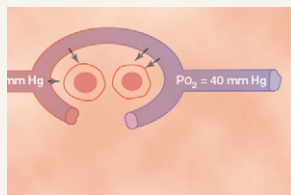


# Transport of Oxygen and Carbon Dioxide in Blood and Tissue Fluids



Once *oxygen* has diffused from the alveoli into the pulmonary blood, it is transported to the peripheral tissue capillaries almost entirely in combination with hemoglobin. The presence of hemoglobin in the red blood cells allows the blood to transport 30 to 100 times as much oxygen as could be transported in the form of dissolved oxygen in the water of the blood.

In the body's tissue cells, oxygen reacts with various foodstuffs to form large quantities of *carbon dioxide*. This carbon dioxide enters the tissue capillaries and is transported back to the lungs. Carbon dioxide, like oxygen, also combines with chemical substances in the blood that increase carbon dioxide transport 15- to 20-fold.

The purpose of this chapter is to present both qualitatively and quantitatively the physical and chemical principles of oxygen and carbon dioxide transport in the blood and tissue fluids.

## Transport of Oxygen from the Lungs to the Body Tissues

In Chapter 39, we pointed out that gases can move from one point to another by diffusion and that the cause of this movement is always a partial pressure difference from the first point to the next. Thus, oxygen diffuses from the alveoli into the pulmonary capillary blood because the oxygen partial pressure ( $P_{O_2}$ ) in the alveoli is greater than the  $P_{O_2}$  in the pulmonary capillary blood. In the other tissues of the body, a higher  $P_{O_2}$  in the capillary blood than in the tissues causes oxygen to diffuse into the surrounding cells.

Conversely, when oxygen is metabolized in the cells to form carbon dioxide, the intracellular carbon dioxide pressure ( $P_{CO_2}$ ) rises to a high value, which causes carbon dioxide to diffuse into the tissue capillaries. After blood flows to the lungs, the carbon dioxide diffuses out of the blood into the alveoli, because the  $P_{CO_2}$  in the pulmonary capillary blood is greater than that in the alveoli. Thus, the transport of oxygen and carbon dioxide by the blood depends on both diffusion and the flow of blood. We now consider quantitatively the factors responsible for these effects.

## Diffusion of Oxygen from the Alveoli to the Pulmonary Capillary Blood

The top part of Figure 40–1 shows a pulmonary alveolus adjacent to a pulmonary capillary, demonstrating diffusion of oxygen molecules between the alveolar air and the pulmonary blood. The  $P_{O_2}$  of the gaseous oxygen in the alveolus averages 104 mm Hg, whereas the  $P_{O_2}$  of the venous blood entering the pulmonary capillary at its arterial end averages only 40 mm Hg because a large amount of oxygen was removed from this blood as it passed through the peripheral tissues. Therefore, the *initial* pressure difference that causes oxygen to diffuse into the pulmonary capillary is  $104 - 40$ , or 64 mm Hg. In the graph at

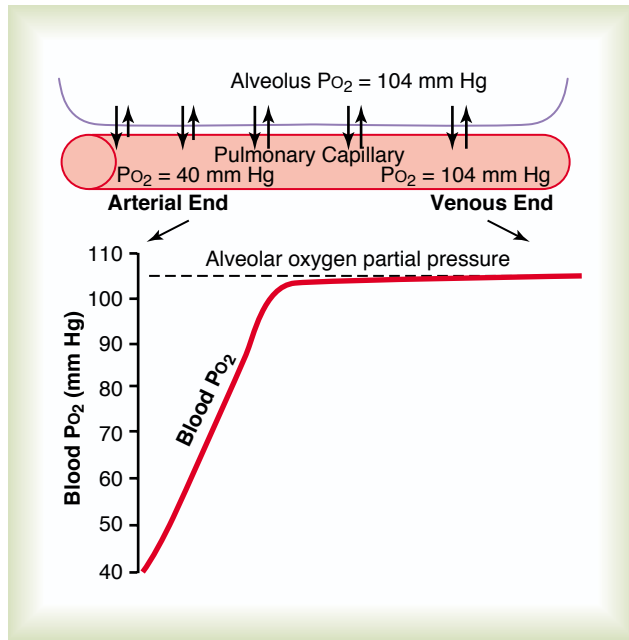


Figure 40-1

Uptake of oxygen by the pulmonary capillary blood. (The curve in this figure was constructed from data in Milhorn HT Jr, Pulley PE Jr: A theoretical study of pulmonary capillary gas exchange and venous admixture. *Biophys J* 8:337, 1968.)

the bottom of the figure, the curve shows the rapid rise in blood  $P_{O_2}$  as the blood passes through the capillary; the blood  $P_{O_2}$  rises almost to that of the alveolar air by the time the blood has moved a third of the distance through the capillary, becoming almost 104 mm Hg.

**Uptake of Oxygen by the Pulmonary Blood During Exercise.** During strenuous exercise, a person's body may require as much as 20 times the normal amount of oxygen. Also, because of increased cardiac output during exercise, the time that the blood remains in the pulmonary capillary may be reduced to less than one half normal. Yet, because of the great *safety factor* for diffusion of oxygen through the pulmonary membrane, the blood still becomes *almost saturated* with oxygen by the time it leaves the pulmonary capillaries. This can be explained as follows.

First, it was pointed out in Chapter 39 that the diffusing capacity for oxygen increases almost threefold during exercise; this results mainly from increased surface area of capillaries participating in the diffusion and also from a more nearly ideal ventilation-perfusion ratio in the upper part of the lungs.

Second, note in the curve of Figure 40-1 that under nonexercising conditions, the blood becomes almost saturated with oxygen by the time it has passed through one third of the pulmonary capillary, and little additional oxygen normally enters the blood during the latter two thirds of its transit. That is, the blood normally stays in the lung capillaries about three times as long as necessary to cause full oxygenation.

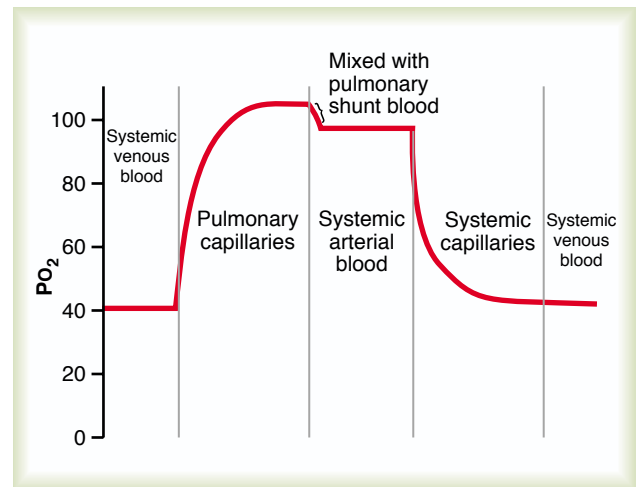


Figure 40-2

Changes in  $P_{O_2}$  in the pulmonary capillary blood, systemic arterial blood, and systemic capillary blood, demonstrating the effect of "venous admixture."

Therefore, during exercise, even with a shortened time of exposure in the capillaries, the blood can still become fully oxygenated, or nearly so.

### Transport of Oxygen in the Arterial Blood

About 98 per cent of the blood that enters the left atrium from the lungs has just passed through the alveolar capillaries and has become oxygenated up to a  $P_{O_2}$  of about 104 mm Hg. Another 2 per cent of the blood has passed from the aorta through the bronchial circulation, which supplies mainly the deep tissues of the lungs and is not exposed to lung air. This blood flow is called "shunt flow," meaning that blood is shunted past the gas exchange areas. On leaving the lungs, the  $P_{O_2}$  of the shunt blood is about that of normal systemic venous blood, about 40 mm Hg. When this blood combines in the pulmonary veins with the oxygenated blood from the alveolar capillaries, this so-called *venous admixture of blood* causes the  $P_{O_2}$  of the blood entering the left heart and pumped into the aorta to fall to about 95 mm Hg. These changes in blood  $P_{O_2}$  at different points in the circulatory system are shown in Figure 40-2.

