Transport of Oxygen in Blood
   - Effect of $P_{O_2}$ on Hemoglobin Saturation
   - Effects of Blood $P_{CO_2}$, $H^+$ Concentration, Temperature, and DPG Concentration on Hemoglobin Saturation

Transport of Carbon Dioxide in Blood

Transport of Hydrogen Ions between Tissues and Lungs

Control of Respiration
   - Neural Generation of Rhythmical Breathing
   - Control of Ventilation by $P_{O_2}$, $P_{CO_2}$, and $H^+$ Concentration
   - Control of Ventilation during Exercise
   - Other Ventilatory Responses

Hypoxia
   - Emphysema
   - Acclimatization to High Altitude

Nonrespiratory Functions of the Lungs

SUMMARY

KEY TERMS

REVIEW QUESTIONS

CLINICAL TERMS

THOUGHT QUESTIONS
Respiration has two quite different meanings: (1) utilization of oxygen in the metabolism of organic molecules by cells (often termed internal or cellular respiration), as described in Chapter 4, and (2) the exchanges of oxygen and carbon dioxide between an organism and the external environment. The second meaning is the subject of this chapter.

Human cells obtain most of their energy from chemical reactions involving oxygen. In addition, cells must be able to eliminate carbon dioxide, the major end product of oxidative metabolism. A unicellular organism can exchange oxygen and carbon dioxide directly with the external environment, but this is obviously impossible for most cells of a complex organism like a human being. Therefore, the evolution of large animals required the development of specialized structures to exchange oxygen and carbon dioxide for the entire animal with the external environment. In humans (and other mammals), the respiratory system includes the lungs, the series of tubes leading to the lungs, and the chest structures responsible for moving air into and out of the lungs during breathing.

### TABLE 15–1 Functions of the Respiratory System

<table>
<thead>
<tr>
<th>Number</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Provides oxygen.</td>
</tr>
<tr>
<td>2.</td>
<td>Eliminates carbon dioxide.</td>
</tr>
<tr>
<td>3.</td>
<td>Regulates the blood’s hydrogen-ion concentration (pH).</td>
</tr>
<tr>
<td>4.</td>
<td>Forms speech sounds (phonation).</td>
</tr>
<tr>
<td>5.</td>
<td>Defends against microbes.</td>
</tr>
<tr>
<td>6.</td>
<td>Influences arterial concentrations of chemical messengers by removing some from pulmonary capillary blood and producing and adding others to this blood.</td>
</tr>
<tr>
<td>7.</td>
<td>Traps and dissolves blood clots.</td>
</tr>
</tbody>
</table>

### Organization of the Respiratory System

There are two lungs, the right and left, each divided into several lobes. Pulmonary is the adjective referring to “lungs.” The lungs consist mainly of tiny air-containing sacs called alveoli (singular, alveolus), which number approximately 300 million in the adult. The alveoli are the sites of gas exchange with the blood. The airways are all the tubes through which air flows between the external environment and the alveoli.

Inspiration (inhalation) is the movement of air from the external environment through the airways into the alveoli during breathing. Expiration (exhalation) is movement in the opposite direction. An inspiration and an expiration constitute a respiratory cycle. During the entire respiratory cycle, the right ventricle of the heart pumps blood through the capillaries surrounding each alveolus. At rest, in a normal adult, approximately 4 L of fresh air enters and leaves the alveoli per minute, while 5 L of blood, the entire cardiac output, flows through the pulmonary capillaries. During heavy exercise, the air flow can increase twentyfold, and the blood flow five- to sixfold.

### The Airways and Blood Vessels

During inspiration air passes through either the nose (the most common site) or mouth into the pharynx (throat), a passage common to both air and food (Figure 15–1). The pharynx branches into two tubes, the esophagus through which food passes to the stomach, and the larynx, which is part of the airways. The larynx houses the vocal cords, two folds of elastic tissue stretched horizontally across its lumen. The flow of air past the vocal cords causes them to vibrate, producing sounds. The nose, mouth, pharynx, and larynx are termed the upper airways.

The larynx opens into a long tube, the trachea, which in turn branches into two bronchi (singular, bronchus), one of which enters each lung. Within the lungs, there are more than 20 generations of branchings, each resulting in narrower, shorter, and more numerous tubes, the names of which are summarized in Figure 15–2. The walls of the trachea and bronchi contain cartilage, which gives them their cylindrical shape and supports them. The first airway branches that no longer contain cartilage are termed bronchioles. Alveoli first begin to appear in respiratory bronchioles, attached to their walls. The number of alveoli increases...
in the alveolar ducts (Figure 15–2), and the airways then end in grapelike clusters consisting entirely of alveoli (Figure 15–3). The airways, like blood vessels, are surrounded by smooth muscle, the contraction or relaxation of which can alter airway radius.

