

# Chapter 5

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## Oxygen and Carbon Dioxide Transport in Blood

The cells of the body carry out a variety of metabolic functions, including some that are essential to maintain cell integrity and others that allow cells to function collectively as tissues and organs. The former category includes processes such as active ion pumping and cell growth and repair, while the latter includes contraction, membrane transport, biosynthesis, and other metabolic processes. These active cell processes require energy expenditure. In most cells these energetic demands are met by oxidative metabolism, which produces adenosine triphosphate (ATP) in the mitochondrial electron transport system as molecular oxygen is consumed.

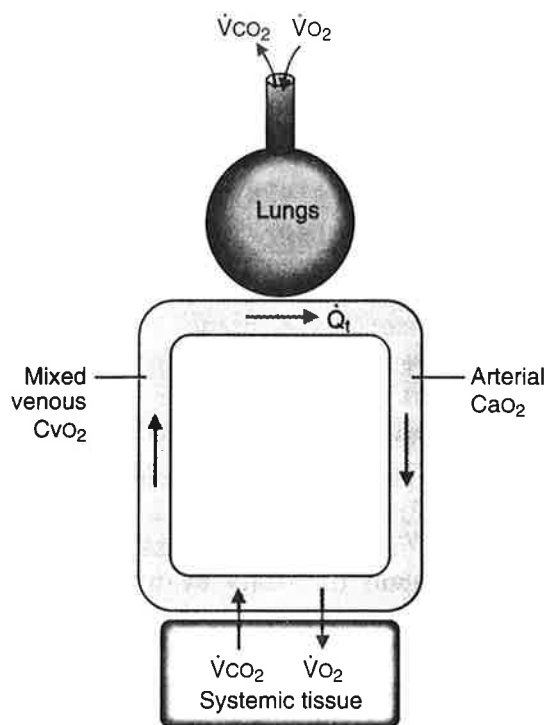
Under resting conditions, the concentration of oxygen within the mitochondria is normally far

greater than required to support electron transport. Consequently, the rate of ATP formation is set by metabolic demand rather than by the local availability of oxygen. The cardiopulmonary system functions to maintain this state by transporting enough oxygen from the lungs to the cells of the body to maintain tissue metabolic activity while carrying carbon dioxide back to the lungs for elimination. In this chapter, the focus is on the mechanisms involved in the carriage of oxygen and carbon dioxide in blood and on the factors that influence the uptake and release of these gases as blood passes through the capillaries of the lung and the systemic tissues. An important concept developed in this chapter is the interdependency of the simul-

taneous oxygen and carbon dioxide transport in blood. In this regard, the uptake of oxygen into blood passing through the pulmonary capillaries is facilitated by the simultaneous release of carbon dioxide from the blood into alveolar gas. Likewise, the release of carbon dioxide is facilitated by the simultaneous uptake of oxygen. In this sense, blood is ideally suited to the simultaneous transport of oxygen to the tissues and the transport of carbon dioxide to the lungs.

### Systemic Oxygen Delivery and Consumption: The Fick Relationship

The cardiac output ( $\dot{Q}_t$ ) is defined as the volume of blood pumped by the heart to the systemic tissues each minute (Figure 5-1). As blood passes through the systemic capillaries, some of the oxygen it carries leaves the capillaries and enters the tissue;



**Figure 5-1.** The Fick relationship for oxygen transport. Systemic oxygen delivery (ml/min) is the product of the cardiac output ( $\dot{Q}_t$ , dl/min) and the content of oxygen in arterial blood ( $C_{aO_2}$ , ml/dl). The rate at which unused oxygen is delivered back to the heart (returning  $O_2$ , ml/min) is calculated as the product of  $\dot{Q}_t$  and the mixed venous blood oxygen content ( $C_{\bar{v}O_2}$ , ml/dl). The difference between these is the rate of systemic oxygen consumption ( $\dot{V}_{O_2}$ ).

the remainder of the oxygen stays in the blood and returns to the heart and lungs. The total volume of oxygen transported to the systemic tissues per minute (*systemic oxygen delivery*) is the product of the  $\dot{Q}_t$  and the oxygen content of arterial blood:

Systemic oxygen delivery =

$$\dot{Q}_t \cdot \text{arterial blood oxygen content}$$

The unused volume of oxygen that returns from the systemic tissues per minute is the product of the cardiac output and the mixed venous blood oxygen content:

Oxygen returning =

$$\dot{Q}_t \cdot \text{mixed venous blood oxygen content}$$

Hence, the rate of oxygen consumption by systemic tissues ( $\dot{V}_{O_2}$ ) must equal the difference between the rates of oxygen delivery and oxygen returning:

$$\dot{V}_{O_2} = \dot{Q}_t \cdot (C_{aO_2} - C_{\bar{v}O_2})$$

where  $C_{aO_2}$  and  $C_{\bar{v}O_2}$  are the oxygen contents of arterial and mixed venous blood, respectively. This is the *Fick relationship*, which is based on the principle of conservation of mass. Oxygen content in blood is usually expressed in units of milliliters of oxygen per deciliter of blood (abbreviated as ml/dl) or equivalently as volume percent (vol%). Note that the units of oxygen content in blood are identical to units of concentration.

**EXAMPLE.** A subject has a cardiac output of 5 liters/min, an arterial blood oxygen content of 19 ml/dl, and a mixed venous blood oxygen content of 14 ml/dl. What is the systemic oxygen consumption?

Using the above relationship,

$$\begin{aligned} \dot{V}_{O_2} &= (50 \text{ dl/min})(19 \text{ ml/dl} - 14 \text{ ml/dl}) \\ &= 250 \text{ ml/min.} \end{aligned}$$

## OXYGEN TRANSPORT IN BLOOD

Blood is composed of red blood cells (erythrocytes), white blood cells (leukocytes), and platelets suspended in plasma, a protein- and lipid-containing liquid. The percentage of the blood volume composed of red blood cells is referred to as the *hematocrit*. Normally, this value is 37% to 42% in premenopausal women and slightly higher in men. Red blood cells contain quantities of *hemoglobin*, a molecule specialized for the transport of oxygen and carbon dioxide. Since each red blood cell contains approximately the same amount of hemoglobin, the overall hemoglobin concentration in blood is proportional to the blood hematocrit. Oxygen is carried in two forms by blood. Most of the oxygen carried is bound to hemoglobin, whereas a smaller portion of the oxygen is physically dissolved in the blood.