### Diffusion of Oxygen from the Peripheral Capillaries into the Tissue Fluid

When the arterial blood reaches the peripheral tissues, its  $P_{O_2}$  in the capillaries is still 95 mm Hg. Yet, as shown in Figure 40-3, the  $P_{O_2}$  in the *interstitial fluid* that surrounds the tissue cells averages only 40 mm Hg. Thus, there is a tremendous initial pressure difference that causes oxygen to diffuse rapidly from the capillary

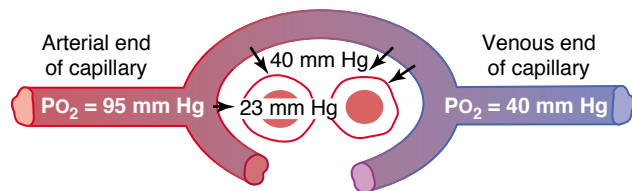


Figure 40-3

Diffusion of oxygen from a tissue capillary to the cells. ( $PO_2$  in interstitial fluid = 40 mm Hg, and in tissue cells = 23 mm Hg.)

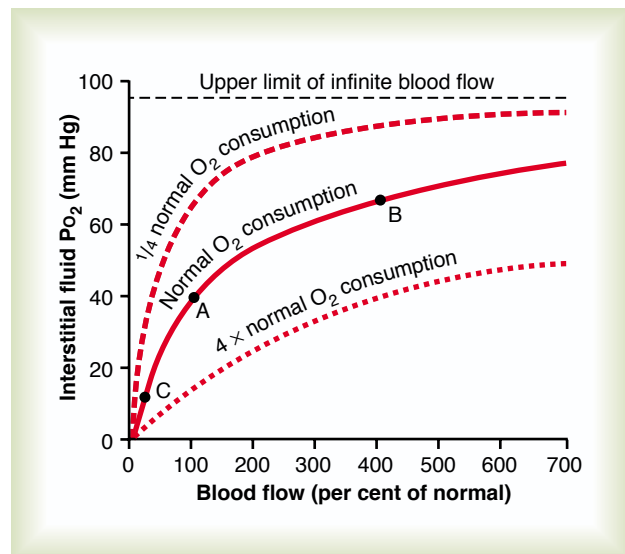


Figure 40-4

Effect of blood flow and rate of oxygen consumption on tissue  $PO_2$ .

blood into the tissues—so rapidly that the capillary  $PO_2$  falls almost to equal the 40 mm Hg pressure in the interstitium. Therefore, the  $PO_2$  of the blood leaving the tissue capillaries and entering the systemic veins is also about 40 mm Hg.

**Effect of Rate of Blood Flow on Interstitial Fluid  $PO_2$ .** If the blood flow through a particular tissue is increased, greater quantities of oxygen are transported into the tissue, and the tissue  $PO_2$  becomes correspondingly higher. This is shown in Figure 40-4. Note that an increase in flow to 400 per cent of normal increases the  $PO_2$  from 40 mm Hg (at point A in the figure) to 66 mm Hg (at point B). However, the upper limit to which the  $PO_2$  can rise, even with maximal blood flow, is 95 mm Hg, because this is the oxygen pressure in the arterial blood. Conversely, if blood flow through the tissue decreases, the tissue  $PO_2$  also decreases, as shown at point C.

**Effect of Rate of Tissue Metabolism on Interstitial Fluid  $PO_2$ .** If the cells use more oxygen for metabolism than normally, this reduces the interstitial fluid  $PO_2$ . Figure 40-4 also demonstrates this effect, showing reduced interstitial fluid  $PO_2$  when the cellular oxygen consumption is increased, and increased  $PO_2$  when consumption is decreased.

In summary, tissue  $PO_2$  is determined by a balance between (1) the rate of oxygen transport to the tissues in the blood and (2) the rate at which the oxygen is used by the tissues.

### Diffusion of Oxygen from the Peripheral Capillaries to the Tissue Cells

Oxygen is always being used by the cells. Therefore, the intracellular  $PO_2$  in the peripheral tissue cells remains lower than the  $PO_2$  in the peripheral capillaries. Also, in many instances, there is considerable physical distance between the capillaries and the cells. Therefore, the normal intracellular  $PO_2$  ranges from as low as 5 mm Hg to as high as 40 mm Hg, averaging (by direct measurement in lower animals) 23 mm Hg. Because only 1 to 3 mm Hg of oxygen pressure is normally required for full support of the chemical processes that use oxygen in the cell, one can see that even this low intracellular  $PO_2$  of 23 mm Hg is more than adequate and provides a large safety factor.

### Diffusion of Carbon Dioxide from the Peripheral Tissue Cells into the Capillaries and from the Pulmonary Capillaries into the Alveoli

When oxygen is used by the cells, virtually all of it becomes carbon dioxide, and this increases the intracellular  $PCO_2$ ; because of this high tissue cell  $PCO_2$ , carbon dioxide diffuses from the cells into the tissue capillaries and is then carried by the blood to the lungs. In the lungs, it diffuses from the pulmonary capillaries into the alveoli and is expired.

Thus, at each point in the gas transport chain, carbon dioxide diffuses in the direction exactly opposite to the diffusion of oxygen. Yet there is one major difference between diffusion of carbon dioxide and of oxygen: *carbon dioxide can diffuse about 20 times as rapidly as oxygen.* Therefore, the pressure differences required to cause carbon dioxide diffusion are, in each instance, far less than the pressure differences required to cause oxygen diffusion. The  $CO_2$  pressures are approximately the following:

1. Intracellular  $PCO_2$ , 46 mm Hg; interstitial  $PCO_2$ , 45 mm Hg. Thus, there is only a 1 mm Hg pressure differential, as shown in Figure 40-5.
2.  $PCO_2$  of the arterial blood entering the tissues, 40 mm Hg;  $PCO_2$  of the venous blood leaving the tissues, 45 mm Hg. Thus, as shown in Figure 40-5, the tissue capillary blood comes almost exactly to equilibrium with the interstitial  $PCO_2$  of 45 mm Hg.
3.  $PCO_2$  of the blood entering the pulmonary capillaries at the arterial end, 45 mm Hg;  $PCO_2$  of the alveolar air, 40 mm Hg. Thus, only a 5 mm Hg pressure difference causes all the required carbon dioxide diffusion out of the pulmonary capillaries

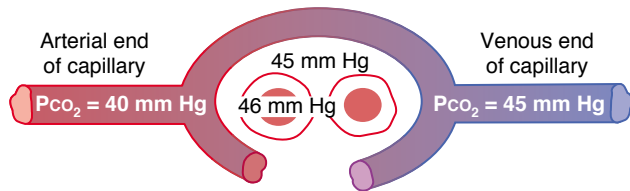


Figure 40-5

Uptake of carbon dioxide by the blood in the tissue capillaries. ( $PCO_2$  in tissue cells = 46 mm Hg, and in interstitial fluid = 45 mm Hg.)

