MJC 4 (Physiology)
Physiology of Respiration

Structures and Mechanisms of Breathing

In mammals, inspired air travels through the trachea, bronchi, and bronchioles to reach the alveoli, where gas exchange occurs. Each alveolus is composed of an epithelium only one cell thick, and is surrounded by blood capillaries with walls that are also only one cell layer thick. There are about 30 billion capillaries in both lungs, or about 100 capillaries per alveolus. Thus, an alveolus can be visualized as a microscopic air bubble whose entire surface is bathed by blood. Because the alveolar air and the capillary blood are separated by only two cell layers, the distance between the air and blood is only 0.5 to 1.5 micrometers, allowing for the rapid exchange of gases by diffusion by decreasing *d* in Fick's Law.

The blood leaving the lungs, as a result of this gas exchange, normally contains a partial oxygen pressure (PO_2) of about 100 millimeters of mercury. The PO_2 is a measure of the concentration of dissolved oxygen—you can think of it as indicating the plasma oxygen. Because the PO_2 of the blood leaving the lungs is close to the PO_2 of the air in the alveoli (about 105 mm Hg), the lungs do a very effective, but not perfect, job of oxygenating the blood. After gas exchange in the systemic capillaries, the blood that returns to the right side of the heart is depleted in oxygen, with a PO_2 of about 40 millimeters of mercury. These changes in the PO_2 of the blood, as well as the changes in plasma carbon dioxide (indicated as the PCO_2).

The outside of each lung is covered by a thin membrane called the **visceral pleural membrane.** A second, **parietal pleural membrane** lines the inner wall of the thoracic cavity. The space between these two membranes, the **pleural cavity,** is normally very small and filled with fluid. This fluid links the two membranes in the same way a thin film of water can hold two plates of glass together, effectively coupling the lungs to the thoracic cavity. The pleural membranes package each lung separately—if one collapses due to a perforation of the membranes, the other lung can still function.

Mechanics of Breathing

As in all other terrestrial vertebrates except amphibians, air is drawn into the lungs by the creation of a negative, or subatmospheric, pressure. In accordance with *Boyle's Law,* when the volume of a given quantity of gas increases its pressure decreases. This occurs because the volume of the thorax is increased during inspiration (inhalation), and the lungs likewise expand because of the adherence of the visceral and parietal pleural membranes. When the pressure within the lungs is lower than the atmospheric pressure, air enters the lungs. The thoracic volume is increased through contraction of two sets of muscles: the *external intercostals* and the *diaphragm.* During inspiration, contraction of the external intercostal muscles between the ribs raises the ribs and expands the rib cage. Contraction of the diaphragm, a convex sheet of striated muscle separating the thoracic cavity from the abdominal cavity, causes the diaphragm to lower and assume a more flattened shape. This expands the volume of the thorax and lungs while it increases the pressure on the abdomen (causing the belly to protrude). You can force a deeper inspiration by contracting other muscles that insert on the sternum or rib cage and expand the thoracic cavity and lungs to a greater extent.

The thorax and lungs have a degree of *elasticity*—they tend to resist distension and they recoil when the distending force subsides. Expansion of the thorax and lungs during inspiration places these structures under elastic tension. It is the relaxation of the external intercostal muscles and diaphragm that produces unforced expiration, because it relieves that elastic tension and allows the thorax and lungs to recoil. You can force a greater expiration by contracting your abdominal muscles and thereby pressing the abdominal organs up against the diaphragm.