### Oxygen Transport by Hemoglobin

Hemoglobin is a molecule composed of four polypeptide chains (*globin*), each of which is linked to an iron-containing porphyrin ring (*heme*). The heme groups give rise to the characteristic red color of blood. Red blood cells formed during intrauterine development contain a fetal form of hemoglobin (*hemoglobin f*) composed of two  $\alpha$  polypeptide chains (141 amino acids each) and two  $\gamma$  polypeptide chains (146 amino acids). (see Chapter 10.) After birth, newly formed red blood cells contain adult hemoglobin (*hemoglobin A*); these gradually replace the cells containing hemoglobin f. Hemoglobin A is also a tetramer, composed of two  $\alpha$  and two  $\beta$  chains (146 amino acids) that share some similarities with the  $\gamma$  chains. These polypeptide chains mesh closely and are held together by hydrogen bonds and hydrophobic attractions. In its normal conformation, the interior of the hemoglobin molecule is highly hydrophobic while the exterior is hydrophilic. Because one oxygen molecule can reversibly bind to each heme group, a maximum of four oxygen molecules can be carried by a single hemoglobin molecule (Figure 5–2). The heme groups are situated within hydrophobic crevices in the globin molecule, and each contains an iron atom oxidized to the ferrous ( $2+$ ) state. This hydrophobic environment protects the iron ion from being oxidized to the ferric ( $3+$ ) state by water. Since molec-

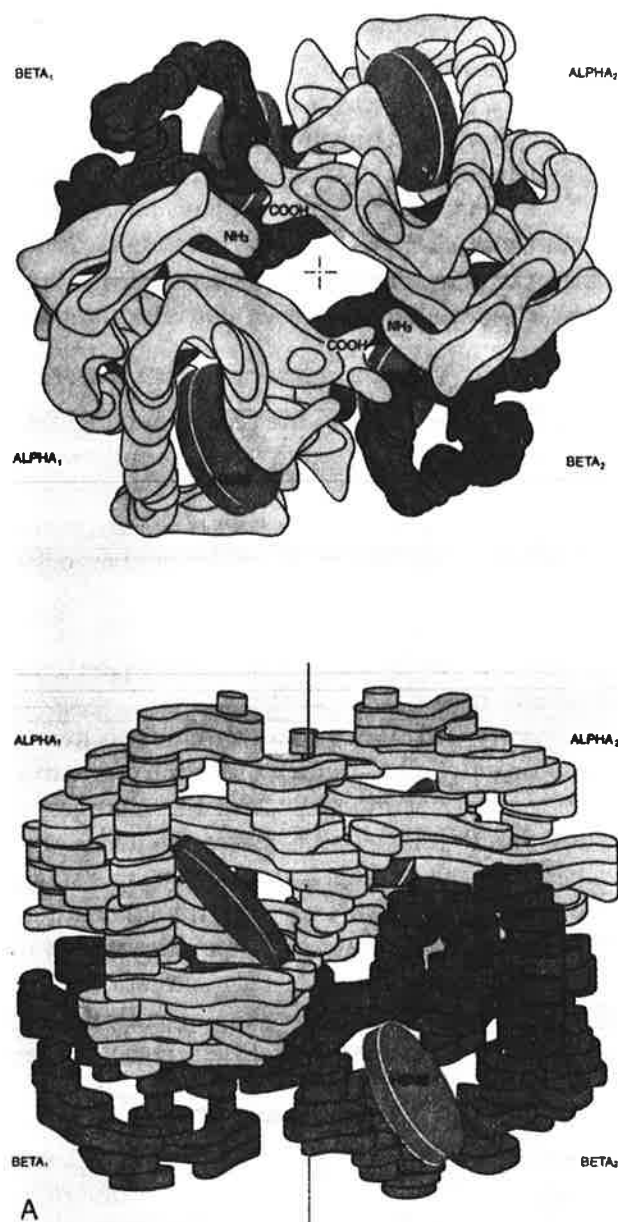
ular oxygen is lipophilic, it can gain access easily to the hydrophobic environment of the heme group where it binds reversibly. The optical absorption spectrum of hemoglobin shifts when oxygen binds to a heme group, which causes the difference in color between oxygenated and deoxygenated hemoglobin forms.

When oxygen combines with hemoglobin, the iron atom normally remains in the ferrous state. However, compounds such as ferricyanide (as well as certain drugs) can oxidize the iron to the ferric state and cause a change in the color of hemoglobin from red to brown. The resulting compound (*methemoglobin*) cannot function as a reversible oxygen carrier. *Glutathione reductase enzymes* present in red blood cells have the ability to reduce methemoglobin to hemoglobin, thereby restoring its ability to function as an oxygen carrier. Normally, 1% to 2% of the binding sites in blood are oxidized to the ferric state at any time.

The avidity with which oxygen binds to hemoglobin is heavily influenced by the tertiary structure of the hemoglobin molecule and the changes in conformation that it undergoes as oxygen is bound or released. A genetic alteration resulting in a single amino acid substitution in one of the chains may produce a dramatic change in the binding affinity of hemoglobin for oxygen. Genetic alterations that produce amino acid substitutions at critical locations in the protein may prove fatal because they render the molecule ineffective as a reversible carrier of oxygen. However, a large number of naturally occurring genetic alterations have been identified, many of which cause moderate alterations in the oxygen binding or other characteristics of the molecule. For example, in sickle cell anemia a valine amino acid replaces a glutamic acid residue on the  $\beta$  chain. This single amino acid substitution promotes the protein to form a gel in its deoxygenated state. When the hemoglobin forms a gel, the red blood cells distort from their normal biconcave disk shape into a crescent-like shape. Sickled cells are liable to form thrombi, resulting in a sickle cell crisis.