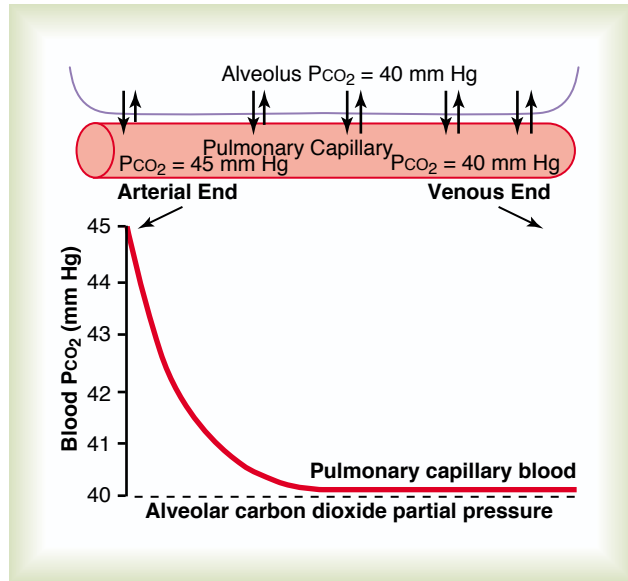


Figure 40-6

Diffusion of carbon dioxide from the pulmonary blood into the alveolus. (This curve was constructed from data in Milhorn HT Jr, Pulley PE Jr: A theoretical study of pulmonary capillary gas exchange and venous admixture. *Biophys J* 8:337, 1968.)

into the alveoli. Furthermore, as shown in Figure 40-6, the  $PCO_2$  of the pulmonary capillary blood falls to almost exactly equal the alveolar  $PCO_2$  of 40 mm Hg before it has passed more than about one third the distance through the capillaries. This is the same effect that was observed earlier for oxygen diffusion, except that it is in the opposite direction.

**Effect of Rate of Tissue Metabolism and Tissue Blood Flow on Interstitial  $PCO_2$ .** Tissue capillary blood flow and tissue metabolism affect the  $PCO_2$  in ways exactly opposite to their effect on tissue  $PO_2$ . Figure 40-7 shows these effects, as follows:

1. A decrease in blood flow from normal (point A) to one quarter normal (point B) increases peripheral tissue  $PCO_2$  from the normal value of 45 mm Hg to an elevated level of 60 mm Hg. Conversely, increasing the blood flow to six times normal (point C) decreases the interstitial

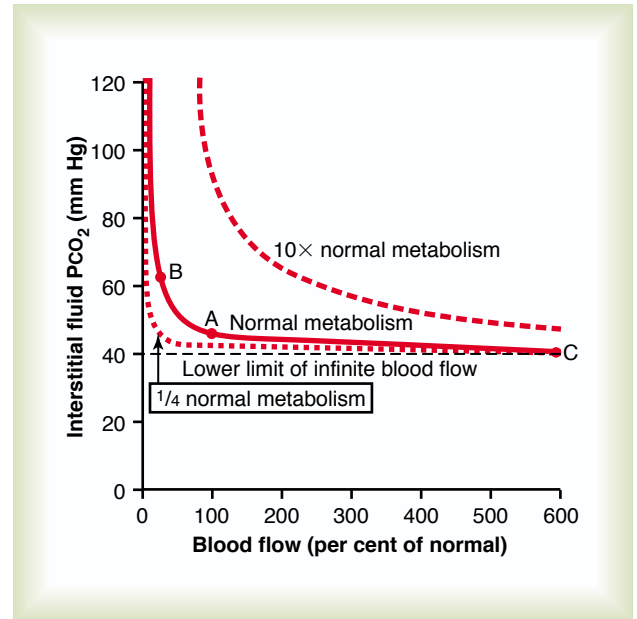


Figure 40-7

Effect of blood flow and metabolic rate on peripheral tissue  $PCO_2$ .

$PCO_2$  from the normal value of 45 mm Hg to 41 mm Hg, down to a level almost equal to the  $PCO_2$  in the arterial blood (40 mm Hg) entering the tissue capillaries.

2. Note also that a 10-fold increase in tissue metabolic rate greatly elevates the interstitial fluid  $PCO_2$  at all rates of blood flow, whereas decreasing the metabolism to one quarter normal causes the interstitial fluid  $PCO_2$  to fall to about 41 mm Hg, closely approaching that of the arterial blood, 40 mm Hg.

## Role of Hemoglobin in Oxygen Transport

Normally, about 97 per cent of the oxygen transported from the lungs to the tissues is carried in chemical combination with hemoglobin in the red blood cells. The remaining 3 per cent is transported in the dissolved state in the water of the plasma and blood cells. Thus, *under normal conditions*, oxygen is carried to the tissues almost entirely by hemoglobin.

## Reversible Combination of Oxygen with Hemoglobin

The chemistry of hemoglobin is presented in Chapter 32, where it was pointed out that the oxygen molecule combines loosely and reversibly with the heme portion of hemoglobin. When  $PO_2$  is high, as in the pulmonary capillaries, oxygen binds with the hemoglobin, but when  $PO_2$  is low, as in the tissue capillaries, oxygen is released from the hemoglobin. This is the basis for

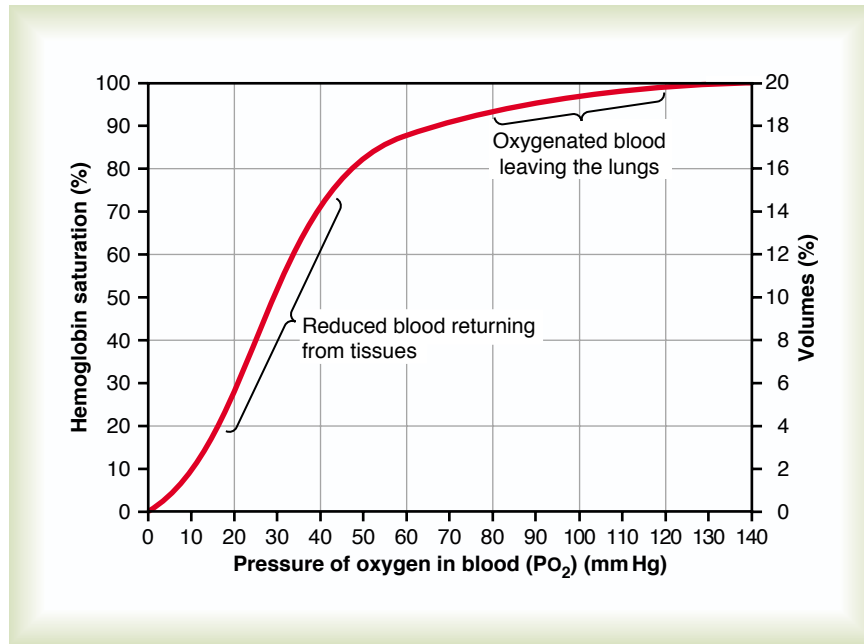


Figure 40-8

Oxygen-hemoglobin dissociation curve.

almost all oxygen transport from the lungs to the tissues.

**Oxygen-Hemoglobin Dissociation Curve.** Figure 40-8 shows the oxygen-hemoglobin dissociation curve, which demonstrates a progressive increase in the percentage of hemoglobin bound with oxygen as blood  $PO_2$  increases, which is called the *per cent saturation of hemoglobin*. Because the blood leaving the lungs and entering the systemic arteries usually has a  $PO_2$  of about 95 mm Hg, one can see from the dissociation curve that the *usual oxygen saturation of systemic arterial blood averages 97 per cent*. Conversely, in normal venous blood returning from the peripheral tissues, the  $PO_2$  is about 40 mm Hg, and the *saturation of hemoglobin averages 75 per cent*.

**Maximum Amount of Oxygen That Can Combine with the Hemoglobin of the Blood.** The blood of a normal person contains about 15 grams of hemoglobin in each 100 milliliters of blood, and each gram of hemoglobin can bind with a maximum of 1.34 milliliters of oxygen (1.39 milliliters when the hemoglobin is chemically pure, but impurities such as methemoglobin reduce this). Therefore, 15 times 1.34 equals 20.1, which means that, on average, the 15 grams of hemoglobin in 100 milliliters of blood can combine with a total of almost exactly 20 milliliters of oxygen if the hemoglobin is 100 per cent saturated. This is usually expressed as *20 volumes per cent*. The oxygen-hemoglobin dissociation curve for the normal person can also be expressed in terms of volume per cent of oxygen, as shown by the far right scale in Figure 40-8, instead of per cent saturation of hemoglobin.