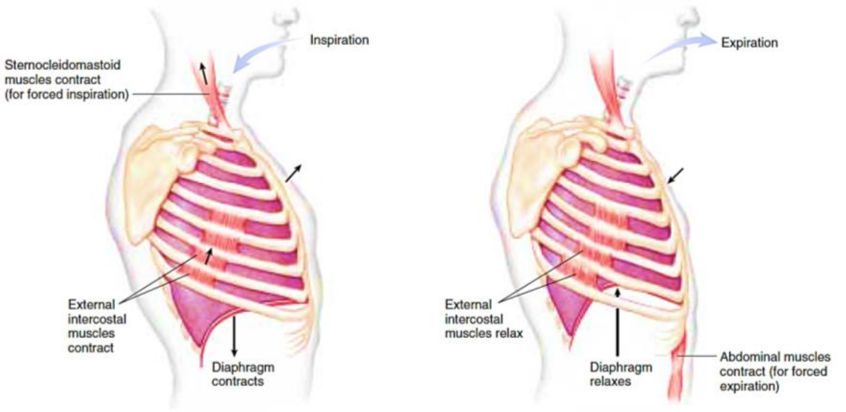


FIGURE 53.12
How a human breathes. (*a*) Inspiration. The diaphragm contracts and the walls of the chest cavity expand, increasing the volume of the chest cavity and lungs. As a result of the larger volume, air is drawn into the lungs. (*b*) Expiration. The diaphragm and chest walls return to their normal positions as a result of elastic recoil, reducing the volume of the chest cavity and forcing air out of the lungs through the trachea. Note that inspiration can be forced by contracting accessory respiratory muscles (such as the sternocleidomastoid), and expiration can be forced by contracting abdominal muscles.

Breathing Measurements

A variety of terms are used to describe the volume changes of the lung during breathing. At rest, each breath moves a **tidal volume** of about 500 milliliters of air into and out of the lungs. About 150 milliliters of the tidal volume is contained in the tubular passages (trachea, bronchi, and bronchioles), where no gas exchange occurs. The air in this *anatomical dead space* mixes with fresh air during inspiration. This is one of the reasons why respiration in mammals is not as efficient as in birds, where air flow through the lungs is one-way.

The maximum amount of air that can be expired after a forceful, maximum inspiration is called the **vital capacity.** This measurement, which averages 4.6 liters in young men and 3.1 liters in young women, can be clinically important, because an abnormally low vital capacity may indicate damage to the alveoli in various pulmonary disorders. For example, in **emphysema,** a potentially fatal condition usually caused by cigarette smoking, vital capacity is reduced as the alveoli are progressively destroyed. A person normally breathes at a rate and depth that properly oxygenate the blood and remove carbon dioxide, keeping the blood PO_2 and PCO_2 within a normal range. If breathing is insufficient to maintain normal blood gas measurements (a rise in the blood PCO_2 is the best indicator), the person is **hypoventilating.** If breathing is excessive for a particular metabolic rate, so that the blood PCO_2 is abnormally lowered, the person is said to be **hyperventilating.**

Perhaps surprisingly, the increased breathing that occurs during moderate exercise is not necessarily hyperventilation, because the faster breathing is matched to the faster metabolic rate, and blood gas measurements remain normal. The next section describes how breathing is regulated to keep pace with metabolism.

Hemoglobin and Oxygen Transport

When oxygen diffuses from the alveoli into the blood, its journey is just beginning. The circulatory system delivers oxygen to tissues for respiration and carries away carbon dioxide. The transport of oxygen and carbon dioxide by the blood is itself an interesting and physiologically important process. The amount of oxygen that can be dissolved in the blood plasma depends directly on the PO_2 of the air in the alveoli, as we explained earlier. When the lungs are functioning normally, the blood plasma leaving the lungs has almost as much dissolved oxygen as is theoretically possible, given the PO_2 of the air. Because of oxygen's low solubility in water, however, blood plasma can contain a maximum of only about 3 milliliters O_2 per liter. Yet whole blood carries almost 200 milliliters O_2 per liter! Most of the oxygen is bound to molecules of hemoglobin inside the red blood cells.

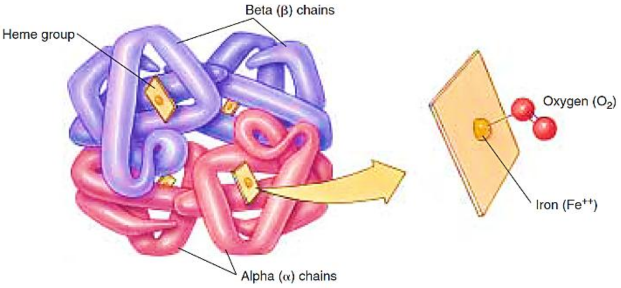


FIGURE 53.15
Hemoglobin consists of four polypeptide chains—two alpha (α) chains and two beta (β) chains. Each chain is associated with a heme group, and each heme group has a central iron atom, which can bind to a molecule of O_2.