The airways beyond the larynx can be divided into two zones: (1) The conducting zone extends from the top of the trachea to the beginning of the respiratory bronchioles; it contains no alveoli and there is no gas exchange with the blood (Table 15–2). (2) The respiratory zone, which extends from the respiratory bronchioles on down, contains alveoli and is the region where gases exchange with the blood.

The epithelial surfaces of the airways, to the end of the respiratory bronchioles, contain cilia that constantly beat toward the pharynx. They also contain glands and individual epithelial cells that secrete mucus. Particulate matter, such as dust contained in the inspired air, sticks to the mucus, which is continuously and slowly moved by the cilia to the pharynx and then swallowed. This mucus escalator is important in keeping the lungs clear of particulate matter and the many bacteria that enter the body on dust particles. Ciliary activity can be inhibited by many noxious agents. For example, smoking a single cigarette can immobilize the cilia for several hours.

The airway epithelium also secretes a watery fluid upon which the mucus can ride freely. The production of this fluid is impaired in the disease cystic fibrosis, the most common lethal genetic disease of Caucasians, and the mucous layer becomes thick and dehydrated, obstructing the airways. The impaired secretion is due to a defect in the chloride channels involved in the secretory process (Chapter 6).

A second protective mechanism against infection is provided by cells that are present in the airways and alveoli and are termed macrophages. These cells, described in detail in Chapter 20, engulf inhaled particles and bacteria, rendering them harmless. Macrophages, like cilia, are injured by cigarette smoke and air pollutants.

The pulmonary blood vessels generally accompany the airways and also undergo numerous branchings. The smallest of these vessels branch into networks of capillaries that richly supply the alveoli (Figure 15–3). As noted in Chapter 14, the pulmonary circulation has a very low resistance compared to the systemic circulation, and for this reason the pressures within all pulmonary blood vessels are low. Therefore, the diameters of the vessels are determined largely by gravitational forces and passive physical forces within

III. Coordinated Body Functions
15. Respiration

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the lungs. The net result is that there are marked regional differences in blood flow. The significance of this phenomenon will be described in the section on ventilation-perfusion inequality.

**Site of Gas Exchange: The Alveoli**

The alveoli are tiny hollow sacs whose open ends are continuous with the lumens of the airways (Figure 15–4a). Typically, the air in two adjacent alveoli is separated by a single alveolar wall. Most of the air-facing surface(s) of the wall are lined by a continuous layer, one cell thick, of flat epithelial cells termed **type I alveolar cells**. Interspersed between these cells are thicker specialized cells termed **type II alveolar cells** (Figure 15–4b) that produce a detergent-like substance, surfactant, to be discussed below.

The alveolar walls contain capillaries and a very small interstitial space, which consists of interstitial fluid and a loose meshwork of connective tissue (Figure 15–4b). In many places, the interstitial space is absent altogether, and the basement membranes of the alveolar-surface epithelium and the capillary-wall endothelium fuse. Thus the blood within an alveolar-wall capillary is separated from the air within the alveolus by an extremely thin barrier (0.2 μm, compared with

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**TABLE 15–2 Functions of the Conducting Zone of the Airways**

<table>
<thead>
<tr>
<th>Function</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Provides a low-resistance pathway for air flow; resistance is physiologically regulated by changes in contraction of airway smooth muscle and by physical forces acting upon the airways.</td>
</tr>
<tr>
<td>2.</td>
<td>Defends against microbes, toxic chemicals, and other foreign matter; cilia, mucus, and phagocytes perform this function.</td>
</tr>
<tr>
<td>3.</td>
<td>Warms and moistens the air.</td>
</tr>
<tr>
<td>4.</td>
<td>Phonates (vocal cords).</td>
</tr>
</tbody>
</table>

**FIGURE 15–3**

Relationships between blood vessels and airways. (a) The lung appears transparent so that the relationships can be seen. The airways beyond the bronchiole are too small to be seen. (b) An enlargement of a small section of Figure 15–3a to show the continuation of the airways and the clusters of alveoli at their ends. Virtually the entire lung, not just the surface, consists of such clusters.
Relation of the Lungs to the Thoracic (Chest) Wall

The lungs, like the heart, are situated in the thorax, the compartment of the body between the neck and abdomen. “Thorax” and “chest” are synonyms. The thorax is a closed compartment that is bounded at the neck by muscles and connective tissue and completely separated from the abdomen by a large, dome-shaped sheet of skeletal muscle, the diaphragm. The wall of the thorax is formed by the spinal column, the ribs, the breastbone (sternum), and several groups of muscles that run between the ribs (collectively termed the intercostal muscles). The thoracic wall also contains large amounts of elastic connective tissue.