### Dissolved Oxygen in Blood

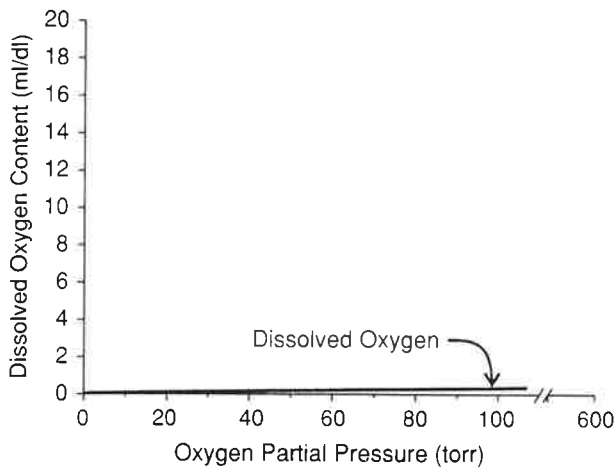
Part of the oxygen carried in blood remains physically dissolved in the lipid and aqueous components of the blood. Figure 5–3 shows the relationship between the concentration of dissolved oxygen and



**Figure 5-2.** The hemoglobin molecule. *A.* Oxygen binds reversibly at four porphyrin (heme) groups on the hemoglobin molecule. The heme groups are situated within hydrophobic nooks in the globin portion, making the ferrous ( $2^+$ ) ion accessible to lipophilic molecules such as oxygen and carbon monoxide but largely inaccessible to water. (*A*, redrawn from Perutz MF: *Sci Am* 239:68–83, 1978. Copyright © 1978, by Scientific American, Inc., George V. Kelvin, all rights reserved.) *B.* Chemical structure of the porphyrin (heme) groups, showing the ferrous ion where oxygen binds reversibly.

the *partial pressure of oxygen in blood*. The partial pressure of a gas in a liquid is somewhat analogous to a hydrostatic pressure of a fluid in a pipe (or a voltage in an electrical conductor), in the sense that it represents a potential force that will determine how vigorously the gas will try to leave the liquid. The partial pressures of gases in blood are impor-

tant, for they determine the direction and velocity at which the gases diffuse into or out of the blood as it passes through a capillary. One could adjust the  $PO_2$  in blood by exposing a volume of blood to a gas mixture with the desired  $PO_2$  and allowing the two to come to equilibrium (Figure 5-4). However, since the *solubility* of oxygen in plasma is relatively



**Figure 5-3.** Dissolved oxygen content in blood. The relationship between the volume of oxygen dissolved in a liquid (ml/dl) and the partial pressure (tension) of oxygen in the liquid is linear. Hence, doubling the partial pressure will double the dissolved oxygen content. Symbol illustrates the dissolved oxygen content that would exist at a  $P_{O_2}$  of 600 torr.

low, the concentration of dissolved oxygen is smaller than the portion bound to hemoglobin (see later). Nevertheless, the dissolved oxygen component is still significant and should always be taken into consideration when considering blood oxygen content. The dissolved portion is proportional to the

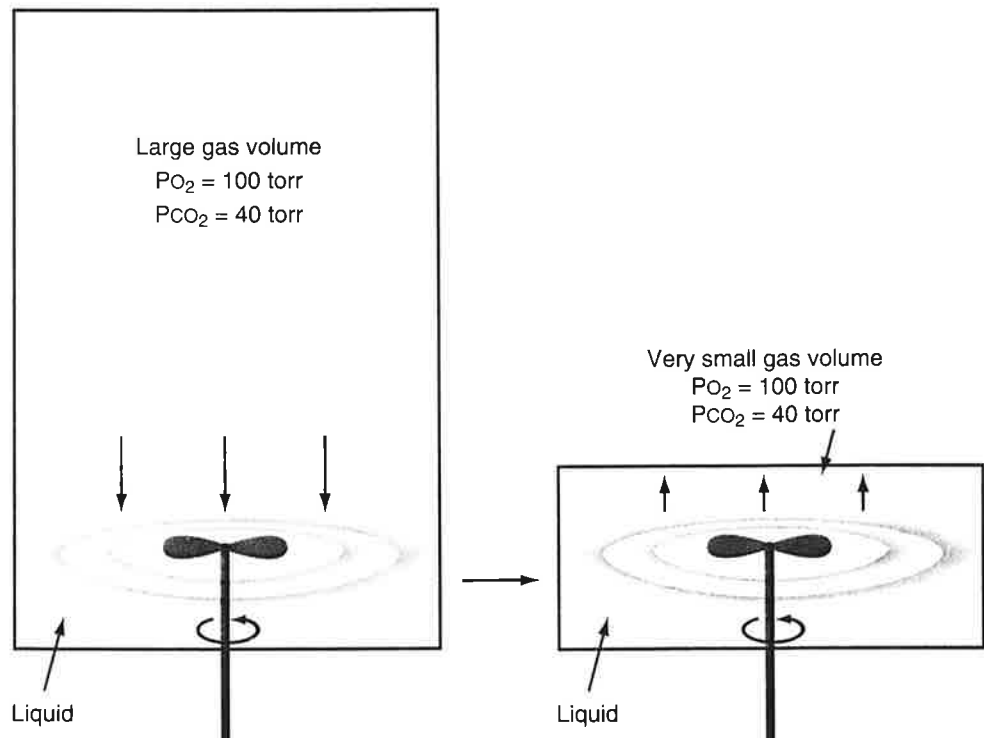
$P_{O_2}$  and is calculated by multiplying the oxygen tension (torr) by the oxygen solubility in plasma ( $0.00304 \text{ ml O}_2/(\text{dl} \cdot \text{torr})$ ).

