6.4 Oxygen and Carbon Dioxide Transport

Learning Objectives

- Be able to calculate the dissolved oxygen content of blood from its solubility
- Be able to calculate the bound oxygen content of blood from its hemoglobin concentration and oxygen saturation
- Write the Hill equation for oxygen binding to hemoglobin
- Describe the consequence of positive cooperativity on the oxygen saturation curve of hemoglobin
- Be able to calculate oxygen delivery to tissue based on blood flow and arteriovenous differences in oxygen content
- Describe the gradient of oxygen partial pressure from capillaries to tissue
- Indicate the site of oxygen consumption within cells
- Describe the function of myoglobin in muscle cells
- Describe the effect on the oxygen saturation curve of the following: temperature, $[H^+]$, P_{CO_2}, and 2,3-DPG
- List three ways CO_2 is carried in the blood
- Distinguish between CO_2 content of the blood and CO_2 transport by the blood
- Identify the quantitatively largest component of CO_2 transport by the blood
- Describe the chloride shift

DISSOLVED OXYGEN CONTENT OF BLOOD IS SMALL

The solubility of oxygen in water at 37°C is given in Table 6.3.3 as 0.003 mL of O_2 at STPD per 100 mL of water per mmHg. The partial pressure of oxygen in arterial blood ($P_{a_{O_2}}$) is about 100 mmHg, so the dissolved $[O_2]$ is about 0.3 mL dL^{-1}. It is actually slightly less than this because blood is not 100% water.

MOST OF THE OXYGEN IN BLOOD IS BOUND TO *HEMOGLOBIN*

The aggregate red blood cells make up about 40–45% of the volume of blood (the **hematocrit**). Each red blood cell is packed with hemoglobin, a protein consisting of four polypeptide chains ($\alpha_2\beta_2$) with an aggregate molecular weight of 64,500 Da. The cell is so full that only about 0.72 of the red cell volume is water. Each of the four polypeptide chains contains a **heme** group consisting of a porphyrin backbone that complexes an Fe^{2+} atom (see Chapter 5.2). Each of the heme groups can bind oxygen noncovalently.

The rate of oxygen binding to hemoglobin depends on the concentration of dissolved O_2 and the concentration of vacant hemoglobin sites. Similarly, the rate of O_2 dissociation depends on the concentration of oxygen bound to hemoglobin $[Hb \cdot O_2]$. Equilibrium is reached when the two rates are equal. Since the concentration of dissolved O_2 is proportional to $P_{a_{O_2}}$, by Henry's law, the binding equilibrium depends on $P_{a_{O_2}}$. Hemoglobin saturation is defined as the percent of binding capacity that is occupied by oxygen. The relationship between hemoglobin saturation and $P_{a_{O_2}}$ is shown in Figure 6.4.1. This curve is called the **oxygen dissociation curve** or the **oxygen saturation curve**. The oxygen saturation curve does *not* obey simple saturation kinetics as described by the Langmuir adsorption isotherm:

$$[6.4.1] \qquad [Hb \cdot O_2] = \frac{[O_2]}{K + [O_2]}[Hb \cdot O_2]_{max}$$

This equation describes a dissociation curve that is hyperbolic, as shown in Figure 6.4.1. The best fit of this

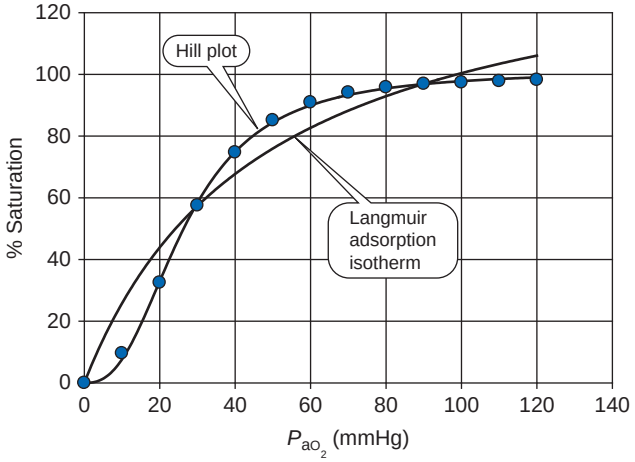

FIGURE 6.4.1 Oxygen dissociation curve. Oxygen binding to hemoglobin is a sigmoidal, or S-shaped, function of the arterial P_{O_2}. The binding is not satisfactorily fit by a simple curve describing saturation kinetics (see Eqn [6.4.1]). The data are much better described when the oxygen tension or partial pressure is raised to a power, *h*, called the Hill coefficient. *Data from F.J.W. Roughton, Transport of oxygen and carbon dioxide, in W.O. Fenn and H. Rahn, eds.,* Handbook of Physiology, *1964.*

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equation to the oxygen binding data is not satisfactory. Binding is better described by the **Hill equation**:

$$[6.4.2] \qquad [\mathrm{Hb}\cdot\mathrm{O_2}] = \frac{[\mathrm{O_2}]^h}{K + [\mathrm{O_2}]^h}[\mathrm{Hb}\cdot\mathrm{O_2}]_{\max}$$

where h is the **Hill coefficient**. For particular choices of K and h, this equation fits the observed binding isotherm much better, as seen in Figure 6.4.1. The Hill coefficient is a measure of the **cooperativity** of binding. There are four sites for O_2 binding to Hb. If binding of the first O_2 increases the affinity of the next binding site for O_2, the binding is said to be **positively cooperative** and $h > 1.0$. This cooperativity arises from interaction between the hemoglobin subunits that depends on their state of oxygen binding. In Figure 6.4.1, the best fit to the Hill plot gives $h = 2.56 \pm 0.07$ indicating that oxygen binding to hemoglobin is highly positively cooperative. See Appendix 9.1.A1 for a discussion of the Langmuir adsorption isotherm and Hill plots.