**Amount of Oxygen Released from the Hemoglobin When Systemic Arterial Blood Flows Through the Tissues.** The total quantity of oxygen *bound with hemoglobin* in normal

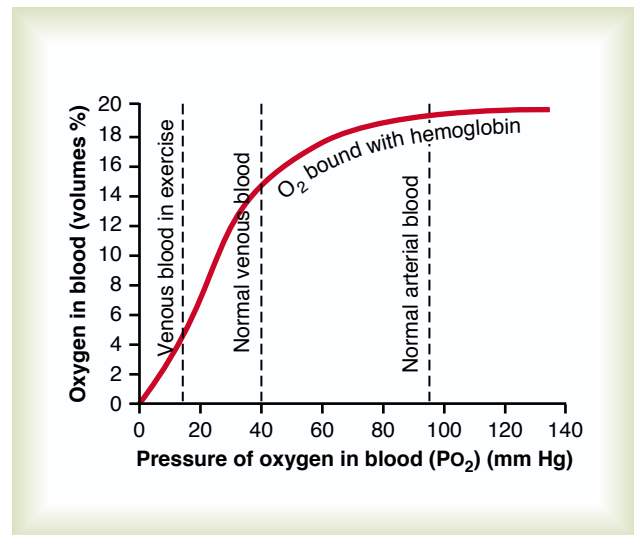


Figure 40-9

Effect of blood  $PO_2$  on the quantity of oxygen bound with hemoglobin in each 100 milliliters of blood.

systemic arterial blood, which is 97 per cent saturated, is about 19.4 milliliters per 100 milliliters of blood. This is shown in Figure 40-9. On passing through the tissue capillaries, this amount is reduced, on average, to 14.4 milliliters ( $PO_2$  of 40 mm Hg, 75 per cent saturated hemoglobin). Thus, *under normal conditions, about 5 milliliters of oxygen are transported from the lungs to the tissues by each 100 milliliters of blood flow*.

**Transport of Oxygen During Strenuous Exercise.** During heavy exercise, the muscle cells use oxygen at a rapid rate, which, in extreme cases, can cause the muscle interstitial fluid  $PO_2$  to fall from the normal 40 mm Hg

to as low as 15 mm Hg. At this low pressure, only 4.4 milliliters of oxygen remain bound with the hemoglobin in each 100 milliliters of blood, as shown in Figure 40–9. Thus, 19.4 – 4.4, or 15 milliliters, is the quantity of oxygen actually delivered to the tissues by each 100 milliliters of blood flow. Thus, three times as much oxygen as normal is delivered in each volume of blood that passes through the tissues. And keep in mind that the cardiac output can increase to six to seven times normal in well-trained marathon runners. Thus, multiplying the increase in cardiac output (six- to sevenfold) by the increase in oxygen transport in each volume of blood (threefold) gives a 20-fold increase in oxygen transport to the tissues. We see later in the chapter that several other factors facilitate delivery of oxygen into muscles during exercise, so that muscle tissue  $P_{O_2}$  often falls very little below normal even during very strenuous exercise.

**Utilization Coefficient.** The percentage of the blood that gives up its oxygen as it passes through the tissue capillaries is called the *utilization coefficient*. The normal value for this is about 25 per cent, as is evident from the preceding discussion—that is, 25 per cent of the oxygenated hemoglobin gives its oxygen to the tissues. During strenuous exercise, the utilization coefficient in the entire body can increase to 75 to 85 per cent. And in local tissue areas where blood flow is extremely slow or the metabolic rate is very high, utilization coefficients approaching 100 per cent have been recorded—that is, essentially all the oxygen is given to the tissues.

### Effect of Hemoglobin to “Buffer” the Tissue $P_{O_2}$

Although hemoglobin is necessary for the transport of oxygen to the tissues, it performs another function essential to life. This is its function as a “tissue oxygen buffer” system. That is, the hemoglobin in the blood is mainly responsible for stabilizing the oxygen pressure in the tissues. This can be explained as follows.

**Role of Hemoglobin in Maintaining Nearly Constant  $P_{O_2}$  in the Tissues.** Under basal conditions, the tissues require about 5 milliliters of oxygen from each 100 milliliters of blood passing through the tissue capillaries. Referring back to the oxygen-hemoglobin dissociation curve in Figure 40–9, one can see that for the normal 5 milliliters of oxygen to be released per 100 milliliters of blood flow, the  $P_{O_2}$  must fall to about 40 mm Hg. Therefore, the tissue  $P_{O_2}$  normally cannot rise above this 40 mm Hg level, because if it did, the amount of oxygen needed by the tissues would not be released from the hemoglobin. In this way, the hemoglobin normally sets an upper limit on the oxygen pressure in the tissues at about 40 mm Hg.

Conversely, during heavy exercise, extra amounts of oxygen (as much as 20 times normal) must be delivered from the hemoglobin to the tissues. But this can be achieved with little further decrease in tissue  $P_{O_2}$

because of (1) the steep slope of the dissociation curve and (2) the increase in tissue blood flow caused by the decreased  $P_{O_2}$ ; that is, a very small fall in  $P_{O_2}$  causes large amounts of extra oxygen to be released from the hemoglobin. It can be seen, then, that the hemoglobin in the blood automatically delivers oxygen to the tissues at a pressure that is held rather tightly between about 15 and 40 mm Hg.

### When Atmospheric Oxygen Concentration Changes Markedly, the Buffer Effect of Hemoglobin Still Maintains Almost Constant Tissue $P_{O_2}$ .

The normal  $P_{O_2}$  in the alveoli is about 104 mm Hg, but as one ascends a mountain or ascends in an airplane, the  $P_{O_2}$  can easily fall to less than half this amount. Alternatively, when one enters areas of compressed air, such as deep in the sea or in pressurized chambers, the  $P_{O_2}$  may rise to 10 times this level. Even so, the tissue  $P_{O_2}$  changes little.

It can be seen from the oxygen-hemoglobin dissociation curve in Figure 40–8 that when the alveolar  $P_{O_2}$  is decreased to as low as 60 mm Hg, the arterial hemoglobin is still 89 per cent saturated with oxygen—only 8 per cent below the normal saturation of 97 per cent. Further, the tissues still remove about 5 milliliters of oxygen from each 100 milliliters of blood passing through the tissues; to remove this oxygen, the  $P_{O_2}$  of the venous blood falls to 35 mm Hg—only 5 mm Hg below the normal value of 40 mm Hg. Thus, the tissue  $P_{O_2}$  hardly changes, despite the marked fall in alveolar  $P_{O_2}$  from 104 to 60 mm Hg.