Each lung is surrounded by a completely closed sac, the pleural sac, consisting of a thin sheet of cells called pleura. The two pleural sacs, one on each side of the midline, are completely separate from each other. The relationship between a lung and its pleural sac can be visualized by imagining what happens when you push a fist into a balloon (Figure 15–5): The arm represents the major bronchus leading to the lung, the fist is the lung, and the balloon is the pleural sac. The fist becomes coated by one surface of the balloon. In addition, the balloon is pushed back upon itself so that its opposite surfaces lie close together. Unlike the hand and balloon, however, the pleural surface coating the lung (the visceral pleura) is firmly attached to

**FIGURE 15–4**
(a) Cross section through an area of the respiratory zone. There are 18 alveoli in this figure, only four of which are labelled. Two frequently share a common wall.
(b) Schematic enlargement of a portion of an alveolar wall.
Adapted from Gong and Drage.

the 7-μm diameter of an average red blood cell). The total surface area of alveoli in contact with capillaries is roughly the size of a tennis court. This extensive area and the thinness of the barrier permit the rapid exchange of large quantities of oxygen and carbon dioxide by diffusion.

In some of the alveolar walls, there are pores that permit the flow of air between alveoli. This route can be very important when the airway leading to an alveolus is occluded by disease, since some air can still enter the alveolus by way of the pores between it and adjacent alveoli.

**FIGURE 15–5**
Relationship of lungs, pleura, and thoracic wall, shown as analogous to pushing a fist into a fluid-filled balloon. Note that there is no communication between the right and left intrapleural fluids. For purposes of illustration in this figure, the volume of intrapleural fluid is greatly exaggerated. It normally consists of an extremely thin layer of fluid between the pleura membrane lining the inner surface of the thoracic wall (the parietal pleura) and that lining the outer surface of the lungs (the visceral pleura).
the lung by connective tissue. Similarly, the outer layer (the parietal pleura) is attached to and lines the interior thoracic wall and diaphragm. The two layers of pleura in each sac are so close to each other that normally they are always in virtual contact, but they are not attached to each other. Rather, they are separated by an extremely thin layer of intrapleural fluid, the total volume of which is only a few milliliters. The intrapleural fluid totally surrounds the lungs and lubricates the pleural surfaces so that they can slide over each other during breathing. More important, as we shall see in the next section, changes in the hydrostatic pressure of the intrapleural fluid—the intrapleural pressure \((P_{ip})\) (also termed intrathoracic pressure)—cause the lungs and thoracic wall to move in and out together during normal breathing.

**Ventilation and Lung Mechanics**

An inventory of steps involved in respiration (Figure 15–6) is provided for orientation before beginning the detailed descriptions of each step, beginning with ventilation.

1. **Ventilation**: Exchange of air between atmosphere and alveoli by bulk flow
2. **Exchange of \(O_2\) and \(CO_2\)** between alveolar air and blood in lung capillaries by diffusion
3. **Transport of \(O_2\) and \(CO_2\)** through pulmonary and systemic circulation by bulk flow
4. **Exchange of \(O_2\) and \(CO_2\)** between blood in tissue capillaries and cells in tissues by diffusion
5. **Cellular utilization of \(O_2\) and production of \(CO_2\)**

**FIGURE 15–6**
The steps of respiration.

**Ventilation** is defined as the exchange of air between the atmosphere and alveoli. Like blood, air moves by bulk flow, from a region of high pressure to one of low pressure. We saw in Chapter 14 that bulk flow can be described by the equation

\[
F = \Delta P/R
\]

That is, flow \((F)\) is proportional to the pressure difference \((\Delta P)\) between two points and inversely proportional to the resistance \((R)\). For air flow into or out of the lungs, the relevant pressures are the gas pressure in the alveoli—the alveolar pressure \((P_{alv})\)—and the gas pressure at the nose and mouth, normally atmospheric pressure \((P_{atm})\), the pressure of the air surrounding the body:

\[
F = (P_{atm} - P_{alv})/R
\]

A very important point must be made at this point: All pressures in the respiratory system, as in the cardiovascular system, are given relative to atmospheric pressure, which is 760 mmHg at sea level. For example, the alveolar pressure between breaths is said to be 0 mmHg, which means that it is the same as atmospheric pressure.

During ventilation, air moves into and out of the lungs because the alveolar pressure is alternately made less than and greater than atmospheric pressure (Figure 15–7). These alveolar pressure changes are caused, as we shall see, by changes in the dimensions of the lungs.

**FIGURE 15–7**
Relationships required for ventilation. When the alveolar pressure \((P_{alv})\) is less than atmospheric pressure \((P_{atm})\), air enters the lungs. Flow \((F)\) is directly proportional to the pressure difference and inversely proportional to airway resistance \((R)\). Black lines show lung's position at beginning of inspiration or expiration, and blue lines at end.
To understand how a change in lung dimensions causes a change in alveolar pressure, you need to learn one more basic concept—Boyle's law (Figure 15–8). At constant temperature, the relationship between the pressure exerted by a fixed number of gas molecules and the volume of their container is as follows: An increase in the volume of the container decreases the pressure of the gas, whereas a decrease in the container volume increases the pressure.