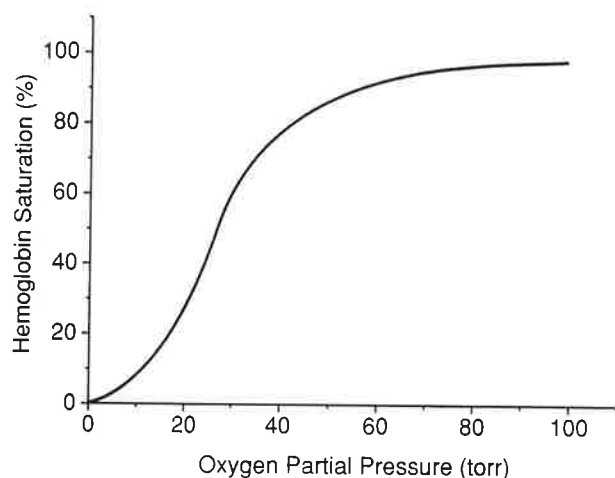
#### Oxyhemoglobin Saturation and Blood Oxygen Content

The molecular weight of hemoglobin is approximately 64,500 daltons, and each molecule has the potential to bind four oxygen atoms. Thus, 1 mmol of hemoglobin (64.5 g) can carry up to 4 mmol of oxygen ( $4 \times 22.4 \text{ ml/mmol} = 89.6 \text{ ml/mmol}$ ) if all of the binding sites are occupied (i.e., when the hemoglobin is *fully saturated*). Hence, each gram of hemoglobin can theoretically bind 1.39 ml of oxygen when the saturation is 100%. The value of 1.39 ml/g is therefore referred to as the *theoretical oxygen binding capacity* of hemoglobin. In practice, about 4% of the binding sites cannot function as oxygen carriers because some of the hemoglobin is present as methemoglobin (1% to 2%) and some of the binding sites are occupied by carbon monoxide (1% to 2%). For this reason, a value of 1.34 ml/g is sometimes used instead of 1.39 to represent the *physiological oxygen binding capacity*.

The number of oxygen molecules bound to hemoglobin depends on the  $P_{O_2}$  in the blood. The

**Figure 5-4.** Gas partial pressure in a liquid. The  $P_{O_2}$  in blood is the oxygen tension that is in equilibrium with the dissolved oxygen. If a reservoir of gas with known oxygen tension is allowed to equilibrate with a volume of blood, oxygen will continue to enter the blood until the partial pressures in blood and gas are equal. If the gas reservoir is then replaced by a small gas volume that contains no oxygen,  $O_2$  will diffuse from the blood into the new gas until the partial pressures in blood and gas are equal.





**Figure 5-5.** Oxyhemoglobin dissociation curve showing the relationship between the oxygen partial pressure in blood ( $P_{O_2}$ ) and the percentage of the hemoglobin binding sites that are occupied by oxygen molecules (percent saturation). Adult hemoglobin (hemoglobin A) is about 50% saturated at a  $P_{O_2}$  of 27 torr, 90% saturated at 60 torr, and about 98% saturated at 100 torr.

curve in Figure 5-5 shows the relationship between the  $P_{O_2}$  in blood and the percentage of the oxygen binding sites that are occupied by oxygen molecules (*hemoglobin percent saturation*). If blood is equilibrated with a gas that contains no oxygen, then the hemoglobin saturation will decrease to zero because oxygen will have left all of the hemoglobin binding sites. Under normal conditions, blood equilibrated to a partial pressure of 27 torr will have about half of the binding sites occupied, while blood equilibrated to more than 150 torr will have essentially 100% of the binding sites occupied.

The hemoglobin molecule undergoes a conformational change as oxygen molecules bind or release, giving rise to the curvilinear shape of the oxyhemoglobin dissociation curve. When the first oxygen molecule leaves a fully oxygenated hemoglobin, the hemoglobin molecule undergoes a conformational change that allows the second and third oxygen molecules to release more easily. Conversely, binding of the first oxygen molecule onto a fully deoxygenated hemoglobin facilitates the binding of the second and third oxygen molecules. This alteration in binding affinity is manifested by a steeper change in saturation for a given change in  $P_{O_2}$  in the middle of the dissociation curve than at the extreme ends. The curvilinear relationship be-

tween  $P_{O_2}$  and percent saturation is well suited for the transport of oxygen from the lungs to the tissues.

#### Physiological Consequences of the Hemoglobin Dissociation Curve Shape

In a healthy subject at sea level, arterial blood normally has a  $P_{O_2}$  of about 95 torr, corresponding to about 97% hemoglobin saturation. Note that even if the  $P_{O_2}$  of blood leaving the lungs is reduced by as much as 20 to 30 torr (because of lung disease or high altitude), the arterial blood hemoglobin will still be nearly fully saturated, since the slope of the dissociation curve is relatively shallow in that range (Figure 5-5). Thus, the shape of the oxyhemoglobin dissociation curve “protects” the level of arterial saturation despite moderate reductions in the arterial  $P_{O_2}$ .

As a red blood cell enters a systemic capillary, the  $P_{O_2}$  in the tissue surrounding the capillary is lower than in the blood and oxygen diffuses out of the capillary into the tissue. As oxygen diffuses out of the capillary, the  $P_{O_2}$  in the plasma surrounding the red blood cells falls. This causes oxygen to dissociate from hemoglobin inside the red blood cells and diffuse into the plasma. Oxygen continues to diffuse out as the blood moves through the capillary, and the hemoglobin saturation falls as progressively more oxygen is released. By the time the red blood cell exits from the end of the capillary, it will have released only a portion of the oxygen it carried. Under resting conditions, blood typically releases about 25% of its oxygen content along capillaries (average venous oxygen saturation = 75%), although the level of venous oxygen saturation varies widely among different tissues. During exercise, muscle tissue  $P_{O_2}$  decreases significantly as the myocytes consume oxygen, thereby augmenting the driving gradient for diffusion out of the capillaries. This allows muscles to extract more than 90% of the oxygen from blood during periods of heavy exercise.

#### Oxygen Content in Blood

The content of oxygen in blood represents the volume of oxygen contained per unit volume of blood and is usually referred to as the total *oxygen content*.