OXYGEN CONSUMPTION CAN BE CALCULATED BY BLOOD FLOW TIMES THE A–V DIFFERENCE IN OXYGEN

The partial pressures of the respiratory gases in alveolar air and blood are shown in Figure 6.4.2. We can use the P_{O_2} from the arterial and venous sides of the circulation, along with the oxygen dissociation curve in Figure 6.4.1, to calculate the oxygen consumption of the tissues. The balance between input and output is as follows:

$$[6.4.3] \qquad Q_a[\mathrm{O_2}]_a = Q_v[\mathrm{O_2}]_v + Q_{\mathrm{O_2}}$$

where Q_a is the total arterial blood flow, in mL min^{-1}, $[O_2]_a$ is the arterial blood total concentration of O_2, Q_v is the venous blood flow, $[O_2]_v$ is the venous blood total $[O_2]$, and Q_{O_2} is the aggregate rate of oxygen consumption.

The concentrations of O_2 are expressed as milliliters gas per unit volume of blood, and the volume of gas is expressed under STPD conditions. This equation is simply the conservation of mass. Since at steady state, the arterial blood flow is nearly equal to the venous drainage, we can rewrite the equation where we identify Q_a with the cardiac output when Q_{O_2} is the total body oxygen consumption in units of milliliters O_2 at STPD per minute:

$$[6.4.4] \qquad Q_a([\mathrm{O_2}]_a - [\mathrm{O_2}]_v) = Q_{\mathrm{O_2}}$$

See Example 6.4.2 for an application of this equation.

EXAMPLE 6.4.1 Blood Carrying Capacity for Oxygen

The normal hemoglobin concentration in whole blood is 15 g%. How much O_2 can this amount of hemoglobin hold?

Each of the four heme groups in hemoglobin can bind oxygen noncovalently. Thus the carrying capacity of blood is four times the concentration of hemoglobin. The molar concentration of hemoglobin is

$$(15\ \mathrm{g\ dL^{-1}})/(64,500\ \mathrm{g\ mol^{-1}}) = 2.32 \times 10^{-4}\ \mathrm{mol\ dL^{-1}}$$
$$= 2.32 \times 10^{-3}\ \mathrm{M}$$

Since each molecule of hemoglobin can bind four molecules of O_2, the oxygen binding capacity is

$$9.30 \times 10^{-4}\mathrm{mol\ dL^{-1}}$$

At STPD the molar volume of O_2 is 22.4 L mol^{-1}, and so this capacity corresponds to

$$9.30 \times 10^{-4}\ \mathrm{mol\ dL^{-1}} \times 22.4\ \mathrm{L\ mol^{-1}} = \mathbf{20.8\ mL\ O_2\ dL^{-1}}$$

Because the hemoglobin concentration varies between individuals, it is convenient to describe the O_2 binding capacity per unit hemoglobin:

$$20.8\ \mathrm{mL\ O_2\ dL^{-1}} / 15\ \ \mathrm{g\ dL^{-1}} = \mathbf{1.39\ mL\ O_2\ g\ hemoglobin^{-1}}$$

Gas concentrations are typically expressed in milliliters of gas at STPD per deciliter.

EXAMPLE 6.4.2 Calculation of O_2 Consumption from A–V $[O_2]$ Difference and Q_a

The cardiac output is typically about 5 L min^{-1}. The $P_{a_{O_2}}$ of arterial blood is 95 mmHg. According to Figure 6.4.1, Hb at this $P_{a_{O_2}}$ is about 98% saturated. We assume a typical [Hb] = 15 g%, which has a carrying capacity of 20.8 mL dL^{-1}, from Example 6.4.1. Therefore, the total $[O_2]$ content of the arterial blood is the dissolved quantity + the amount bound to Hb:

$[O_2]_a = \alpha \times 95\ \mathrm{mmHg} + 0.98 \times 20.8\ \mathrm{mL\ dL^{-1}}$, where $\alpha = 0.003$ is the solubility given in Table 6.3.3:

$$[O_2]_a = 0.3\ \mathrm{mL\ dL^{-1}} + 19.8\ \mathrm{mL\ dL^{-1}} = 20.7\ \mathrm{mL\ dL^{-1}}$$

The venous P_{O_2}, $P_{v_{O_2}}$, drops to about 40 mmHg. According to Figure 6.4.1, this P_{O_2} is in equilibrium with blood that is about 75% saturated. The $[O_2]_v$ is calculated as

$$[O_2]_a = 0.003\ \mathrm{mL\ dL^{-1}\ mmHg^{-1}} \times 40\ \mathrm{mmHg} + 0.75 \times 20.8\ \mathrm{mL\ dL^{-1}}$$
$$\approx 15.72\ \mathrm{mL\ dL^{-1}}.$$

Inserting this into Eqn [6.4.4], we get

$$Q_{O_2} = 5\ \mathrm{L\ min^{-1}} \times (20.7\ \mathrm{mL\ dL^{-1}} - 15.72\ \mathrm{mL\ dL^{-1}}) = \mathbf{249\ mL\ min^{-1}}$$