Hemoglobin is a protein composed of four polypeptide chains and four organic compounds called *heme groups.* At the center of each heme group is an atom of iron, which can bind to a molecule of oxygen. Thus, each hemoglobin molecule can carry up to four molecules of oxygen. Hemoglobin loads up with oxygen in the lungs, forming **oxyhemoglobin.** This molecule has a bright red, tomato juice color. As blood passes through capillaries in the rest of the body, some of the oxyhemoglobin releases oxygen and becomes **deoxyhemoglobin.** Deoxyhemoglobin has a dark red color (the color of blood that is collected from the veins of blood donors), but it imparts a bluish tinge to tissues. Because of these color changes, vessels that carry oxygenated blood are always shown in artwork with a red color, and vessels that carry oxygen-depleted blood are indicated with a blue color. Hemoglobin is an ancient protein that is not only the oxygen-carrying molecule in all vertebrates, but is also used as an oxygen carrier by many invertebrates, including annelids, mollusks, echinoderms, flatworms, and even some protists. Many other invertebrates, however, employ different oxygen carriers, such as *hemocyanin.* In hemocyanin, the oxygen-binding atom is copper instead of iron. Hemocyanin is not found in blood cells, but is instead dissolved in the circulating fluid (hemolymph) of invertebrates.

Oxygen Transport

The PO_2 of the air within alveoli at sea level is approximately 105 millimeters of mercury (mm Hg), which is less than the PO_2 of the atmosphere because of the mixing of freshly inspired air with "old" air in the anatomical dead space of the respiratory system. The PO_2 of the blood leaving the alveoli is slightly less than this, about 100 mm Hg, because the blood plasma is not completely saturated with oxygen due to slight inefficiencies in lung function. At a blood PO_2 of 100 mm Hg, approximately 97% of the hemoglobin within red blood cells is in the form of oxyhemoglobin—indicated as a percent oxyhemoglobin saturation of 97%.

As the blood travels through the systemic blood capillaries, oxygen leaves the blood and diffuses into the tissues. Consequently, the blood that leaves the tissue in the veins has a PO_2 that is decreased (in a resting person) to about 40 mm Hg. At this lower PO_2, the percent saturation of hemoglobin is only 75%. A graphic representation of these changes is called an oxyhemoglobin dissociation curve. In a person at rest, therefore, 22% (97% minus 75%) of the oxyhemoglobin has released its oxygen to the tissues. Put another way, roughly one-fifth of the oxygen is unloaded in the tissues, leaving four-fifths of the oxygen in the blood as a reserve.

This large reserve of oxygen serves an important function. It enables the blood to supply the body's oxygen needs during exercise as well as at rest. During exercise, the muscles' accelerated metabolism uses more oxygen from the capillary blood and thus decreases the venous blood PO_2. For example, the PO_2 of the venous blood could drop to 20 mm Hg; in this case, the percent saturation of hemoglobin will be only 35%.

Because arterial blood still contains 97% oxyhemoglobin (ventilation increases proportionately with exercise), the amount of oxygen unloaded is now 62% (97% minus 35%), instead of the 22% at rest. In addition to this function, the oxygen reserve also ensures that the blood contains enough oxygen to maintain life for four to five minutes if breathing is interrupted or if the heart stops pumping.

Oxygen transport in the blood is affected by other conditions. The CO_2 produced by metabolizing tissues as a product of aerobic respiration combines with H_2O to ultimately form bicarbonate and H^+, lowering the pH of the blood. This reaction occurs primarily inside red blood cells, where the lowered pH reduces hemoglobin's affinity for oxygen and thus causes it to release oxygen more readily. The effect of pH on hemoglobin's affinity for oxygen is known as the Bohr effect and is shown graphically by a shift of the oxyhemoglobin dissociation curve to the right. Increasing temperature has a similar effect on hemoglobin's affinity for oxygen. Because skeletal muscles produce carbon dioxide more rapidly during exercise and active muscles produce heat, the blood unloads a higher percentage of the oxygen it carries during exercise.