Conversely, when the alveolar  $P_{O_2}$  rises as high as 500 mm Hg, the maximum oxygen saturation of hemoglobin can never rise above 100 per cent, which is only 3 per cent above the normal level of 97 per cent. Only a small amount of additional oxygen dissolves in the fluid of the blood, as will be discussed subsequently. Then, when the blood passes through the tissue capillaries and loses several milliliters of oxygen to the tissues, this reduces the  $P_{O_2}$  of the capillary blood to a value only a few millimeters greater than the normal 40 mm Hg. Consequently, the level of alveolar oxygen may vary greatly—from 60 to more than 500 mm Hg  $P_{O_2}$ —and still the  $P_{O_2}$  in the peripheral tissues does not vary more than a few millimeters from normal, *demonstrating beautifully the tissue “oxygen buffer” function of the blood hemoglobin system.*

### Factors That Shift the Oxygen-Hemoglobin Dissociation Curve—Their Importance for Oxygen Transport

The oxygen-hemoglobin dissociation curves of Figures 40–8 and 40–9 are for normal, average blood. However, a number of factors can displace the dissociation curve in one direction or the other in the manner shown in Figure 40–10. This figure shows that when the blood becomes slightly acidic, with the pH decreasing from the normal value of 7.4 to 7.2, the oxygen-hemoglobin dissociation curve shifts, on



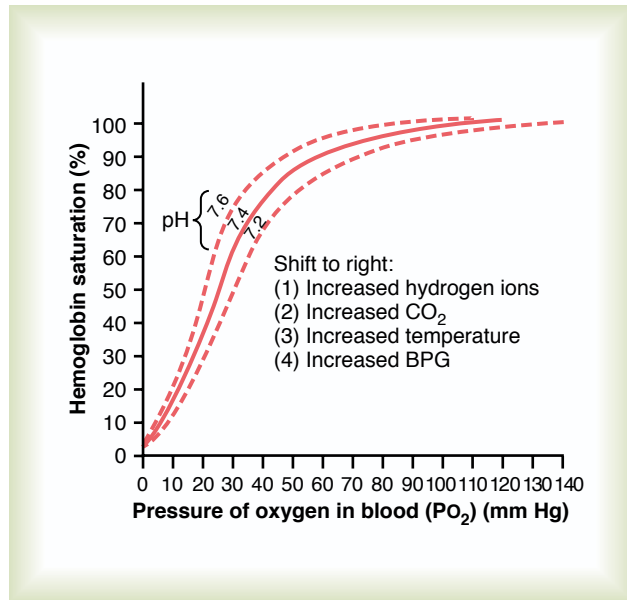


Figure 40-10

Shift of the oxygen-hemoglobin dissociation curve to the right caused by an increase in hydrogen ion concentration (decrease in pH). BPG, 2,3-biphosphoglycerate.

average, about 15 per cent to the right. Conversely, an increase in pH from the normal 7.4 to 7.6 shifts the curve a similar amount to the left.

In addition to pH changes, several other factors are known to shift the curve. Three of these, all of which shift the curve to the *right*, are (1) increased carbon dioxide concentration, (2) increased blood temperature, and (3) increased 2,3-biphosphoglycerate (BPG), a metabolically important phosphate compound present in the blood in different concentrations under different metabolic conditions.

**Increased Delivery of Oxygen to the Tissues When Carbon Dioxide and Hydrogen Ions Shift the Oxygen-Hemoglobin Dissociation Curve—The Bohr Effect.** A shift of the oxygen-hemoglobin dissociation curve to the right in response to increases in blood carbon dioxide and hydrogen ions has a significant effect by enhancing the release of oxygen from the blood in the tissues and enhancing oxygenation of the blood in the lungs. This is called the Bohr effect, which can be explained as follows: As the blood passes through the tissues, carbon dioxide diffuses from the tissue cells into the blood. This increases the blood  $\text{PO}_2$  which in turn raises the blood  $\text{H}_2\text{CO}_3$  (carbonic acid) and the hydrogen ion concentration. These effects shift the oxygen-hemoglobin dissociation curve to the right and downward, as shown in Figure 40-10, forcing oxygen away from the hemoglobin and therefore delivering increased amounts of oxygen to the tissues.

Exactly the opposite effects occur in the lungs, where carbon dioxide diffuses from the blood into the alveoli. This reduces the blood  $\text{Pco}_2$  and decreases the hydrogen ion concentration, shifting the

oxygen-hemoglobin dissociation curve to the left and upward. Therefore, the quantity of oxygen that binds with the hemoglobin at any given alveolar  $\text{PO}_2$  becomes considerably increased, thus allowing greater oxygen transport to the tissues.

**Effect of BPG to Shift the Oxygen-Hemoglobin Dissociation Curve.** The normal BPG in the blood keeps the oxygen-hemoglobin dissociation curve shifted slightly to the right all the time. In hypoxic conditions that last longer than a few hours, the quantity of BPG in the blood increases considerably, thus shifting the oxygen-hemoglobin dissociation curve even farther to the right. This causes oxygen to be released to the tissues at as much as 10 mm Hg higher tissue oxygen pressure than would be the case without this increased BPG. Therefore, under some conditions, the BPG mechanism can be important for adaptation to hypoxia, especially to hypoxia caused by poor tissue blood flow.

**Shift of the Dissociation Curve During Exercise.** During exercise, several factors shift the dissociation curve considerably to the right, thus delivering extra amounts of oxygen to the active, exercising muscle fibers. The exercising muscles, in turn, release large quantities of carbon dioxide; this and several other acids released by the muscles increase the hydrogen ion concentration in the muscle capillary blood. In addition, the temperature of the muscle often rises  $2^\circ$  to  $3^\circ\text{C}$ , which can increase oxygen delivery to the muscle fibers even more. All these factors act together to shift the oxygen-hemoglobin dissociation curve of the muscle capillary blood considerably to the right. This right-hand shift of the curve forces oxygen to be released from the blood hemoglobin to the muscle at  $\text{PO}_2$  levels as great as 40 mm Hg, even when 70 per cent of the oxygen has already been removed from the hemoglobin. Then, in the lungs, the shift occurs in the opposite direction, allowing the pickup of extra amounts of oxygen from the alveoli.

## Metabolic Use of Oxygen by the Cells

**Effect of Intracellular  $\text{PO}_2$  on Rate of Oxygen Usage.** Only a minute level of oxygen pressure is required in the cells for normal intracellular chemical reactions to take place. The reason for this is that the respiratory enzyme systems of the cell, which are discussed in Chapter 67, are geared so that when the cellular  $\text{PO}_2$  is more than 1 mm Hg, oxygen availability is no longer a limiting factor in the rates of the chemical reactions. Instead, the main limiting factor is the *concentration of adenosine diphosphate* (ADP) in the cells. This effect is demonstrated in Figure 40-11, which shows the relation between intracellular  $\text{PO}_2$  and the rate of oxygen usage at different concentrations of ADP. Note that whenever the intracellular  $\text{PO}_2$  is above 1 mm Hg, the rate of oxygen usage becomes constant for any given concentration of ADP in the cell. Conversely, when the ADP concentration is altered, the rate of

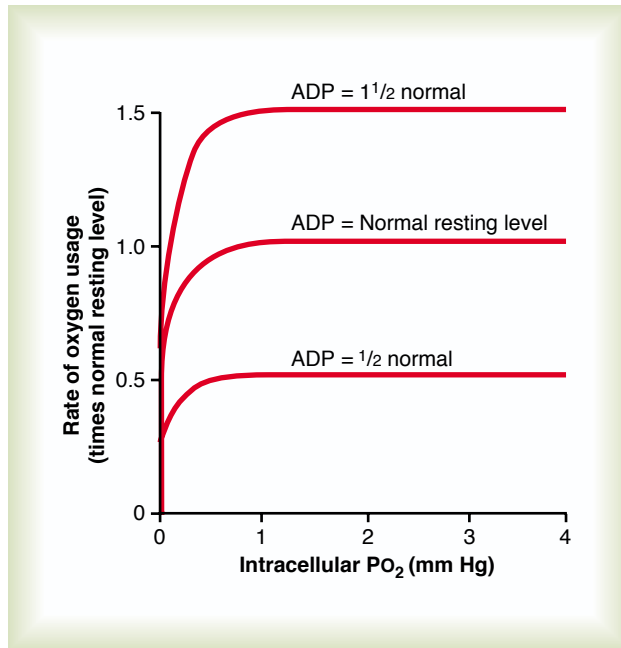


Figure 40-11

Effect of intracellular adenosine diphosphate (ADP) and  $\text{PO}_2$  on rate of oxygen usage by the cells. Note that as long as the intracellular  $\text{PO}_2$  remains above 1 mm Hg, the controlling factor for the rate of oxygen usage is the intracellular concentration of ADP.

oxygen usage changes in proportion to the change in ADP concentration.