It is essential to recognize the correct causal sequences in ventilation: During inspiration and expiration the volume of the “container”—the lungs—is made to change, and these changes then cause, by Boyle’s law, the alveolar pressure changes that drive air flow into or out of the lungs. Our descriptions of ventilation must focus, therefore, on how the changes in lung dimensions are brought about.

There are no muscles attached to the lung surface to pull the lungs open or push them shut. Rather, the lungs are passive elastic structures—like balloons—and their volume, therefore, depends upon: (1) the difference in pressure—termed the transpulmonary pressure—between the inside and the outside of the lungs; and (2) how stretchable the lungs are. The rest of this section and the next three sections focus only on transpulmonary pressure; stretchability will be discussed later in the section on lung compliance.

The pressure inside the lungs is the air pressure inside the alveoli ($P_{alv}$), and the pressure outside the lungs is the pressure of the intrapleural fluid ($P_{ip}$). Thus,

Transpulmonary pressure = $P_{alv} - P_{ip}$ (15-3)

Compare this equation to Equation 15-2 (the equation that describes air flow into or out of the lungs), as it will be essential to distinguish these equations from each other (Figure 15–9).

To summarize, the muscles used in respiration are not attached to the lung surface. Rather these muscles are part of the chest wall. When they contract or relax, they directly change the dimensions of the chest, which in turn causes the transpulmonary pressure ($P_{alv} - P_{ip}$) to change. The change in transpulmonary pressure then causes a change in lung size, which causes changes in alveolar pressure and, thereby, in the difference in pressure between the atmosphere and the alveoli ($P_{atm} - P_{alv}$). It is this difference in pressure that causes air flow into or out of the lungs.

Let us now apply these concepts to the three phases of the respiratory cycle: the period between breaths, inspiration, and expiration.

**The Stable Balance between Breaths**

Figure 15–10 illustrates the situation that normally exists at the end of an unforced expiration—that is, between breaths when the respiratory muscles are relaxed and no air is flowing. The alveolar pressure ($P_{alv}$) is 0 mmHg; that is, it is the same as atmospheric pressure. The intrapleural pressure ($P_{ip}$) is approximately 4 mmHg less than atmospheric pressure—that is, −4 mmHg, using the standard convention of
The transpulmonary pressure is the force acting to expand the lungs; it is opposed by the elastic recoil of the partially expanded lungs. Elastic recoil is defined as the tendency of an elastic structure to oppose stretching or distortion. In other words, inherent elastic recoil tending to collapse the lungs is exactly balanced by the transpulmonary pressure tending to expand them, and the volume of the lungs is stable at this point. As we shall see, a considerable volume of air is present in the lungs between breaths.

At the same time, there is also a pressure difference of 4 mmHg pushing inward on the chest wall—that is, tending to compress the chest—for the following reason. The pressure difference across the chest wall is the difference between atmospheric pressure and intrapleural pressure \( (P_{\text{atm}} - P_{\text{ip}}) \). \( P_{\text{atm}} \) is 0 mmHg, and \( P_{\text{ip}} \) is −4 mmHg; accordingly, \( P_{\text{atm}} - P_{\text{ip}} \) is \( [0 \text{ mmHg} - (-4 \text{ mmHg})] = 4 \text{ mmHg} \) directed inward. This pressure difference across the chest wall just balances the tendency of the partially compressed elastic chest wall to move outward, and so the chest wall, like the lungs, is stable in the absence of any respiratory muscular contraction.

Clearly, the subatmospheric intrapleural pressure is the essential factor keeping the lungs partially expanded and the chest wall partially compressed between breaths. The important question now is: What has caused the intrapleural pressure to be subatmospheric? As the lungs (tending to move inward from their stretched position because of their elastic recoil) and the thoracic wall (tending to move outward from its compressed position because of its elastic recoil) “try” to move ever so slightly away from each other, there occurs an infinitesimal enlargement of the fluid-filled intrapleural space between them. But fluid cannot expand the way air can, and so even this tiny enlargement of the intrapleural space—so small that the pleural surfaces still remain in contact with each other—drops the intrapleural pressure below atmospheric pressure. In this way, the elastic recoil of both the lungs and chest wall creates the subatmospheric intrapleural pressure that keeps them from moving apart more than a very tiny amount.

The importance of the transpulmonary pressure in achieving this stable balance can be seen when, during surgery or trauma, the chest wall is pierced without damaging the lung. Atmospheric air rushes through the wound into the intrapleural space (a phenomenon called pneumothorax), and the intrapleural pressure goes from −4 mmHg to 0 mmHg. The transpulmonary pressure acting to hold the lung open is thus eliminated, and the lung collapses. At the same time, the chest wall moves outward since its elastic recoil is also no longer opposed.