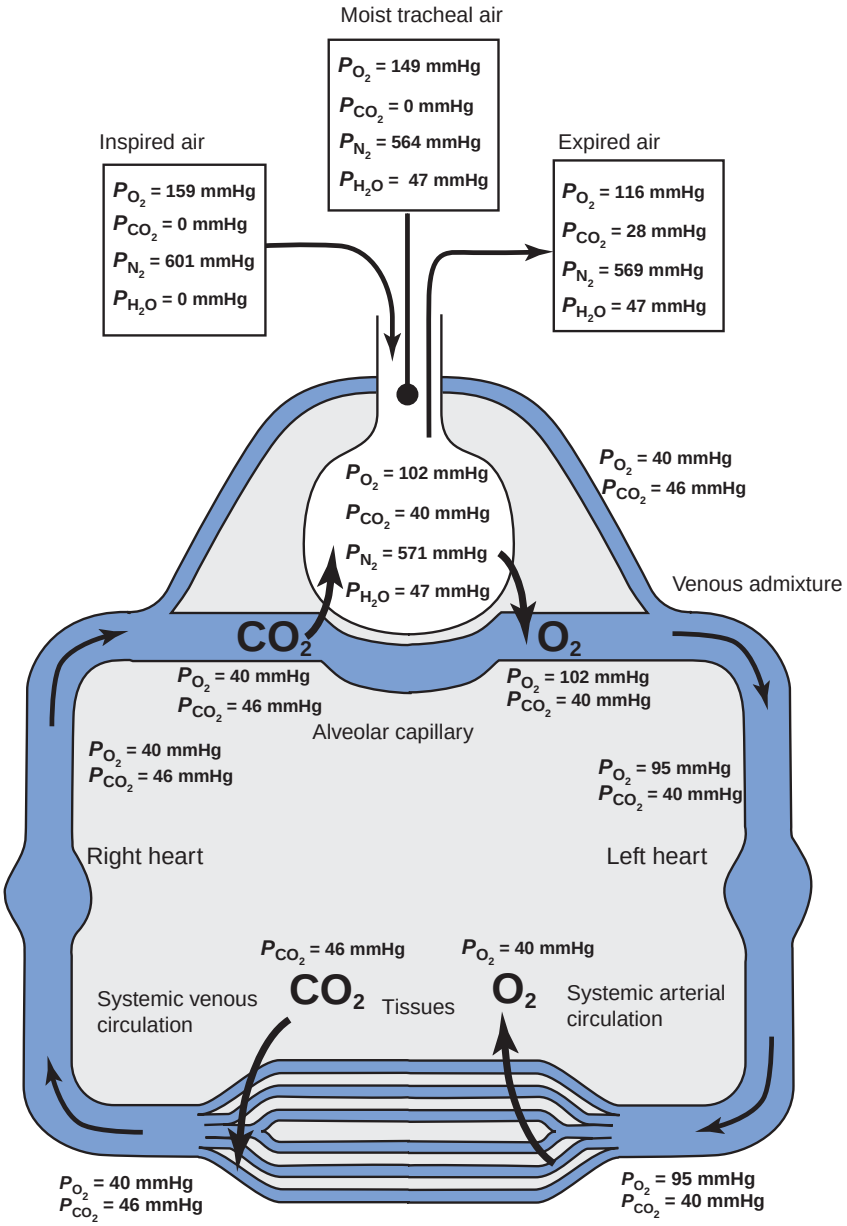

FIGURE 6.4.2 Partial pressures of respiratory gases in respiratory air samples and in the blood. Partial pressures in dry inspired air are proportional to the mole fraction of the gas in atmospheric air. Humidifying the moist tracheal air dilutes all respiratory gases because water is added to the inspired air. Alveolar air has stable partial pressures because the volume of air entering the alveoli with each breath is a small fraction of the air remaining in the lung. The expired air consists of a mixture of the moist tracheal air that does not exchange gas (the dead volume) and expired alveolar air. Venous blood entering the alveolar capillaries is partially depleted of O_2 and enriched in CO_2 from exchange with the tissues. The alveolar capillaries have a large surface area and small diffusion distances, so the blood in the alveolar capillaries equilibrates with alveolar air. Some blood that perfuses poorly ventilated regions of the lungs or from anatomic shunts contributes volume but less O_2 to the arterial blood. This **venous admixture** reduces the $P_{a_{O_2}}$ from 102 mmHg to about 95 mmHg. The gradients for O_2 diffusion from alveolar air to blood and from blood to tissue are much greater than the gradients for CO_2 diffusion because the higher solubility of CO_2 enables faster diffusion.

OXYGEN CONSUMPTION CAN BE CALCULATED FROM THE DIFFERENCE BETWEEN O_2 INSPIRED AND O_2 EXPIRED

At steady state, the oxygen consumption calculated by the cardiac output times the arterial–venous difference in $[O_2]$ should match the oxygen that is taken up by the respiratory system. Oxygen uptake by the respiratory system is governed by its own conservation relation, written as

$$Q_T^* f_{I_{O_2}} = Q_T f_{E_{O_2}} + Q_{O_2} \quad [6.4.5]$$

where Q_T^* is the flow of inspired air, Q_T is the flow of expired air, f_{IO_2} and f_{EO_2} are the mole fractions of O_2 in the inspired and expired tidal volumes, respectively. Because Q_{O_2} is expressed in terms of volumes of O_2 gas at STPD, both Q_T^* and Q_T must also be expressed in

EXAMPLE 6.4.3 Calculation of O_2 Consumption from Inspired and Expired Volumes and P_{O_2}

The *expired* volume at BTPS is about 500 mL per breath, and the respiratory rate is about 12 min^{-1}. Using the values for the gases in Figure 6.4.1, and respiratory quotient $R = 0.8$, estimate the oxygen consumption.

The flow of *expired* air, $Q_T = 500\ mL \times 12\ min^{-1}/1.2104 = 4.96\ L\ min^{-1}$. The value of 1.2104 is used to convert Q_T at BTPS to STPD, according to Eqn [6.3.A2.3].

$f_{I_{O_2}}$ is the mole fraction of O_2 in inspired air, which is $159/760 = 0.209$.

$f_{E_{O_2}}$ can be calculated from $P_{E_{O_2}}$ shown in Figure 6.4.2 and Eqn (6.3.8): $f_{E_{O_2}} = P_{E_{O_2}}/(P_B - P_{H_2O})$:

$$f_{E_{O_2}} = 116\ mm\ Hg/713\ mm\ Hg = 0.163$$

The flow of inspired air, Q_T^* at STPD can be calculated from $Q_T + Q_{O_2} - Q_{CO_2}$. If $R = 1.0$, then $Q_T^* = Q_T$.

If we use $R = 0.8$ and estimate $Q_{O_2} = 250\ mL\ min^{-1}/12\ min^{-1} = 21\ mL\ breath^{-1}$ and $Q_{CO_2} = 200\ mL\ min^{-1}/12\ min^{-1} = 17\ mL$ breath, then $V_T^* = V_T + 4\ mL = 504\ mL$; converting this to STPD per minute, we have $Q_T^* = 504\ mL \times 12\ min^{-1}/1.2104 = 5.00\ L\ min^{-1}$.

Then we calculate $Q_{O_2} = 5.00\ L\ min^{-1} \times 0.209 - 4.96\ L\ min^{-1} \times 0.163 =$ **237 mL min^{-1}**.

This is in reasonable agreement with Q_{O_2} calculated in Example 6.4.2. The discrepancy in the values is due to rounding and in the rounded value of V_T. If we use just a slightly larger value for V_T the discrepancy disappears.

STPD, and f_{IO_2} and f_{EO_2} are the mole fractions of O_2 in dry inspired or expired airs, respectively.