As explained in Chapter 3, when adenosine triphosphate (ATP) is used in the cells to provide energy, it is converted into ADP. The increasing concentration of ADP increases the metabolic usage of oxygen as it combines with the various cell nutrients, releasing energy that reconverts the ADP back to ATP. *Under normal operating conditions, the rate of oxygen usage by the cells is controlled ultimately by the rate of energy expenditure within the cells—that is, by the rate at which ADP is formed from ATP.*

**Effect of Diffusion Distance from the Capillary to the Cell on Oxygen Usage.** Tissue cells are seldom more than 50 micrometers away from a capillary, and oxygen normally can diffuse readily enough from the capillary to the cell to supply all the required amounts of oxygen for metabolism. However, occasionally, cells are located farther from the capillaries, and the rate of oxygen diffusion to these cells can become so low that intracellular  $\text{PO}_2$  falls below the critical level required to maintain maximal intracellular metabolism. Thus, under these conditions, oxygen usage by the cells is said to be *diffusion limited* and is no longer determined by the amount of ADP formed in the cells. But this almost never occurs, except in pathological states.

**Effect of Blood Flow on Metabolic Use of Oxygen.** The total amount of oxygen available each minute for use in any given tissue is determined by (1) the quantity of

oxygen that can be transported to the tissue in each 100 milliliters of blood and (2) the rate of blood flow. If the rate of blood flow falls to zero, the amount of available oxygen also falls to zero. Thus, there are times when the rate of blood flow through a tissue can be so low that tissue  $\text{PO}_2$  falls below the critical 1 mm Hg required for intracellular metabolism. Under these conditions, the rate of tissue usage of oxygen is *blood flow limited*. Neither diffusion-limited nor blood flow-limited oxygen states can continue for long, because the cells receive less oxygen than is required to continue the life of the cells.

### Transport of Oxygen in the Dissolved State

At the normal arterial  $\text{PO}_2$  of 95 mm Hg, about 0.29 milliliter of oxygen is dissolved in every 100 milliliters of water in the blood, and when the  $\text{PO}_2$  of the blood falls to the normal 40 mm Hg in the tissue capillaries, only 0.12 milliliter of oxygen remains dissolved. In other words, 0.17 milliliter of oxygen is normally transported in the dissolved state to the tissues by each 100 milliliters of arterial blood flow. This compares with almost 5 milliliters of oxygen transported by the red cell hemoglobin. Therefore, the amount of oxygen transported to the tissues in the dissolved state is normally slight, only about 3 per cent of the total, as compared with 97 per cent transported by the hemoglobin.

During strenuous exercise, when hemoglobin release of oxygen to the tissues increases another threefold, the relative quantity of oxygen transported in the dissolved state falls to as little as 1.5 per cent. But if a person breathes oxygen at very high alveolar  $\text{PO}_2$  levels, the amount transported in the dissolved state can become much greater, sometimes so much so that a serious excess of oxygen occurs in the tissues, and “oxygen poisoning” ensues. This often leads to brain convulsions and even death, as discussed in detail in Chapter 44 in relation to the high-pressure breathing of oxygen among deep-sea divers.

### Combination of Hemoglobin with Carbon Monoxide—Displacement of Oxygen

Carbon monoxide combines with hemoglobin at the same point on the hemoglobin molecule as does oxygen; it can therefore displace oxygen from the hemoglobin, thereby decreasing the oxygen carrying capacity of blood. Further, it binds with about 250 times as much tenacity as oxygen, which is demonstrated by the carbon monoxide-hemoglobin dissociation curve in Figure 40-12. This curve is almost identical to the oxygen-hemoglobin dissociation curve, except that the carbon monoxide partial pressures, shown on the abscissa, are at a level  $1/250$  of those for the oxygen-hemoglobin dissociation curve of Figure 40-8. Therefore, a carbon monoxide partial pressure of only 0.4 mm Hg in the alveoli,  $1/250$  that of normal alveolar oxygen (100 mm Hg  $\text{PO}_2$ ), allows the carbon monoxide to compete equally with the oxygen for combination with the hemoglobin and causes half the hemoglobin in the blood to become bound with carbon monoxide instead of with oxygen. Therefore, a carbon monoxide pressure of only



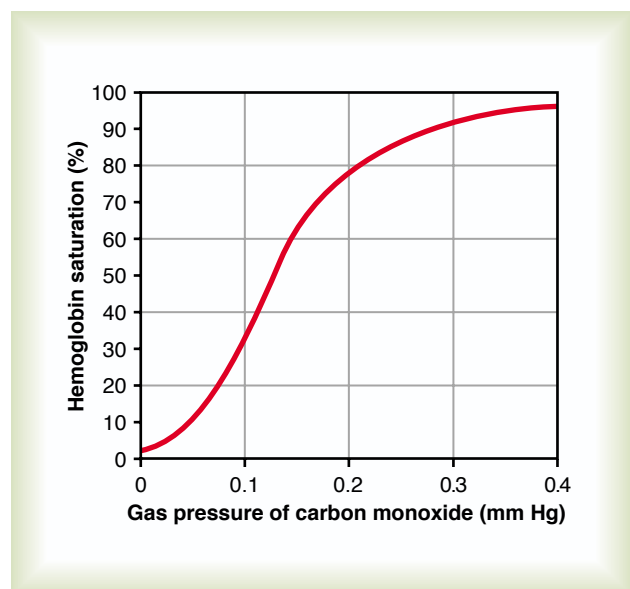


Figure 40-12

Carbon monoxide-hemoglobin dissociation curve. Note the extremely low carbon monoxide pressures at which carbon monoxide combines with hemoglobin.

0.6 mm Hg (a volume concentration of less than one part per thousand in air) can be lethal.

Even though the oxygen content of blood is greatly reduced in carbon monoxide poisoning, the  $P_{O_2}$  of the blood may be normal. This makes exposure to carbon monoxide especially dangerous, because the blood is bright red and there are no obvious signs of hypoxemia, such as a bluish color of the fingertips or lips (cyanosis). Also,  $P_{O_2}$  is not reduced, and the feedback mechanism that usually stimulates increased respiration rate in response to lack of oxygen (usually reflected by a low  $P_{O_2}$ ) is absent. Because the brain is one of the first organs affected by lack of oxygen, the person may become disoriented and unconscious before becoming aware of the danger.

A patient severely poisoned with carbon monoxide can be treated by administering pure oxygen, because oxygen at high alveolar pressure can displace carbon monoxide rapidly from its combination with hemoglobin. The patient can also benefit from simultaneous administration of 5 per cent carbon dioxide, because this strongly stimulates the respiratory center, which increases alveolar ventilation and reduces the alveolar carbon monoxide. With intensive oxygen and carbon dioxide therapy, carbon monoxide can be removed from the blood as much as 10 times as rapidly as without therapy.

