_2 gradient?
    (A) 16 mm Hg
    (B) 24 mm Hg
    (C) 26 mm Hg
    (D) 30 mm Hg
    (E) 40 mm Hg
11. A patient inspired a gas mixture containing a trace amount of carbon monoxide and then held his breath for 10 sec. During breath holding, the

alveolar P_{CO} averaged 0.5 mm Hg and CO uptake was 10 mL/min. What is his pulmonary diffusing capacity ($D_{L_{CO}}$)?
(A) 2.0 mL/min per mm Hg
(B) 5.0 mL/min per mm Hg
(C) 10 mL/min per mm Hg
(D) 20 mL/min per mm Hg
(E) 200 mL/min per mm Hg

SUGGESTED READING

Cotes JE. Lung Function: Assessment and Application in Medicine. 5th Ed. Boston: Blackwell Scientific, 1993.
Fishman AP. The Fick principle and the steady state. Am J Respir Crit Care Med 2000;161:692–694.
Staub NC. Basic Respiratory Physiology. New York: Churchill Livingstone, 1991.
Wagner PD. Determinants of maximal oxygen transport and utilization. Annu Rev Physiol 1996;58:21–50.
West JB. Ventilation/Blood Flow and Gas Exchange. 4th Ed. Oxford, UK: Blackwell Scientific, 1985.