Although most of the oxygen contained in blood is bound to hemoglobin, the total oxygen content of blood is the sum of the hemoglobin-bound and the dissolved portions. The hemoglobin-bound portion of the oxygen content depends on the concentration of hemoglobin present (in g/dl), the oxygen binding capacity of the hemoglobin (1.39 ml O<sub>2</sub>/g Hb), and the hemoglobin percent saturation. This point is best illustrated by a calculation of the oxygen content in a sample of blood.

**EXAMPLE.** A sample of arterial blood is obtained from a patient. Analysis reveals the following: PO<sub>2</sub> = 95 torr, hemoglobin concentration = 14 g/dl, hemoglobin saturation = 97%. Calculate the oxygen content as the sum of the dissolved and hemoglobin-bound components:

Dissolved oxygen content = PO<sub>2</sub>(torr) · Solubility

$$\text{in } \left( \frac{\text{ml O}_2}{\text{dl} \cdot \text{torr}} \right) = 95 \cdot 0.00304 = 0.29 \left( \frac{\text{ml}}{\text{dl}} \right)$$

Hemoglobin-bound oxygen content =

$$1.39 \frac{\text{ml}}{\text{g Hb}} \cdot 14 \frac{\text{g Hb}}{\text{dl blood}} \cdot 0.97 \left( \frac{\% \text{ saturation}}{100} \right) = 18.88 \frac{\text{ml}}{\text{dl}}$$

Thus, the total oxygen content of the blood =  
 $0.29 + 18.88 = 19.17 \frac{\text{ml}}{\text{dl}}$  ■

**EXAMPLE.** A sample of mixed venous blood is obtained from a patient by way of a catheter whose tip is positioned in the pulmonary artery. Analysis reveals the following: PO<sub>2</sub> = 40 torr, hemoglobin concentration = 14 g/dl, hemoglobin saturation = 74%. Calculate the oxygen content as the sum of the dissolved and hemoglobin-bound components:

Dissolved oxygen content = PO<sub>2</sub>(torr) · Solubility

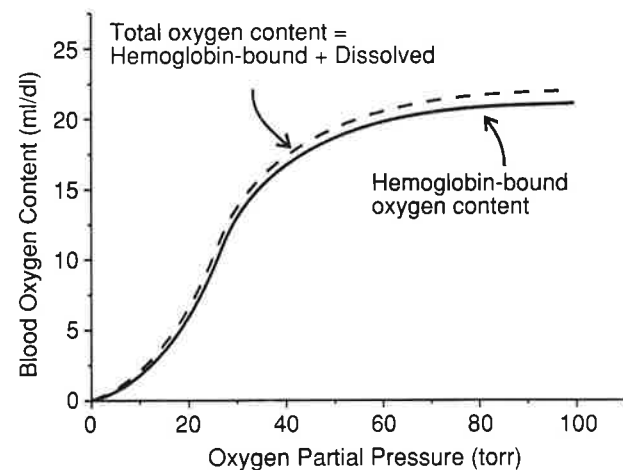
$$\text{in } \left( \frac{\text{ml O}_2}{\text{dl} \cdot \text{torr}} \right) = 40 \cdot 0.00304 = 0.12 \left( \frac{\text{ml}}{\text{dl}} \right)$$

Hemoglobin-bound oxygen content =

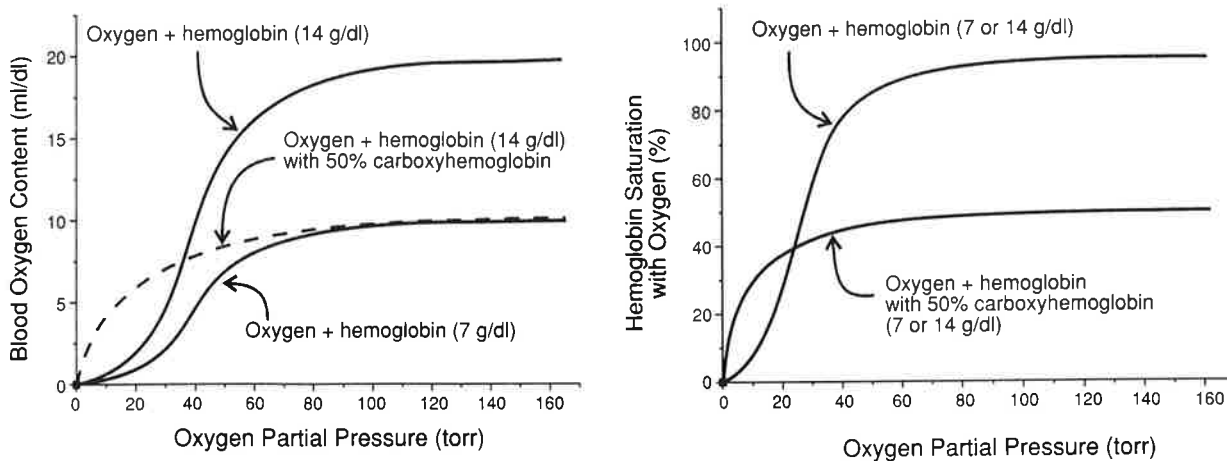
$$1.39 \frac{\text{ml}}{\text{g Hb}} \cdot 14 \frac{\text{g Hb}}{\text{dl blood}} \cdot 0.74 \left( \frac{\% \text{ saturation}}{100} \right) = 14.40 \frac{\text{ml}}{\text{dl}}$$

Thus, the total oxygen content of the blood =  
 $0.12 + 14.40 = 14.52 \frac{\text{ml}}{\text{dl}}$  ■

Figure 5–6 shows the total oxygen content of blood as a function of PO<sub>2</sub>, i.e., as the sum of hemoglobin-bound and dissolved components. Note that the dissolved oxygen portion represents less than 2% of the oxygen content in arterial blood. If the arterial PO<sub>2</sub> is increased to 600 torr by breathing 100% oxygen, the dissolved oxygen concentration will increase to about 1.8 ml/dl, or about 10% of the oxygen content in arterial blood. Since hemoglobin is fully oxygenated when the arterial PO<sub>2</sub> increases above about 150 torr, increasing the PO<sub>2</sub> further to 600 torr produces only a minor increment in arterial content.