## Transport of Carbon Dioxide in the Blood

Transport of carbon dioxide by the blood is not nearly as problematical as transport of oxygen is, because even in the most abnormal conditions, carbon dioxide can usually be transported in far greater quantities than oxygen can be. However, the amount of carbon

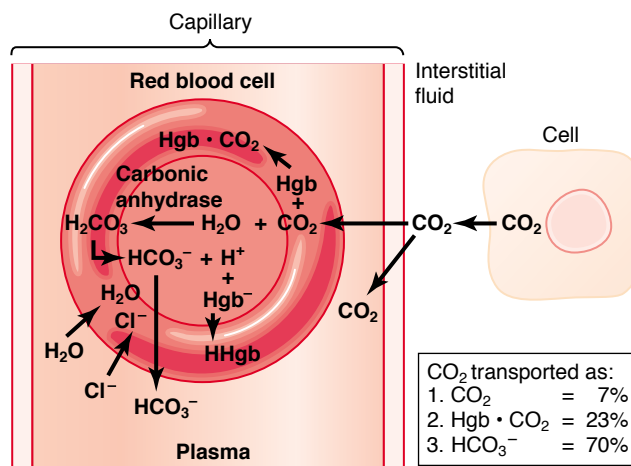


Figure 40-13

Transport of carbon dioxide in the blood.

dioxide in the blood has a lot to do with the acid-base balance of the body fluids, which is discussed in Chapter 30. Under normal resting conditions, *an average of 4 milliliters of carbon dioxide is transported from the tissues to the lungs in each 100 milliliters of blood.*

## Chemical Forms in Which Carbon Dioxide Is Transported

To begin the process of carbon dioxide transport, carbon dioxide diffuses out of the tissue cells in the dissolved molecular carbon dioxide form. On entering the tissue capillaries, the carbon dioxide initiates a host of almost instantaneous physical and chemical reactions, shown in Figure 40-13, which are essential for carbon dioxide transport.

**Transport of Carbon Dioxide in the Dissolved State.** A small portion of the carbon dioxide is transported in the dissolved state to the lungs. Recall that the  $P_{CO_2}$  of venous blood is 45 mm Hg and that of arterial blood is 40 mm Hg. The amount of carbon dioxide dissolved in the fluid of the blood at 45 mm Hg is about 2.7 ml/dl (2.7 volumes per cent). The amount dissolved at 40 mm Hg is about 2.4 milliliters, or a difference of 0.3 milliliter. Therefore, only about 0.3 milliliter of carbon dioxide is transported in the dissolved form by each 100 milliliters of blood flow. This is about 7 per cent of all the carbon dioxide normally transported.

**Transport of Carbon Dioxide in the Form of Bicarbonate Ion**  
**Reaction of Carbon Dioxide with Water in the Red Blood Cells—Effect of Carbonic Anhydrase.** The dissolved carbon dioxide in the blood reacts with water to form *carbonic acid*. This reaction would occur much too slowly to be of importance were it not for the fact that inside the red blood cells is a protein enzyme called *carbonic anhydrase*, which catalyzes the

reaction between carbon dioxide and water and accelerates its reaction rate about 5000-fold. Therefore, instead of requiring many seconds or minutes to occur, as is true in the plasma, the reaction occurs so rapidly in the red blood cells that it reaches almost complete equilibrium within a very small fraction of a second. This allows tremendous amounts of carbon dioxide to react with the red blood cell water even before the blood leaves the tissue capillaries.

**Dissociation of Carbonic Acid into Bicarbonate and Hydrogen Ions.** In another fraction of a second, the carbonic acid formed in the red cells ( $\text{H}_2\text{CO}_3$ ) dissociates into *hydrogen* and *bicarbonate ions* ( $\text{H}^+$  and  $\text{HCO}_3^-$ ). Most of the hydrogen ions then combine with the hemoglobin in the red blood cells, because the hemoglobin protein is a powerful acid-base buffer. In turn, many of the bicarbonate ions diffuse from the red cells into the plasma, while chloride ions diffuse into the red cells to take their place. This is made possible by the presence of a special *bicarbonate-chloride carrier protein* in the red cell membrane that shuttles these two ions in opposite directions at rapid velocities. Thus, the chloride content of venous red blood cells is greater than that of arterial red cells, a phenomenon called the *chloride shift*.

The reversible combination of carbon dioxide with water in the red blood cells under the influence of carbonic anhydrase accounts for about 70 per cent of the carbon dioxide transported from the tissues to the lungs. Thus, this means of transporting carbon dioxide is by far the most important. Indeed, when a carbonic anhydrase inhibitor (acetazolamide) is administered to an animal to block the action of carbonic anhydrase in the red blood cells, carbon dioxide transport from the tissues becomes so poor that the tissue  $\text{PCO}_2$  can be made to rise to 80 mm Hg instead of the normal 45 mm Hg.

**Transport of Carbon Dioxide in Combination with Hemoglobin and Plasma Proteins—Carbaminohemoglobin.** In addition to reacting with water, carbon dioxide reacts directly with amine radicals of the hemoglobin molecule to form the compound *carbaminohemoglobin* ( $\text{CO}_2\text{Hgb}$ ). This combination of carbon dioxide and hemoglobin is a reversible reaction that occurs with a loose bond, so that the carbon dioxide is easily released into the alveoli, where the  $\text{PCO}_2$  is lower than in the pulmonary capillaries.

A small amount of carbon dioxide also reacts in the same way with the plasma proteins in the tissue capillaries. This is much less significant for the transport of carbon dioxide because the quantity of these proteins in the blood is only one fourth as great as the quantity of hemoglobin.

The quantity of carbon dioxide that can be carried from the peripheral tissues to the lungs by carbamino combination with hemoglobin and plasma proteins is about 30 per cent of the total quantity transported—that is, normally about 1.5 milliliters of carbon dioxide in each 100 milliliters of blood. However, because this reaction is much slower than the reaction of carbon

dioxide with water inside the red blood cells, it is doubtful that under normal conditions this carbamino mechanism transports more than 20 per cent of the total carbon dioxide.

### Carbon Dioxide Dissociation Curve

The curve shown in Figure 40–14—called the *carbon dioxide dissociation curve*—depicts the dependence of total blood carbon dioxide in all its forms on  $\text{PCO}_2$ . Note that the normal blood  $\text{PCO}_2$  ranges between the limits of 40 mm Hg in arterial blood and 45 mm Hg in venous blood, which is a very narrow range. Note also that the normal concentration of carbon dioxide in the blood in all its different forms is about 50 volumes per cent, but only 4 volumes per cent of this is exchanged during normal transport of carbon dioxide from the tissues to the lungs. That is, the concentration rises to about 52 volumes per cent as the blood passes through the tissues and falls to about 48 volumes per cent as it passes through the lungs.

### When Oxygen Binds with Hemoglobin, Carbon Dioxide Is Released (the Haldane Effect) to Increase $\text{CO}_2$ Transport

Earlier in the chapter, it was pointed out that an increase in carbon dioxide in the blood causes oxygen to be displaced from the hemoglobin (the Bohr effect), which is an important factor in increasing oxygen transport. The reverse is also true: binding of oxygen with hemoglobin tends to displace carbon dioxide from the blood. Indeed, this effect, called the *Haldane effect*, is quantitatively far more important in

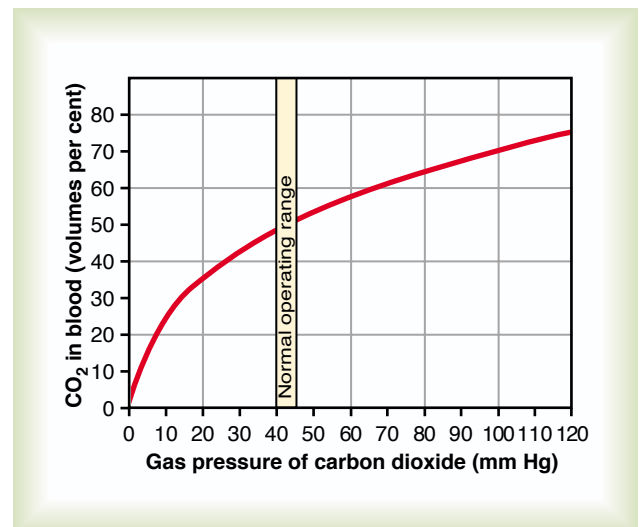


Figure 40–14

Carbon dioxide dissociation curve.