O_2 DIFFUSES FROM BLOOD TO THE INTERSTITIAL FLUIDS AND THEN TO THE CELLS

Oxygen diffuses down its partial pressure gradient from blood to the interstitial fluid (ISF). The systemic arterial blood has a $P_{a_{O_2}}$ of about 95 mmHg. The average ISF P_{O_2} is variable, depending on the metabolism of the tissue, but it is generally near 40 mmHg. The higher P_{O_2} in the blood produces a net diffusion of O_2 out of the blood and into the ISF. Only the dissolved O_2 diffuses. Because of Henry's law, the dissolved $[O_2]$ is directly proportional to P_{O_2}, so the gradient of P_{O_2} is proportional to the gradient in $[O_2]$ in any single phase. The large area and small diffusion distance between blood and the ISF lead to rapid exchange between blood and the ISF.

The low P_{O_2} in the ISF is caused by diffusion of O_2 into the cells, where the P_{O_2} is even lower because the mitochondria consume the O_2. Mitochondria typically require 3–5 mmHg P_{O_2}, which is considerably lower than the P_{O_2} of the interstitial fluid. The cytosolic $[O_2]$ is intermediate between that of the interstitial fluid and the intracellular fluid, with a P_{O_2} of nearly 20 mmHg. Thus there is a continuous gradient of P_{O_2} from about 95 mmHg in the arterial blood to 40 mmHg in the interstitial fluid to 20 mmHg in the cytosol to 5 mmHg in the mitochondria. Figure 6.4.3 illustrates the P_{O_2} gradients that drive diffusion from the blood to its place of consumption, the mitochondria.

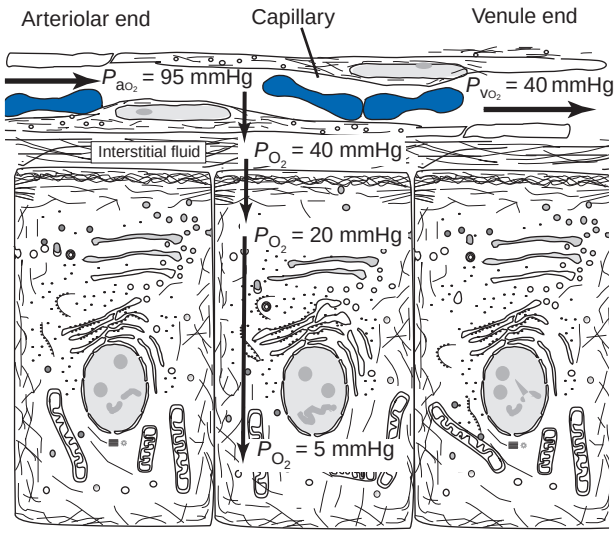

FIGURE 6.4.3 Diffusion of O_2 from blood to the mitochondria. The arteriolar blood has a $P_{a_{O_2}}$ of about 95 mmHg. The interstitial fluid P_{O_2} is about 40 mmHg. Thus there is a gradient of dissolved O_2 from blood to ISF. As O_2 diffuses, other O_2 molecules bound to Hb dissociate. The cytosolic P_{O_2} is lower still, being least near the mitochondria where the O_2 is being consumed. Thus O_2 diffuses down its P_{O_2} gradient from its source, the blood, to its sink, the mitochondria. By the time blood leaves the tissue, it has equilibrated with the ISF P_{O_2} of about 40 mmHg.

HEMOGLOBIN DELIVERS OXYGEN TO THE TISSUES

Only dissolved O_2 can diffuse across membranes. When O_2 diffuses out of the capillaries into the interstitial fluid, blood P_{O_2} decreases. According to the law of mass action, O_2 dissociates from hemoglobin and thereby resists the fall in P_{O_2}. In the process, the amount of bound O_2 decreases. When the blood finally leaves the capillaries, its P_{O_2} has equilibrated with the interstitial fluid P_{O_2} and the percent saturation of blood hemoglobin decreases according to the oxygen dissociation curve.

MYOGLOBIN STORES O_2 IN OXIDATIVE MUSCLE AND MAY ENHANCE DIFFUSION

Myoglobin is a low-molecular weight protein of 16,000 Da that contains one heme and binds one

molecule of O_2 per molecule of protein. Tissue content of myoglobin depends on the tissue and the species. Highly oxidative muscle fibers contain a lot of myoglobin. Because it consists of a single polypeptide chain, myoglobin does not have subunits that can interact to produce cooperative binding. Instead, oxygen binding to myoglobin obeys a simple saturation equation with half-maximal saturation at about 5 mmHg P_{O_2} (see Figure 6.4.4). It has two functions in muscle: it stores oxygen for use during heavy exercise, and it enhances diffusion through the cytosol by carrying the oxygen. By binding O_2, myoglobin (Mb) provides a second diffusive pathway for O_2 through the cell cytosol. The total diffusion is the sum of the diffusion of dissolved O_2 and the diffusion of oxygen carried by Mb, $Mb \cdot O_2$. The diffusion of oxygen through aqueous solutions in the presence of myoglobin is described in Eqn [6.4.6].

$$J_{total} = -D_{O_2}\frac{d[O_2]}{dx} - D_{Mb}\frac{d[Mb - O_2]}{dx} = -D_{O_2}\frac{d[O_2]}{dx} - D_{Mb}[Mb]_{total}\frac{d\nu}{dx} \quad [6.4.6]$$

where ν is the fraction of myoglobin that is bound with O_2. The diffusion coefficient of O_2 in water is about 1.5×10^{-5} cm^2 s^{-1}, whereas the diffusion coefficient of myoglobin is about 0.1×10^{-5} cm^2 s^{-1}, about 15-fold lower than that of oxygen. Even though the diffusion coefficient of myoglobin is small compared to that of dissolved O_2, its concentration gradient can be much higher and so myoglobin can contribute to the overall diffusion of O_2 through the tissue.