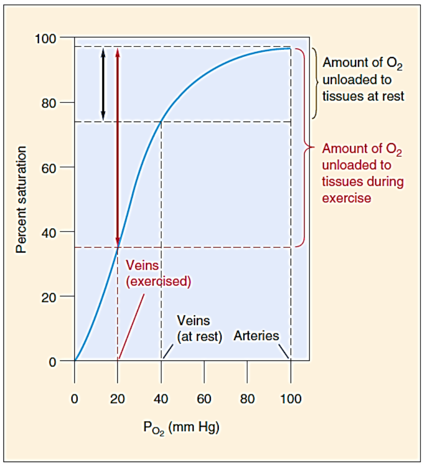


FIGURE 53.16
The oxyhemoglobin dissociation curve. Hemoglobin combines with O_2 in the lungs, and this oxygenated blood is carried by arteries to the body cells. After oxygen is removed from the blood to support cell respiration, the blood entering the veins contains less oxygen. The difference in O_2 content between arteries and veins during rest and exercise shows how much O_2 was unloaded to the tissues.

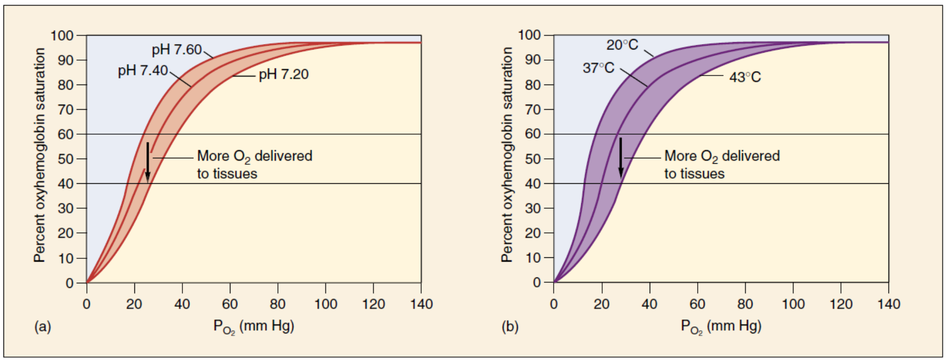


FIGURE 53.17
The effect of pH and temperature on the oxyhemoglobin dissociation curve. Lower blood pH (*a*) and higher blood temperatures (*b*) shift the oxyhemoglobin dissociation curve to the right, facilitating oxygen unloading. This can be seen as a lowering of the oxyhemoglobin percent saturation from 60 to 40% in the example shown, indicating that the difference of 20% more oxygen is unloaded to the tissues.

Carbon Dioxide Transport

The systemic capillaries deliver oxygen to the tissues and remove carbon dioxide. About 8% of the CO_2 in blood is simply dissolved in plasma; another 20% is bound to hemoglobin. (Because CO_2 binds to the protein portion of hemoglobin, however, and not to the heme irons, it does not compete with oxygen.) The remaining 72% of the CO_2 diffuses into the red blood cells, where the enzyme carbonic anhydrase catalyzes the combination of CO_2 with water to form carbonic acid (H_2CO_3). Carbonic acid dissociates into bicarbonate (HCO_3^-) and hydrogen (H^+) ions. The H^+ binds to deoxyhemoglobin, and the bicarbonate moves out of the erythrocyte into the plasma via a transporter that exchanges one chloride ion for a bicarbonate (this is called the "chloride shift"). This reaction removes large amounts of CO_2 from the plasma, facilitating the diffusion of additional CO_2 into the plasma from the surrounding tissues. The formation of