**Figure 5–6.** The oxygen concentration in blood (oxygen content) as the sum of the dissolved oxygen content and the hemoglobin-bound content. The dissolved oxygen content is proportional to the blood PO<sub>2</sub>. The hemoglobin-bound content depends on the total number of hemoglobin binding sites (the hemoglobin concentration) and the percent of those sites occupied by oxygen molecules (saturation). At a blood PO<sub>2</sub> of 150 torr, further increases in PO<sub>2</sub> augment only the dissolved oxygen component, since the hemoglobin binding sites are virtually fully occupied (100% saturation).



**Figure 5-8.** Effects of anemia and carbon monoxide on blood oxygen content (*left*) and hemoglobin saturation (*right*). Blood oxygen content depends on the  $P_{O_2}$ , the percent hemoglobin saturation, and the concentration of hemoglobin present. For example, at a concentration of 14 g/dl, hemoglobin can bind a maximum of 19.46 ml of oxygen per deciliter when fully saturated. When the concentration of hemoglobin is reduced to 7 g/dl because of a low hematocrit, the maximum oxyhemoglobin binding is reduced to 9.73 at 100% saturation. At a hemoglobin concentration of 14 g/dl, if carbon monoxide binds to 50% of the hemoglobin binding sites, the maximal oxyhemoglobin saturation is reduced to 50% and the maximal oxyhemoglobin binding is reduced to 9.73 ml/dl. Moreover, the oxyhemoglobin dissociation curve becomes hyperbolic when carbon monoxide binds to some of the sites, thereby hindering oxygen release in the systemic capillaries.

tal carbon monoxide poisoning, patients are given high concentrations of oxygen to breathe. The higher concentration of oxygen competes more effectively for hemoglobin binding sites and speeds up the rate of carbon monoxide elimination from the body. Even more rapid elimination of carbon monoxide can be achieved using a *hyperbaric chamber* to increase the barometric pressure above atmospheric. Under hyperbaric conditions arterial oxygen tensions in excess of 1,000 torr can be achieved, which hastens displacement of carbon monoxide molecules from hemoglobin binding sites and promotes their elimination.

### Hemoglobin Affinity for Oxygen

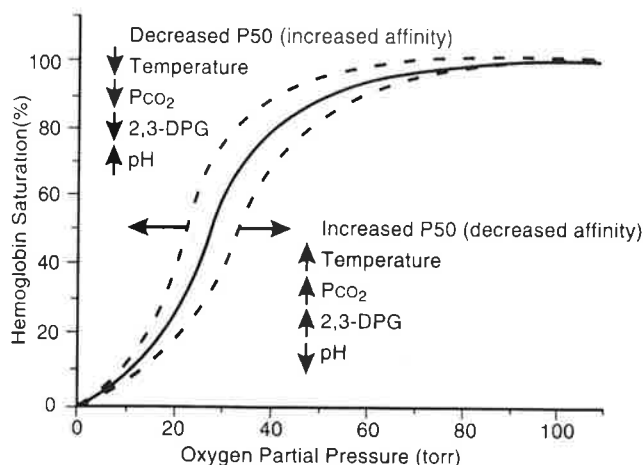
The binding affinity of hemoglobin for oxygen is expressed by the *hemoglobin  $P_{50}$* , defined as the  $P_{O_2}$  corresponding to a 50% oxyhemoglobin saturation. A *higher  $P_{50}$*  implies a *lower* affinity, because a higher  $P_{O_2}$  is needed to achieve a given oxygen saturation. Under normal conditions, adult hemoglobin is half-saturated at a  $P_{O_2}$  of about 27 torr. Fetal hemoglobin exhibits higher affinity for oxygen ( $P_{50} = 20$  to 22 torr), a feature that may enhance

fetal uptake of oxygen from maternal blood (Chapter 10).

The affinity of hemoglobin for oxygen varies under physiological conditions including blood temperature,  $P_{CO_2}$ , and pH (Figure 5-9). For example, decreases in blood pH below 7.4 tend to decrease the affinity of hemoglobin for oxygen (rightward shift in the oxyhemoglobin dissociation curve), while increases in pH shift the relationship to the left (increased affinity). Increases in blood temperature above  $37^\circ\text{C}$  shift the dissociation curve to the right, while decreases in temperature shift the curve leftward. Finally, blood carbon dioxide tensions greater than 40 torr tend to shift the dissociation curve to the right, while reductions in  $P_{CO_2}$  shift the curve to the left. The effect of carbon dioxide on the affinity of hemoglobin for oxygen has been attributed to the Danish physiologist Christian Bohr and has come to be known as the *Bohr effect*.<sup>1</sup> Part of the Bohr effect is due to the decrease in pH that occurs as  $P_{CO_2}$  is increased, and part of it is caused by direct effects of carbon dioxide on the hemoglobin molecule.

<sup>1</sup> Interestingly, it appears that August Krogh was actually the first to note the existence of this effect.





**Figure 5-9.** Oxyhemoglobin affinity. The affinity of hemoglobin for oxygen is expressed as the  $P_{50}$ . Increases in  $PCO_2$ , temperature, or 2,3-diphosphoglycerate (2,3-DPG) or decreases in pH shift the oxyhemoglobin dissociation curve to the right (increased  $P_{50}$  = decreased affinity), while opposite changes shift the curve to the left (decreased  $P_{50}$  = increased affinity) relative to the standard value of 27 torr.