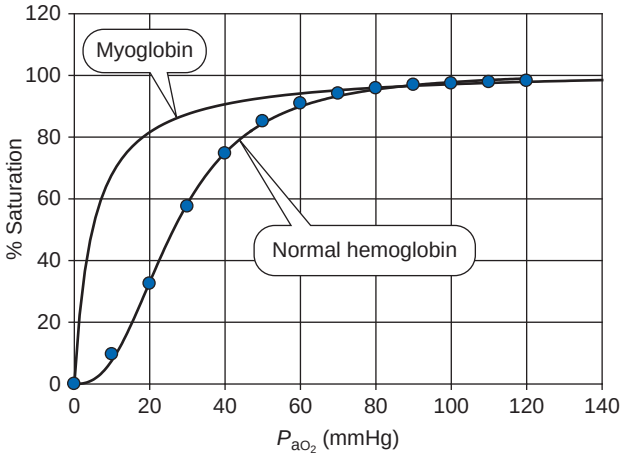

FIGURE 6.4.4 Comparison of the oxygen dissociation curve for hemoglobin and myoglobin. Hemoglobin consists of four subunits that can interact, giving rise to cooperative behavior, and causing deviations from simple saturation kinetics. Myoglobin consists of a single polypeptide chain that cannot interact with other subunits, and thus its dissociation curve shows simple saturation behavior. Half-saturation of myoglobin occurs at P_{O_2} of about 5 mmHg, intermediate between the P_{O_2} of the ISF and the mitochondria.

SHIFT OF THE O_2 DISSOCIATION CURVE TO THE RIGHT HELPS DELIVER O_2 TO EXERCISING MUSCLES

Increased body temperature, increased $[H^+]$ in the red blood cell, increased P_{CO_2} in the blood, and increased concentrations of 2,3-diphosphoglycerate (DPG) all shift the O_2 dissociation curve to the right (see Figures 6.4.5–6.4.8). These shifts to the right mean that higher P_{O_2} is required to saturate hemoglobin; alternatively, at any given P_{O_2}, hemoglobin gives up more of its bound O_2. Thus, increased temperature, increased $[H^+]$, increased P_{CO_2}, and increased 2,3-DPG all increase the availability of O_2 to the tissues.

Consider the situation with increased temperature. At rest, blood enters the muscles at 37°C with $P_{a_{O_2}} = 95$ mmHg. According to our earlier calculation (see Example 6.4.1), blood contains about 20 mL O_2 dL^{-1} at $P_{a_{O_2}} = 95$ mmHg. When it equilibrates with ISF at 40 mmHg and 37°C, the saturation is 75%, and the blood's O_2 content is 15 mL dL^{-1}: the muscles extract 5 mL dL^{-1}. When the muscles are exercising, their temperature increases. Arterial blood still contains 20 mL dL^{-1} but the venous blood at 40 mmHg $P_{v_{O_2}}$ and 43°C is only about 50% saturated: it contains 10 mL dL^{-1}. Thus the exercising muscles at the increased temperature extract 10 mL dL^{-1} if the ISF is kept at 40 mmHg.

The O_2 dissociation curve also is sensitive to blood pH (see Figure 6.4.6). Increasing $[H^+]$ (lowering the pH) shifts the curve to the right, and decreasing $[H^+]$ (raising the pH) shifts the curve to the left. Because exercising muscles also produce acid, this effect helps unload O_2 to active muscles.

Decreasing the P_{CO_2} from the normal value of 40 mmHg shifts the curve to the left; increasing P_{CO_2} shifts the curve to the right. This is called the **Bohr effect** after its discoverer. This effect also helps unload

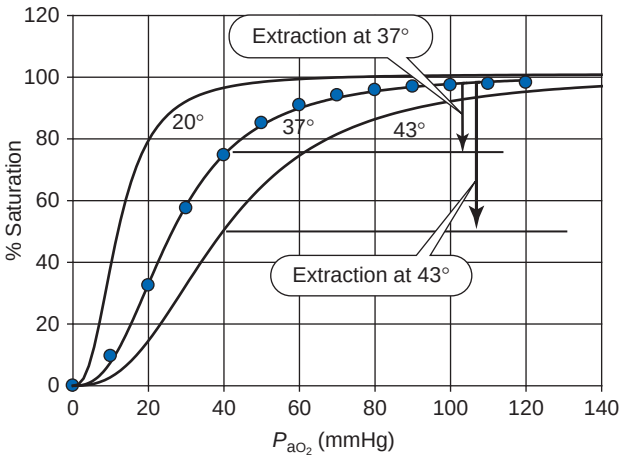

FIGURE 6.4.5 Effect of temperature on the oxygen dissociation curve. Reduced temperature shifts the curve to the left and elevated temperature shifts the curve to the right. The reduced affinity for O_2 at higher temperatures helps dissociate O_2 from Hb during exercise. Therefore, at the same P_{O_2}, increased temperature results in more O_2 being delivered to the hot, exercising muscles.

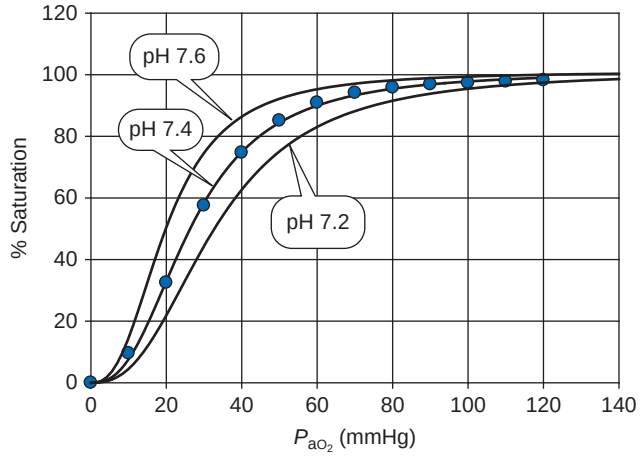

FIGURE 6.4.6 Effect of pH on the oxygen dissociation curves. Alkalinization shifts the curve to the left; acidification shifts the curve to the right. Shifting the curve to the right means that Hb can hold less oxygen at the same P_{O_2}, and thus the blood unloads more O_2 when the tissues are acidic, as happens when muscles are active.

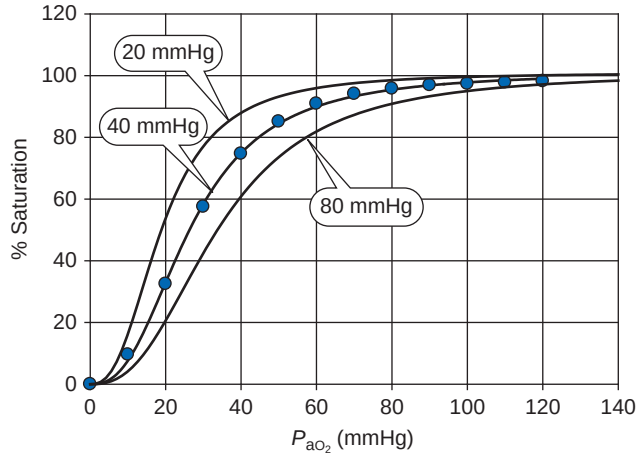

FIGURE 6.4.7 Effect of CO_2 on the oxygen dissociation curve. Half-maximal saturation of Hb is shifted to lower P_{O_2} by reducing P_{CO_2} and is shifted to higher P_{O_2} by raising P_{CO_2}.