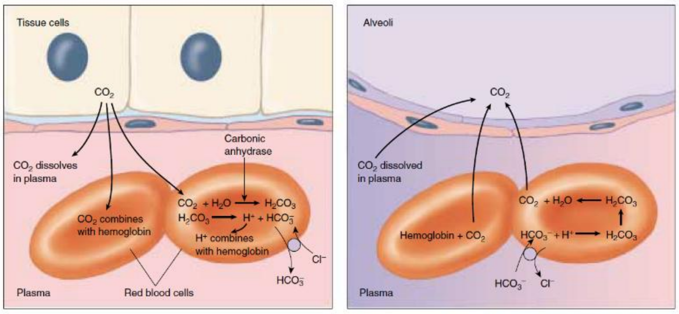
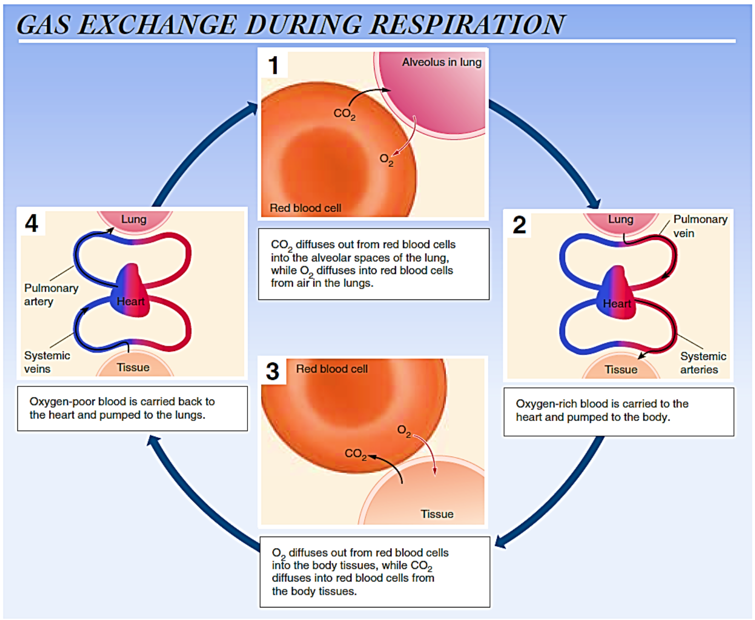


FIGURE 53.18
The transport of carbon dioxide by the blood. CO_2 is transported in three ways: dissolved in plasma, bound to the protein portion of hemoglobin, and as carbonic acid and bicarbonate, which form in the red blood cells. When the blood passes through the pulmonary capillaries, these reactions are reversed so that CO_2 gas is formed, which is exhaled.

carbonic acid is also important in maintaining the acid-base balance of the blood, because bicarbonate serves as the major buffer of the blood plasma. The blood carries CO_2 in these forms to the lungs. The lower PCO_2 of the air inside the alveoli causes the carbonic anhydase reaction to proceed in the reverse direction, converting H_2CO_3 into H_2O and CO_2. The CO_2 diffuses out of the red blood cells and into the alveoli, so that it can leave the body in the next exhalation.

Nitric Oxide Transport

Hemoglobin also has the ability to hold and release nitric oxide gas (NO). Although a noxious gas in the atmosphere, nitric oxide has an important physiological role in the body and acts on many kinds of cells to change their shapes and functions. For example, in blood vessels the presence of NO causes the blood vessels to expand because it relaxes the surrounding muscle cells. Thus, blood flow and blood pressure are regulated by the amount of NO released into the bloodstream. A current hypothesis proposes that hemoglobin carries NO in a special form called super nitric oxide. In this form, NO has acquired an extra electron and is able to bind to the amino acid cysteine in hemoglobin. In the lungs, hemoglobin that is dumping CO_2 and picking up O_2 also picks up NO as super nitric oxide. In blood vessels at the tissues, hemoglobin that is releasing its O_2 and picking up CO_2 can do one of two things with nitric oxide. To increase blood flow, hemoglobin can release the super nitric oxide as NO into the blood, making blood vessels expand because NO acts as a relaxing agent. Or, hemoglobin can trap any excess of NO on its iron atoms left vacant by the release of oxygen, causing blood vessels to constrict. When the red blood cells return to the lungs, hemoglobin dumps its CO_2 and the regular form of NO bound to the iron atoms. It is then ready to pick up O_2 and super nitric oxide and continue the cycle.



CO$_2$ diffuses out from red blood cells into the alveolar spaces of the lung, while O$_2$ diffuses into red blood cells from air in the lungs.

Oxygen-rich blood is carried to the heart and pumped to the body.

O$_2$ diffuses out from red blood cells into the body tissues, while CO$_2$ diffuses into red blood cells from the body tissues.

Oxygen-poor blood is carried back to the heart and pumped to the lungs.

FIGURE 53.19
Summary of respiratory gas exchange.