**Inspiration**

Figures 15–11 and 15–12 summarize the events during normal inspiration at rest. Inspiration is initiated by the neurally induced contraction of the diaphragm and the “inspiratory” intercostal muscles located between the ribs. (The adjective “inspiratory” here is a functional term, not an anatomical one; it denotes the several groups of intercostal muscles that contract during inspiration.) The diaphragm is the most important inspiratory muscle during normal quiet breathing. When activation of the nerves to it causes it to contract, its dome moves downward into the abdomen, enlarging the thorax. Simultaneously, activation of the nerves to the inspiratory intercostal muscles causes them to contract, leading to an upward and outward movement of the ribs and a further increase in thoracic size.

The crucial point is that contraction of the inspiratory muscles, by actively increasing the size of the thorax, upsets the stability set up by purely elastic forces between breaths. As the thorax enlarges, the thoracic wall moves ever so slightly farther away from the lung surface, and the intrapleural fluid pressure therefore becomes even more subatmospheric than it was between breaths. This decrease in intrapleural pressure increases the transpulmonary pressure. Therefore, the
force acting to expand the lungs—the transpulmonary pressure—is now greater than the elastic recoil exerted by the lungs at this moment, and so the lungs expand further. Note in Figure 15–12 that, by the end of inspiration, equilibrium across the lungs is once again established since the more inflated lungs exert a greater elastic recoil, which equals the increased transpulmonary pressure. In other words, lung volume is stable whenever transpulmonary pressure is balanced by the elastic recoil of the lungs (that is, after both inspiration and expiration).

Thus, when contraction of the inspiratory muscles actively increases the thoracic dimensions, the lungs are passively forced to enlarge virtually to the same degree because of the change in intrapleural pressure and hence transpulmonary pressure. The enlargement of the lungs causes an increase in the sizes of the alveoli throughout the lungs. Therefore, by Boyle’s law, the pressure within the alveoli drops to less than atmospheric (see Figure 15–12). This produces the difference in pressure ($P_{alv} < P_{atm}$) that causes a bulk-flow of air from the atmosphere through the airways into the alveoli. By the end of the inspiration, the pressure in the alveoli again equals atmospheric pressure because of this additional air, and air flow ceases.

**Expiration**

Figures 15–12 and 15–13 summarize the sequence of events during expiration. At the end of inspiration, the nerves to the diaphragm and inspiratory intercostal muscles decrease their firing, and so these muscles relax. The chest wall is no longer being actively pulled outward and upward by the muscle contractions and so it starts to recoil inward to its original smaller dimensions existing between breaths. This immediately makes the intrapleural pressure less subatmospheric and hence decreases the transpulmonary pressure. Therefore, the transpulmonary pressure acting to expand the lungs is now smaller than the elastic recoil exerted by the more expanded lungs, and the lungs passively recoil to their original dimensions.

As the lungs become smaller, air in the alveoli becomes temporarily compressed so that, by Boyle’s law, alveolar pressure exceeds atmospheric pressure (see Figure 15–12). Therefore, air flows from the alveoli through the airways out into the atmosphere. Thus, expiration at rest is completely passive, depending only upon the relaxation of the inspiratory muscles and recoil of the chest wall and stretched lungs.

Under certain conditions (during exercise, for example), expiration of larger volumes is achieved by contraction of a different set of intercostal muscles and the abdominal muscles, which actively decreases thoracic dimensions. The “expiratory” intercostal muscles (again a functional term, not an anatomical one) insert on the ribs in such a way that their contraction pulls the chest wall downward and inward. Contraction of the abdominal muscles increases intraabdominal pressure and forces the relaxed diaphragm up into the thorax.

**Lung Compliance**

To repeat, the degree of lung expansion at any instant is proportional to the transpulmonary pressure; that is, $P_{alv} - P_{ip}$. But just how much any given transpulmonary pressure expands the lungs depends upon the stretchability, or compliance, of the lungs. **Lung compliance ($C_L$)** is defined as the magnitude of the change in lung volume ($\Delta V_L$) produced by a given change in the transpulmonary pressure:

$$C_L = \frac{\Delta V_L}{\Delta (P_{alv} - P_{ip})}$$  \hspace{1cm} (15-4)

Thus, the greater the lung compliance, the easier it is to expand the lungs at any given transpulmonary pressure (Figure 15–14). A low lung compliance means...
that a greater-than-normal transpulmonary pressure must be developed across the lung to produce a given amount of lung expansion. In other words, when lung compliance is abnormally low, intrapleural pressure must be made more subatmospheric than usual during inspiration to achieve lung expansion. This requires more vigorous contractions of the diaphragm and inspiratory intercostal muscles. Thus, the less compliant the lung, the more energy is required for a given amount of expansion. Persons with low lung compliance due to disease therefore tend to breathe shallowly and must breathe at a higher frequency to inspire an adequate volume of air.