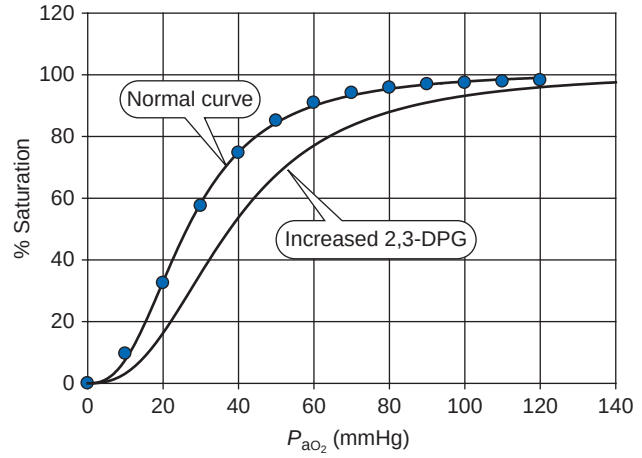

FIGURE 6.4.8 Shift of the O_2 dissociation curve to the right by 2,3-DPG.

O_2 during the transit of blood through active tissue. When the tissues are actively metabolizing, P_{CO_2} rises and more O_2 dissociates from hemoglobin. Figure 6.4.7 illustrates this effect.

Since mature red blood cells have no mitochondria, they derive their energy by anaerobic metabolism or glycolysis. The high concentrations of glycolytic intermediates create high concentrations of 2,3-DPG from a side reaction. The concentration of 2,3-DPG increases during hypoxia (low P_{O_2}) and alkalosis; it decreases with increased blood $[H^+]$. By shifting the O_2 dissociation curve to the right, the increased 2,3-DPG helps deliver O_2 to the tissues despite the hypoxia (see Figure 6.4.8).

INCREASED O_2 DELIVERY IN EXERCISE IS CAUSED BY INCREASED BLOOD FLOW AND SHORTER DIFFUSION

Although pH, P_{CO_2}, temperature, and 2,3-DPG all shift the O_2 dissociation curve for hemoglobin, **the main mechanism for increasing O_2 delivery to active tissues is by increasing blood flow**. Dilation of arterioles increases the number of open capillaries, increases the pressure that drives flow, increases the cross-sectional area through which blood moves, decreases the effective diffusion distance, and increases the effective diffusion surface area. All of these factors increase O_2 delivery.

DISSOLVED CO_2 ACCOUNTS FOR A SMALL FRACTION OF BLOOD CO_2 TRANSPORT

The dissolved $[CO_2]$ is given by Henry's law as $\alpha \times P_{CO_2}$. The value of α at 37°C and in water is given in Table 6.3.3 as 0.0747 mL dL^{-1} mmHg^{-1}. However, only 93% of plasma is water, and hemoglobin in red blood cells displaces blood water still further (about 0.72 of the red cell volume is water) so this solubility coefficient must be adjusted. In normal blood, the overall solubility is about 0.062 mL dL^{-1} mmHg^{-1}. Thus arterial blood with $P_{a_{CO_2}} = 40$ mmHg contains about 2.5 mL CO_2 dL^{-1}; venous blood with $P_{v_{CO_2}} = 46$ mmHg contains about 2.9 mL CO_2 dL^{-1}. The net transport of dissolved CO_2 from tissues to lungs is thus $Q_a \alpha (P_{v_{CO_2}} - P_{a_{CO_2}}) = 5$ L min^{-1} $(2.9 - 2.5$ mL dL$^{-1}) \approx 20$ mL min^{-1}. **Since the overall CO_2 production is about 200 mL min^{-1}, only about 0.10 of the total is transported as dissolved CO_2.**

MOST CO_2 IS CARRIED IN THE BLOOD AS HCO_3^-

Dissolved CO_2 reacts with water to form carbonic acid, H_2CO_3, which then dissociates into H^+ and bicarbonate, HCO_3^-. The sequential reactions are written as

$$[6.4.7] \qquad \begin{aligned} CO_2 + H_2O &\rightleftharpoons H_2CO_3 \\ H_2CO_3 &\rightleftharpoons H^+ + HCO_3^- \end{aligned}$$

Clinical Applications: Carbon Monoxide Poisoning

Carbon monoxide is a lipophilic gas that binds to hemoglobin at the same site as oxygen, forming **carboxyhemoglobin**. Its binding, however, is about 220 times stronger than that of oxygen. Hemoglobin saturates with CO at a partial pressure of about 0.5 mmHg. CO binding to hemoglobin shifts the oxygen dissociation curve to the left and converts it from a sigmoidal to a more hyperbolic shape. This interferes with the ability of Hb to dissociate O_2 at low P_{O_2}, and therefore CO severely hampers the extraction of O_2 by the tissues.

CO occupies some 1–2% of the O_2 binding sites on Hb in people living in urban environments. Heavy smokers may have 10% of their Hb binding capacity occupied by Hb · CO. Because the binding reaction is reversible, high Hb · CO levels can be brought down by simply breathing air devoid of CO. The high affinity of Hb for CO means that the off rate constant is slow, and therefore the reversal of CO binding to Hb is slow. The half-time of the reverse reaction is about 4 h.

Persons with acute CO poisoning present a cherry-red appearance. Their main difficulty lies in the ability to extract O_2 in the tissues. Treatment consists of providing the victim with high concentrations of O_2 to breathe. The high P_{O_2} increases the dissolved $[O_2]$ and competes better with the CO for Hb binding sites. The high P_{O_2} also speeds up CO elimination by competitive interference with the rebinding of CO. **Hyperbaric** O_2, in which P_{O_2} exceeds atmospheric pressures, speeds up CO elimination further.