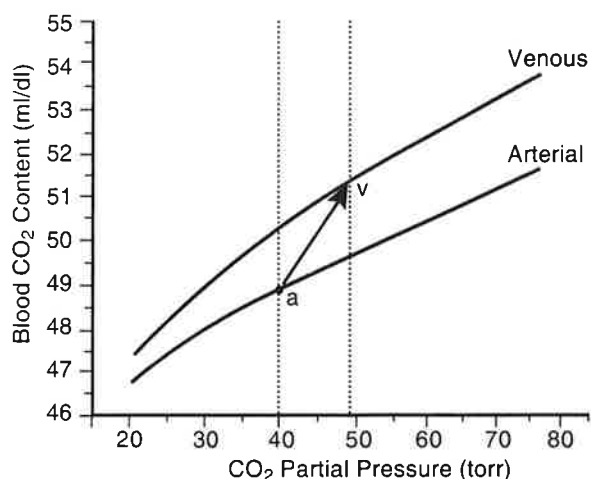
The changes in hemoglobin affinity that occur with altered temperature, carbon dioxide, and pH occur rapidly and can enhance oxygen uptake in the lung and release in the systemic tissues. For example, during exercise a working muscle produces carbon dioxide and heat and may produce lactic acid. As blood flows through muscle capillaries, oxygen diffuses out. Simultaneously, heat, carbon dioxide, and lactic acid diffuse into the blood. These factors all tend to shift the dissociation curve dynamically to the right, thereby promoting a greater amount of oxygen release from hemoglobin for a given capillary  $PO_2$ . The importance of the shift in the oxyhemoglobin dissociation curve is that it augments the capillary  $PO_2$ , enhancing oxygen diffusion out of the blood for a given decrease in oxygen content from arterial to venous blood. When this blood travels to the lungs and enters the pulmonary capillaries the  $PCO_2$  decreases, the pH increases, and the blood temperature decreases slightly. These factors enhance the quantity of oxygen taken up into blood for a given alveolar  $PO_2$ . Note that in both of the above examples, changes in hemoglobin affinity occur rapidly within the time span of a red blood cell traversing a capillary.

### Red Blood Cell 2,3-Diphosphoglycerate

Mature human red blood cells synthesize the compound 2,3-diphosphoglycerate (2,3-DPG) from the glycolytic intermediate 1,3-diphosphoglycerate using the enzyme 2,3-diphosphoglycerate mutase. The 2,3-DPG remains inside the red blood cell and reduces the affinity of hemoglobin for oxygen, thus shifting the dissociation curve to the right by an amount proportional to the concentration of 2,3-DPG (see Figure 5-9). This effect on hemoglobin affinity for oxygen occurs for two reasons. First, 2,3-DPG binds directly to the hemoglobin molecule, causing a conformational change that decreases its affinity for oxygen. Second, increases in 2,3-DPG tend to lower red blood cell pH, which further promotes a rightward shift in the dissociation curve. Although the regulation of red blood cell 2,3-DPG concentration is influenced by many factors, the most important appears to be the average level of blood oxyhemoglobin saturation. Factors that reduce average blood saturation, such as chronic hypoxemia (due to lung disease or residence at high altitude), tend to augment the red blood cell 2,3-DPG concentration and cause a rightward shift in the dissociation curve. Blood bank storage of blood in acid-citrate-dextrose anticoagulant solution is associated with a gradual depletion of red blood cell 2,3-DPG concentration, causing a decrease in the  $P_{50}$  (leftward shift) of the blood over a 2-week period. The physiological importance of changes in hemoglobin  $P_{50}$  caused by changes in 2,3-DPG has been the subject of some debate. It now appears that the significance of this effect is relatively small.

### CARBON DIOXIDE TRANSPORT IN BLOOD

Under resting conditions, the cells in an adult human typically produce about 200 ml of carbon dioxide per minute. To prevent its buildup in the tissues, carbon dioxide must be carried back to the lungs where it can be eliminated in exhaled gas. In this process, carbon dioxide first diffuses into capillary blood because the tissue  $PCO_2$  is higher than the  $PCO_2$  in arterial blood entering the capillaries. As carbon dioxide enters the capillary, the blood  $PCO_2$  and carbon dioxide content increase. After traveling to the lungs, the blood passes through the pulmo-



**Figure 5-11.** Changes in the relationship between  $P_{CO_2}$  and blood carbon dioxide content when the blood is partially deoxygenated. Arterial line shows the carbon dioxide dissociation curve in oxygenated blood (same as in Fig. 5-10); venous line shows the changes in the curve when oxyhemoglobin saturation is reduced to 75%. Deoxygenation shifts the composite carbon dioxide content curve upward, owing mostly to the enhanced carbamino uptake. Arrow shows the change in carbon dioxide content that occurs as arterial blood ( $P_{CO_2} = 40$  torr,  $O_2$  saturation = 98%) passes through systemic capillaries and becomes venous blood ( $P_{CO_2} = 47$  torr,  $O_2$  saturation = 75%). This facilitates a greater change in  $CO_2$  content for a given increase in  $P_{CO_2}$ .

carbon dioxide dissociation curve downward, thereby unloading more carbon dioxide content for a given alveolar  $P_{CO_2}$ . The effect of changes in oxyhemoglobin saturation on the relationship of the carbon dioxide content to  $P_{CO_2}$  is referred to as the *Haldane effect*, after the 19th century physiologist J. S. Haldane.

**EXAMPLE.** Blood passing through the lungs of a resting subject undergoes a decrease in  $P_{CO_2}$  of 7 torr ( $47 \rightarrow 40$ ). This is associated with a decrease in carbon dioxide content from 54 to 49 ml/dl. If the metabolic production of carbon dioxide ( $\dot{V}_{CO_2}$ ) is 225 ml/min, what is this subject's cardiac output?