Determinants of Lung Compliance  There are two major determinants of lung compliance. One is the stretchability of the lung tissues, particularly their elastic connective tissues. Thus a thickening of the lung tissues decreases lung compliance. However, an equally important determinant of lung compliance is not the elasticity of the lung tissues, but the surface tension at the air-water interfaces within the alveoli.

The surface of the alveolar cells is moist, and so the alveoli can be pictured as air-filled sacs lined with water. At an air-water interface, the attractive forces between the water molecules, known as surface tension, make the water lining like a stretched balloon that constantly tries to shrink and resists further stretching. Thus, expansion of the lung requires energy not only to stretch the connective tissue of the lung but also to overcome the surface tension of the water layer lining the alveoli.

Indeed, the surface tension of pure water is so great that were the alveoli lined with pure water, lung expansion would require exhausting muscular effort and the lungs would tend to collapse. It is extremely important, therefore, that the type II alveolar cells secrete a detergent-like substance known as pulmonary surfactant, which markedly reduces the cohesive forces between water molecules on the alveolar surface. Therefore, surfactant lowers the surface tension, which increases lung compliance and makes it easier to expand the lungs (Table 15–3).
Surfactant is a complex of both lipids and proteins, but its major component is a phospholipid that forms a monomolecular layer between the air and water at the alveolar surface. The amount of surfactant tends to decrease when breaths are small and constant. A deep breath, which people normally intersperse frequently in their breathing pattern, stretches the type II cells, which stimulates the secretion of surfactant. This is why patients who have had thoracic or abdominal surgery and are breathing shallowly because of the pain must be urged to take occasional deep breaths.

A striking example of what occurs when surfactant is deficient is the disease known as respiratory-distress syndrome of the newborn. This is the second leading cause of death in premature infants, in whom the surfactant-synthesizing cells may be too immature to function adequately. Because of low lung compliance, the infant is able to inspire only by the most strenuous efforts, which may ultimately cause complete exhaustion, inability to breathe, lung collapse, and death. Therapy in such cases is assisted breathing with a mechanical ventilator and the administration of natural or synthetic surfactant via the infant’s trachea.
Airway Resistance

As previously stated, the volume of air that flows into or out of the alveoli per unit time is directly proportional to the pressure difference between the atmosphere and alveoli and inversely proportional to the resistance to flow offered by the airways (Equation 15-2). The factors that determine airway resistance are analogous to those determining vascular resistance in the circulatory system: tube length, tube radius, and interactions between moving molecules (gas molecules, in this case). As in the circulatory system, the most important factor by far is the tube radius: Airway resistance is inversely proportional to the fourth power of the airway radii.

Airway resistance to air flow is normally so small that very small pressure differences suffice to produce large volumes of air flow. As we have seen (see Figure 15–12), the average atmosphere-to-alveoli pressure difference during a normal breath at rest is less than 1 mmHg; yet, approximately 500 ml of air is moved by this tiny difference.

Airway radii and therefore resistance are affected by physical, neural, and chemical factors. One important physical factor is the transpulmonary pressure, which exerts a distending force on the airways, just as on the alveoli. This is a major factor keeping the smaller airways—those without cartilage to support them—from collapsing. Because, as we have seen, transpulmonary pressure increases during inspiration, airway radius becomes larger and airway resistance smaller as the lungs expand during inspiration. The opposite occurs during expiration.

A second physical factor holding the airways open is the elastic connective-tissue fibers that link the outside of the airways to the surrounding alveolar tissue. These fibers are pulled upon as the lungs expand during inspiration, and in turn they help pull the airways open even more than between breaths. This is termed lateral traction. Thus, putting this information and that of the previous paragraph together, both the transpulmonary pressure and lateral traction act in the same direction, reducing airway resistance during inspiration.

Such physical factors also explain why the airways become narrower and airway resistance increases during a forced expiration. Indeed, because of increased airway resistance, there is a limit as to how much one can increase the air flow rate during a forced expiration no matter how intense the effort.

In addition to these physical factors, a variety of neuroendocrine and paracrine factors can influence airway smooth muscle and thereby airway resistance. For example, the hormone epinephrine relaxes airway smooth muscle (via an effect on beta-adrenergic receptors), whereas the leukotrienes (members of the eicosanoid family) produced in the lungs during inflammation contract the muscle.

One might wonder why physiologists are concerned with all the many physical and chemical factors that can influence airway resistance when we earlier stated that airway resistance is normally so low that it is no impediment to air flow. The reason is that, under abnormal circumstances, changes in these factors may cause serious increases in airway resistance. Asthma and chronic obstructive pulmonary disease provide important examples.