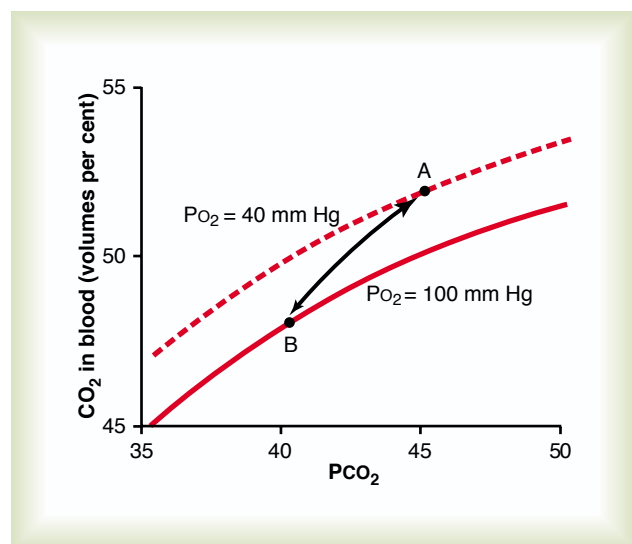


Figure 40-15

Portions of the carbon dioxide dissociation curve when the  $PO_2$  is 100 mm Hg or 40 mm Hg. The arrow represents the Haldane effect on the transport of carbon dioxide, as discussed in the text.

promoting carbon dioxide transport than is the Bohr effect in promoting oxygen transport.

The Haldane effect results from the simple fact that the combination of oxygen with hemoglobin in the lungs causes the hemoglobin to become a stronger acid. This displaces carbon dioxide from the blood and into the alveoli in two ways: (1) The more highly acidic hemoglobin has less tendency to combine with carbon dioxide to form carbaminohemoglobin, thus displacing much of the carbon dioxide that is present in the carbamino form from the blood. (2) The increased acidity of the hemoglobin also causes it to release an excess of hydrogen ions, and these bind with bicarbonate ions to form carbonic acid; this then dissociates into water and carbon dioxide, and the carbon dioxide is released from the blood into the alveoli and, finally, into the air.

Figure 40-15 demonstrates quantitatively the significance of the Haldane effect on the transport of carbon dioxide from the tissues to the lungs. This figure shows small portions of two carbon dioxide dissociation curves: (1) when the  $PO_2$  is 100 mm Hg, which is the case in the blood capillaries of the lungs, and (2) when the  $PO_2$  is 40 mm Hg, which is the case in the tissue capillaries. Point A shows that the normal  $PCO_2$  of 45 mm Hg in the tissues causes 52 volumes per cent of carbon dioxide to combine with the blood. On entering the lungs, the  $PCO_2$  falls to 40 mm Hg and the  $PO_2$  rises to 100 mm Hg. If the carbon dioxide dissociation curve did not shift because of the Haldane effect, the carbon dioxide content of the blood would fall only to 50 volumes per cent, which would be a loss of only 2 volumes per cent of carbon dioxide. However, the increase in  $PO_2$  in the lungs lowers the carbon dioxide dissociation curve from the top curve to the lower curve of the figure, so that the carbon dioxide content

falls to 48 volumes per cent (point B). This represents an additional 2 volumes per cent loss of carbon dioxide. Thus, the Haldane effect approximately doubles the amount of carbon dioxide released from the blood in the lungs and approximately doubles the pickup of carbon dioxide in the tissues.

### Change in Blood Acidity During Carbon Dioxide Transport

The carbonic acid formed when carbon dioxide enters the blood in the peripheral tissues decreases the blood pH. However, reaction of this acid with the acid-base buffers of the blood prevents the hydrogen ion concentration from rising greatly (and the pH from falling greatly). Ordinarily, arterial blood has a pH of about 7.41, and as the blood acquires carbon dioxide in the tissue capillaries, the pH falls to a venous value of about 7.37. In other words, a pH change of 0.04 unit takes place. The reverse occurs when carbon dioxide is released from the blood in the lungs, with the pH rising to the arterial value of 7.41 once again. In heavy exercise or other conditions of high metabolic activity, or when blood flow through the tissues is sluggish, the decrease in pH in the tissue blood (and in the tissues themselves) can be as much as 0.50, about 12 times normal, thus causing significant tissue acidosis.

### Respiratory Exchange Ratio

The discerning student will have noted that normal transport of oxygen from the lungs to the tissues by each 100 milliliters of blood is about 5 milliliters, whereas normal transport of carbon dioxide from the tissues to the lungs is about 4 milliliters. Thus, under normal resting conditions, only about 82 per cent as much carbon dioxide is expired from the lungs as oxygen is taken up by the lungs. The ratio of carbon dioxide output to oxygen uptake is called the *respiratory exchange ratio* (R). That is,

$$R = \frac{\text{Rate of carbon dioxide output}}{\text{Rate of oxygen uptake}}$$

The value for R changes under different metabolic conditions. When a person is using exclusively carbohydrates for body metabolism, R rises to 1.00. Conversely, when a person is using exclusively fats for metabolic energy, the R level falls to as low as 0.7. The reason for this difference is that when oxygen is metabolized with carbohydrates, one molecule of carbon dioxide is formed for each molecule of oxygen consumed; when oxygen reacts with fats, a large share of the oxygen combines with hydrogen atoms from the fats to form water instead of carbon dioxide. In other words, when fats are metabolized, the *respiratory quotient of the chemical reactions* in the tissues is about 0.70 instead of 1.00. (The tissue respiratory quotient is discussed in Chapter 71.) For a person on a normal diet consuming average amounts of carbohydrates, fats, and proteins, the average value for R is considered to be 0.825.

### References

Albert R, Spiro S, Jett J: Comprehensive Respiratory Medicine. Philadelphia: Mosby, 2002.

- Dempsey JA, Wagner PD: Exercise-induced arterial hypoxemia. *J Appl Physiol* 87:1997, 1999.
- Geers C, Gros G: Carbon dioxide transport and carbonic anhydrase in blood and muscle. *Physiol Rev* 80:681, 2000.
- Henry RP, Swenson ER: The distribution and physiological significance of carbonic anhydrase in vertebrate gas exchange organs. *Respir Physiol* 121:1, 2000.
- Jones AM, Koppo K, Burnley M: Effects of prior exercise on metabolic and gas exchange responses to exercise. *Sports Med* 33:949, 2003.
- Nikinmaa M: Membrane transport and control of hemoglobin-oxygen affinity in nucleated erythrocytes. *Physiol Rev* 72:301, 1992.
- Piiper J: Perfusion, diffusion and their heterogeneities limiting blood-tissue O<sub>2</sub> transfer in muscle. *Acta Physiol Scand* 168:603, 2000.
- Richardson RS: Oxygen transport and utilization: an integration of the muscle systems. *Adv Physiol Educ* 27:183, 2003.
- Roy TK, Popel AS: Theoretical predictions of end-capillary Po<sub>2</sub> in muscles of athletic and nonathletic animals at Vo<sub>2</sub>max. *Am J Physiol* 271:H721, 1996.
- Spahn DR, Pasch T: Physiological properties of blood substitutes. *News Physiol Sci* 16:38, 2001.
- Tsai AG, Johnson PC, Intaglietta M: Oxygen gradients in the microcirculation. *Physiol Rev* 83:933, 2003.
- Wagner PD: Diffusive resistance to O<sub>2</sub> transport in muscle. *Acta Physiol Scand* 168:609, 2000.
- West JB: *Pulmonary Physiology and Pathophysiology: An Integrated, Case-Based Approach*. Philadelphia: Lippincott Williams & Wilkins, 2001.
- West JB: *Pulmonary Physiology—The Essentials*. Baltimore: Lippincott Williams & Wilkins, 2003.