Note that the Fick equation can be applied to carbon dioxide as well as to oxygen. From this equation

$$\dot{Q}_t = \frac{\dot{V}_{CO_2}}{(C\bar{V}_{CO_2} - C_{ACO_2})}$$

where  $C\bar{V}_{CO_2}$  and  $C_{ACO_2}$  are the carbon dioxide con-

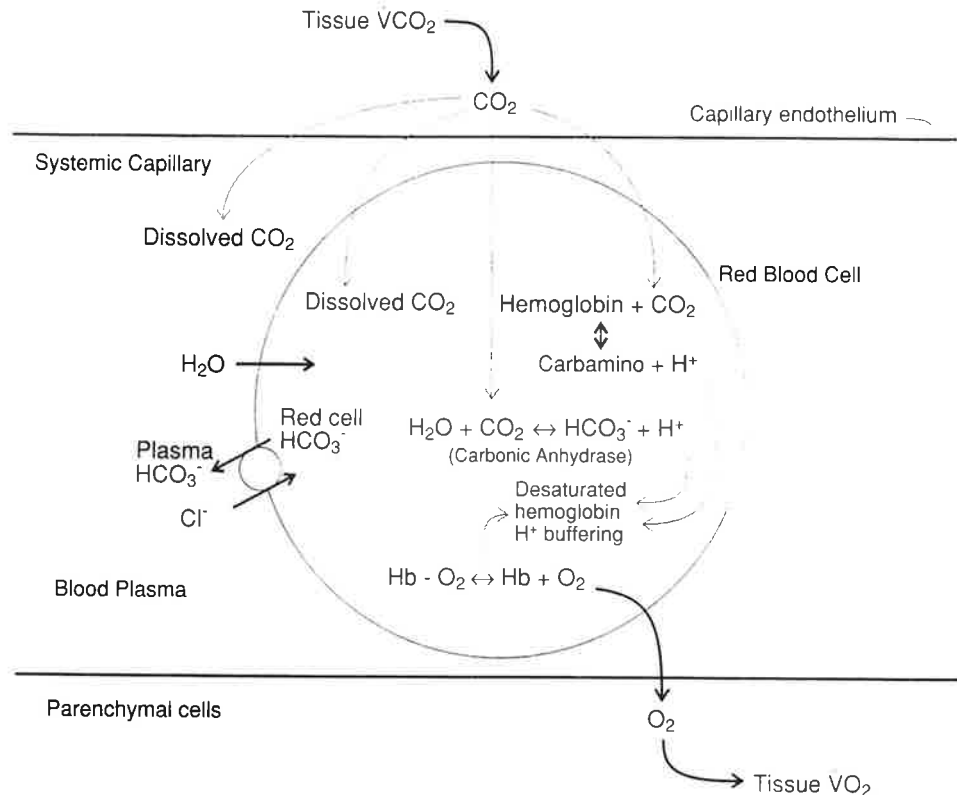
tents of mixed venous and arterial blood (in ml/dl), and  $\dot{Q}_t$  is the cardiac output (in dl/min). Thus,

$$\dot{Q}_t = 225/5 = 45 \text{ dl/min} = 4.5 \text{ liters/min.}$$

## INTERACTIONS OF OXYGEN AND CARBON DIOXIDE TRANSPORT

Figure 5-12 summarizes the events that take place in a red blood cell and the surrounding plasma as blood moves through a systemic capillary. Carbon dioxide in the tissue diffuses down its partial pressure gradient into the plasma. Some carbon dioxide molecules remain in the plasma as dissolved carbon dioxide, whereas others diffuse farther into the red blood cell where they meet up with one of three fates. Although a small amount may remain in dissolved form in the red blood cell, most of the carbon dioxide molecules are hydrated into bicarbonate and hydrogen ions by carbonic anhydrase. As the concentration of bicarbonate ions in the red blood cell begins to increase, bicarbonate is transported through the cell membrane in exchange for chloride ions through a coupled membrane transporter. Positively charged hydrogen ions do not cross the cell membrane readily and are instead buffered by hemoglobin (chiefly through the imidazole rings on histidine). Other carbon dioxide molecules bind to the amino terminus of hemoglobin  $\alpha$  and  $\beta$  chains, forming carbamino groups. While all of this is happening, oxygen diffuses down its partial pressure gradient from the red blood cell into the plasma and from the plasma into the tissue. As oxygen diffuses out of the cells, more oxygen dissociates from hemoglobin as it attempts to remain in equilibrium with the changing  $P_{O_2}$  in plasma. Note that the hydrogen ions released by the hydration of carbon dioxide and the increase in  $P_{CO_2}$  in the red blood cell both tend to alter the shape of the hemoglobin molecule, causing its affinity for oxygen to decrease. This change shifts the oxyhemoglobin dissociation curve to the right, promoting the release of more oxygen at any given  $P_{O_2}$  (the Bohr effect). As the hemoglobin saturation decreases, two important changes take place. First, desaturated hemoglobin is more effective at buffering hydrogen ions than oxygenated hemoglobin. This promotes the production of bicarbonate in the red blood cell, because it re-

**Figure 5-12.** Summary of events that occur as a red blood cell passes through a systemic capillary. Oxygen unloading along the capillary is enhanced by increases in  $P_{CO_2}$  and decreases in pH (the Bohr effect), while carbon dioxide loading into blood is enhanced by the simultaneous desaturation of hemoglobin (the Haldane effect). Most of the oxygen is bound to hemoglobin in the red blood cells, whereas most of the bicarbonate produced in the red blood cells is transported to the plasma. See text for further explanation.



duces the accumulation of free hydrogen ions released by the carbon dioxide hydration reaction. Second, deoxygenated hemoglobin is better able to form carbamino compounds, so the uptake of carbon dioxide as carbamino is enhanced. [These changes mediate the Haldane effect.] Finally, water moves into the red blood cell in response to the increase in the number of osmotically active ions present and the cell swells slightly. This entire set of processes reverses direction as the blood passes through the pulmonary circulation, where oxygen is loaded into blood, and carbon dioxide is unloaded.

The above reactions occur very rapidly and are nearly complete within the short time that it takes a red blood cell to pass through a capillary. After the cell leaves the capillary, a small amount of additional equilibration of bicarbonate continues to occur between the plasma and cell, owing to the limited speed of the cell membrane bicarbonate-chloride transporter. This effect causes minor changes in postcapillary  $P_{CO_2}$  and pH. However, complete equilibration between red blood cells and plasma is again restored within 2 seconds after the blood exits the end of the capillary.