Asthma Asthma is a disease characterized by intermittent attacks in which airway smooth muscle contracts strongly, markedly increasing airway resistance. The basic defect in asthma is chronic inflammation of the airways, the causes of which vary from person to person and include, among others, allergy and virus infections. The important point is that the underlying inflammation causes the airway smooth muscle to be hyperresponsive and to contract strongly when, depending upon the individual, the person exercises (especially in cold, dry air) or is exposed to cigarette smoke, environmental pollutants, viruses, allergens, normally released bronchoconstrictor chemicals, and a variety of other potential triggers.

The therapy for asthma is twofold: (1) to reduce the chronic inflammation and hence the airway hyperresponsiveness with so-called anti-inflammatory drugs, particularly glucocorticoids (Chapter 20) taken by inhalation; and (2) to overcome acute excessive airway smooth-muscle contraction with bronchodilator drugs—that is, drugs that relax the airways. The latter drugs work on the airways either by enhancing the actions of bronchodilator neuroendocrine or paracrine messengers or by blocking the actions of bronchoconstrictors. For example, one class of bronchodilator drug mimics the normal action of epinephrine on beta-adrenergic receptors.

Chronic Obstructive Pulmonary Disease The term chronic obstructive pulmonary disease refers to (1) emphysema, (2) chronic bronchitis, or (3) a combination of the two. These diseases, which cause severe difficulties not only in ventilation but in oxygenation of the blood, are among the major causes of disability and death in the United States. In contrast to asthma, increased smooth-muscle contraction is not the cause of the airway obstruction in these diseases.

Emphysema is discussed later in this chapter; suffice it to say here that the cause of obstruction in this disease is destruction and collapse of the smaller airways. Chronic bronchitis is characterized by excessive mucus production in the bronchi and chronic inflammatory changes in the small airways. The cause of obstruction is an accumulation of mucus in the airways...
and thickening of the inflamed airways. The same agents that cause emphysema—smoking, for example—also cause chronic bronchitis, which is why the two diseases frequently coexist.

The Heimlich Maneuver  The Heimlich maneuver is used to aid a person choking on a foreign body caught in and obstructing the upper airways. A sudden increase in abdominal pressure is produced as the rescuer’s fists, placed against the victim’s abdomen slightly above the navel and well below the tip of the sternum, are pressed into the abdomen with a quick upward thrust (Figure 15–15). The increased abdominal pressure forces the diaphragm upward into the thorax, reducing thoracic size and, by Boyle’s Law, increasing alveolar pressure. The forceful expiration produced by the increased alveolar pressure often expels the object caught in the respiratory tract.

**Lung Volumes and Capacities**

Normally the volume of air entering the lungs during a single inspiration is approximately equal to the volume leaving on the subsequent expiration and is called the tidal volume. The tidal volume during normal quiet breathing is termed the resting tidal volume and is approximately 500 ml. As illustrated in Figure 15–16, the maximal amount of air that can be increased above this value during deepest inspiration is termed the inspiratory reserve volume (and is about 3000 ml—that is, sixfold greater than resting tidal volume).

After expiration of a resting tidal volume, the lungs still contain a very large volume of air. As described earlier, this is the resting position of the lungs and chest wall (that is, the position that exists when there is no contraction of the respiratory muscles); it is termed the functional residual capacity (and averages about 2500 ml). Thus, the 500 ml of air inspired with each resting breath adds to and mixes with the much larger volume of air already in the lungs, and then 500 ml of the total is expired. Through maximal active contraction of the expiratory muscles, it is possible to expire much more of the air remaining after the resting tidal volume has been expired; this additional expired volume is termed the expiratory reserve volume (about 1500 ml). Even after a maximal active expiration, approximately 1000 ml of air still remains in the lungs and is termed the residual volume.

A useful clinical measurement is the vital capacity, the maximal volume of air that a person can expire after a maximal inspiration. Under these conditions, the person is expiring both the resting tidal volume and inspiratory reserve volume just inspired, plus the expiratory reserve volume (Figure 15–16). In other words, the vital capacity is the sum of these three volumes.

A variant on this method is the forced expiratory volume in 1 s, (FEV1), in which the person takes a maximal inspiration and then exhales maximally as fast as possible. The important value is the fraction of the total “forced” vital capacity expired in 1 s. Normal individuals can expire approximately 80 percent of the vital capacity in this time.

These pulmonary function tests are useful diagnostic tools. For example, people with obstructive lung diseases (increased airway resistance) typically have a FEV1 which is less than 80 percent of the vital capacity because it is difficult for them to expire air rapidly through the narrowed airways. In contrast to obstructive lung diseases, restrictive lung diseases are characterized by normal airway resistance but impaired respiratory movements because of abnormalities in the lung tissue, the pleura, the chest wall, or the neuromuscular machinery. Restrictive lung diseases are
characterized by a reduced vital capacity but a normal ratio of FEV₁ to vital capacity.