Unaided, the formation of H_2CO_3 is slow, with a half-time greater than 5 s. CO_2 readily enters the red blood cell where **carbonic anhydrase**, a Zn-containing enzyme of 30,000 Da, converts CO_2 and H_2O to HCO_3^- and H^+ directly. These can then combine readily to form H_2CO_3. This enzyme completes the equilibration of CO_2, H_2CO_3, HCO_3^-, and H^+ within milliseconds. The dissociation of carbonic acid is rapid, and most of the CO_2 is converted to HCO_3^-. Most of the HCO_3^- formed in the red blood cell exchanges for Cl^- in the plasma, so that the HCO_3^- is largely carried in the plasma instead of the red blood cells. The exchange of HCO_3^- for Cl^- is called the **chloride shift** (see Figure 6.4.9). Because the P_{CO_2} is different in venous and arterial blood, the $[HCO_3^-]$ is also different. Venous blood typically contains 20.7 mM HCO_3^-, whereas arterial blood contains about 19.1 mM HCO_3^-. The net transport of HCO_3^- is therefore Q_a (20.66 − 19.14 mM) = 5 L min^{-1} × 1.52 mM = 7.6 mmol min^{-1}. This converts to about 171 mL min^{-1} of CO_2 at STPD. **Thus, the fraction of CO_2 transported as HCO_3^- is 171 mL min^{-1}/200 mL min^{-1} = 0.85.**

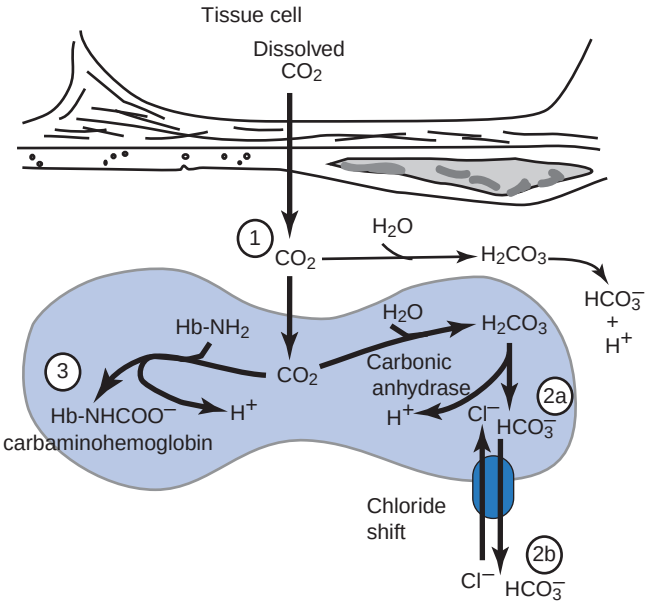

FIGURE 6.4.9 Transport of CO_2 in blood. CO_2 produced in the tissues diffuses through the interstitial fluid and capillaries in the dissolved state. It diffuses through the red blood cell membrane and encounters carbonic anhydrase, which catalyzes the hydration of CO_2 to form bicarbonate, HCO_3^-, and H^+. Hemoglobin within the red blood cell is a potent buffer for the released H^+. The HCO_3^- exchanges for Cl^- across the red blood cell membrane, a movement called the chloride shift. CO_2 reversibly combines with NH_2 groups on the hemoglobin to form carbaminohemoglobin. Thus CO_2 is carried in three ways: (1) dissolved in plasma and the red blood cell cytoplasm; (2) as HCO_3^- in the red blood cell cytoplasm (2a) and plasma (2b); and (3) as carbaminohemoglobin.

CARBAMINOHEMOGLOBIN ACCOUNTS FOR A SMALL FRACTION OF TRANSPORTED CO_2

CO_2 reacts with free NH_2 terminal groups on both the α and β chains of hemoglobin to form a new compound, **carbaminohemoglobin** (see Figure 6.4.9). This reaction can also occur with plasma proteins. The combination of CO_2 with NH_2 groups is called a **carbamate**. Carbamate formation is reversible and influenced by P_{O_2}, pH, and [2,3-DPG]. When P_{O_2} increases, as it does when the blood enters the alveoli and exchanges O_2 with alveolar air, carbaminohemoglobin dissociates to CO_2 and Hb–NH_2. The reduction in CO_2 content of the hemoglobin by increased P_{O_2} is called the **Haldane effect** (see Figure 6.4.10). It is the converse of the Bohr effect, in which O_2 binding by Hb is reduced by increased P_{CO_2}. Typically arterial blood contains about 0.75 mM carbaminohemoglobin, whereas venous blood contains 0.84 mM. **Thus carbaminohemoglobin contributes Q_a (0.84 mM − 0.75 mM) = 5 L min^{-1} × 0.09 mM = 0.45 mmol min^{-1} = 10 mL min^{-1} or about 0.05 of the total CO_2 transport.**

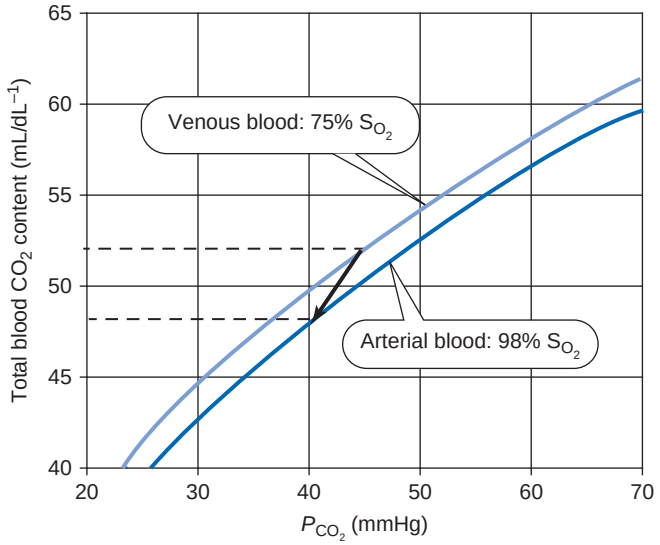

FIGURE 6.4.10 Effect of oxygenation on the total CO_2 content of blood. The reduction in the CO_2 content at the same P_{CO_2} by oxygenation is called the Haldane effect. In this way, oxygenation in the lungs aids in the removal of CO_2 from the venous blood. Without the Haldane effect, the change from $P_{v_{CO_2}} = 46$ mmHg to $P_{a_{CO_2}} = 40$ mmHg would follow the venous curve to release about 2.2 mL dL^{-1}. With the additional change from 75% O_2 saturation to 98% O_2 saturation, the CO_2 content follows the arrow to jump to the arterial curve, releasing a total of about 4 mL dL^{-1}. *Adapted from N.C. Staub,* Basic Respiratory Physiology, *Churchill Livingstone, New York, NY, 1991.*

SUMMARY

Oxygen is carried in two ways: dissolved in the plasma and bound to hemoglobin within red blood cells. The arterial blood contains about 20 mL dL^{-1} O_2, and about 98% of this is bound to hemoglobin. Hemoglobin can carry about 1.35 mL O_2 per gram, and blood normally contains about 15 g Hb dL^{-1}. Venous blood normally contains about 15 mL O_2 dL^{-1}, so the tissues extract at rest about 25% of the arterial O_2. With a cardiac output of 5 L min^{-1}, the net transport of O_2 is therefore about

$$5\,\text{L}\,\text{min}^{-1} \times (20\,\text{mL}\,\text{dL}^{-1} - 15\,\text{mL}\,\text{dL}^{-1}) = 250\,\text{mL}\,O_2\,\text{min}^{-1}$$

This O_2 transport matches the metabolic consumption of O_2 and the amount calculated from the flow of respiratory air and the difference between inspired air and expired air O_2 content.

Hemoglobin displays marked cooperativity in O_2 binding, so that its O_2 dissociation curve is steepest at physiological P_{O_2} levels. There is a continuous gradient of P_{O_2} from about 100 mmHg in the blood to 40 mmHg in the interstitial fluid, 20 mmHg in the cell, and about 5 mmHg in the mitochondria. The Hb dissociation curve shifts to the right with increased temperature, increased P_{CO_2}, decreased pH, and increased DPG. The Bohr effect describes the decreased affinity for O_2

Clinical Applications: Blood Substitutes

Trauma at disaster sites, automobile accidents, and on the battlefield often entail loss of blood and consequent hypotension and hypovolemic shock that can be fatal. The best treatment is to replace the lost blood. Transfusion with other people's blood poses numerous problems. Human blood requires donors, exacting storage conditions in order to prolong clinical effectiveness and reduce risk of infections, and an entire infrastructure of collection and storage centers. Human blood comes in a variety of types that are not compatible and so each recipient must be cross-matched with the potential transfused blood. Lastly, human blood transmits communicable diseases such as the human immunodeficiency virus (HIV) and hepatitis C virus (HCV). Each problem has been overcome. The infrastructure is in place, cross-matching is routinely performed, and screening of donors and testing for contaminants make the donor supply increasingly safe. All of this effort comes at significant cost. Donor blood shortages and all of the problems listed here have given impetus to developing safe and economical blood and plasma substitutes.

Blood substitutes must: (1) carry oxygen in the circulation; (2) deliver oxygen to the tissues; (3) require no cross-matching or compatibility testing; (4) have a long shelf-life; (5) survive in the circulation for suitable times before being cleared; (6) have no side effects; (7) have no pathogens; (8) not significantly alter blood viscosity. Two general types of blood substitutes that are currently being developed are broadly classed as hemoglobin-based oxygen carriers (HBOCs) and perfluorocarbon emulsions.

The best blood substitute would mimic hemoglobin's O_2 dissociation curve. A cell-free hemoglobin solution retains its ability to bind oxygen, and it does not possess the surface proteins responsible for transfusion reactions, so cross-matching is not required. However, unaltered hemoglobin has unacceptably short survival times in the circulation, an abnormally high O_2 affinity, and its clearance by the kidneys gums up the works. The attempted solution to these problems has been to polymerize the hemoglobin. Three such polymerized HBOCs are currently in advanced clinical trials.

Perfluorocarbons are biochemically inert liquids that carry O_2 as dissolved gas. Their O_2 content is linearly related to P_{O_2}. Perfluorocarbons are not miscible with watery solutions and can be used only as an emulsified preparation. The second generation of fluorocarbon preparations uses egg yolk phospholipids as emulsifiers. The droplets must be a specific size (about 0.17 μm) in order to be tolerated. The droplets are taken up by cells of the reticuloendothelial system and the perfluorocarbons are eventually excreted by exhalation through the lungs. (J.E. Squires, Artificial blood, *Science* **295**:1002–1005, 2002; R. Winslow, Blood substitutes, *Adv. Drug Del. Rev.* **40**:131–142, 2000; D.R. Spahn, Current status of artificial oxygen carriers, *Adv. Drug. Del. Rev.* **40**:143–151, 2000.)

caused by CO_2. These shifts help hemoglobin unload O_2 to the tissues when they become more active.

Blood transports CO_2 from the tissues to the lungs in three ways: dissolved as CO_2, as HCO_3^-, and bound to hemoglobin as carbaminohemoglobin. Dissolved CO_2 accounts for about 10% of the total CO_2 transport; about 85% of the CO_2 transport is carried as HCO_3^-, and only about 5% is transported as carbaminohemoglobin. In the lungs, increased P_{O_2} helps unload CO_2 so that each 100 mL of blood transports about 4 mL of CO_2 to the atmosphere. Overall CO_2 production is about 200 mL min^{-1}.

REVIEW QUESTIONS

1. Use Henry's law to calculate the dissolved oxygen concentration at $P_{a_{O_2}} = 100$ and 40 mmHg.
2. What is the utility of an S-shaped oxygen dissociation curve? What equation describes this curve? What parameter of the curve indicates cooperativity? What does cooperativity mean?
3. What causes a rightward shift in the oxygen dissociation curve? Does a rightward shift mean oxygen dissociates more or less easily from Hb?
4. Where is hemoglobin in the body? Where is myoglobin? How do these differ in their oxygen binding? What are their functions within the body?
5. Where would you expect to find the lowest P_{O_2} within a cell?
6. In what forms is CO_2 carried in the blood? Which form accounts for the greatest transport?
7. Distinguish between transport of gas (O_2 or CO_2) and content of gas in the blood.
8. Would you expect fetal hemoglobin to have a higher or lower affinity for O_2 than adult hemoglobin? Why?