**Alveolar Ventilation**

The total ventilation per minute, termed the minute ventilation, is equal to the tidal volume multiplied by the respiratory rate:

\[
\text{Minute ventilation} = \frac{\text{Tidal volume} \times \text{Respiratory rate}}{\text{Respiratory rate (ml/breath) (breaths/min)}}
\]

For example, at rest, a normal person moves approximately 500 ml of air in and out of the lungs with each breath and takes 10 breaths each minute. The minute ventilation is therefore 500 ml/breath × 10 breaths/minute = 5000 ml of air per minute. However, because of dead space, not all this air is available for exchange with the blood.

**Dead Space** The conducting airways have a volume of about 150 ml. Exchanges of gases with the blood occur only in the alveoli and not in this 150 ml of the airways. Picture, then, what occurs during expiration of a tidal volume, which in this example we’ll set at 450 ml instead of the 500 ml mentioned earlier. The 450 ml of air is forced out of the alveoli and through the airways. Approximately 300 ml of this alveolar air is exhaled at the nose or mouth, but approximately 150 ml still remains in the airways at the end of expiration.

During the next inspiration (Figure 15–17), 450 ml of air flows into the alveoli, but the first 150 ml entering the alveoli is not atmospheric air but the 150 ml left behind in the airways from the last breath. Thus, only 300 ml of new atmospheric air enters the alveoli during the inspiration. The end result is that 150 ml of the 450 ml of atmospheric air entering the respiratory system during each inspiration never reaches the alveoli but is merely moved in and out of the airways. Because these airways do not permit gas exchange with the blood, the space within them is termed the anatomic dead space.

Thus the volume of fresh air entering the alveoli during each inspiration equals the tidal volume minus the volume of air in the anatomic dead space. For the previous example:

\[
\begin{align*}
\text{Tidal volume} &= 450 \text{ ml} \\
\text{Anatomic dead space} &= 150 \text{ ml} \\
\text{Fresh air entering alveoli in one inspiration} &= 450 \text{ ml} - 150 \text{ ml} = 300 \text{ ml}
\end{align*}
\]

The total volume of fresh air entering the alveoli per minute is called the alveolar ventilation:

\[
\text{Alveolar ventilation} = \frac{(\text{Tidal volume} - \text{Dead space}) \times \text{Respiratory rate}}{\text{Respiratory rate (ml/breath) (ml/breath) (breath/min)}}
\]

When evaluating the efficacy of ventilation, one should always focus on the alveolar ventilation, not...
the minute ventilation. This generalization is demonstrated readily by the data in Table 15–4. In this experiment, subject A breathes rapidly and shallowly, B normally, and C slowly and deeply. Each subject has exactly the same minute ventilation; that is, each is moving the same amount of air in and out of the lungs per minute. Yet, when we subtract the anatomic dead-space ventilation from the minute ventilation, we find marked differences in alveolar ventilation. Subject A has no alveolar ventilation and would become unconscious in several minutes, whereas C has a considerably greater alveolar ventilation than B, who is breathing normally.

Another important generalization to be drawn from this example is that increased depth of breathing is far more effective in elevating alveolar ventilation than is an equivalent increase in breathing rate. Conversely, a decrease in depth can lead to a critical reduction in alveolar ventilation. This is because a fixed volume of each tidal volume goes to the dead space. If the tidal volume decreases, the fraction of the tidal volume going to the dead space increases until, as in subject A, it may represent the entire tidal volume. On the other hand, any increase in tidal volume goes entirely toward increasing alveolar ventilation. These concepts have important physiological implications. Most situations that produce an increased ventilation, such as exercise, reflexly call forth a relatively greater increase in breathing depth than rate.

The anatomic dead space is not the only type of dead space. Some fresh inspired air is not used for gas exchange with the blood even though it reaches the alveoli because some alveoli, for various reasons, have little or no blood supply. This volume of air is known as alveolar dead space. It is quite small in normal persons but may be very large in several kinds of lung disease. As we shall see, it is minimized by local mechanisms that match air and blood flows. The sum of the anatomic and alveolar dead spaces is known as the physiologic dead space.

**TABLE 15–4 Effect of Breathing Patterns on Alveolar Ventilation**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Tidal Volume, ml/breath</th>
<th>×</th>
<th>Frequency, breaths/min</th>
<th>=</th>
<th>Minute Ventilation, ml/min</th>
<th>Anatomic Dead-Space Ventilation, ml/min</th>
<th>Alveolar Ventilation, ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>150</td>
<td></td>
<td>40</td>
<td></td>
<td>6000</td>
<td>150 × 40 = 6000</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>500</td>
<td></td>
<td>12</td>
<td></td>
<td>6000</td>
<td>150 × 12 = 1800</td>
<td>4200</td>
</tr>
<tr>
<td>C</td>
<td>1000</td>
<td></td>
<td>6</td>
<td></td>
<td>6000</td>
<td>150 × 6 = 900</td>
<td>5100</td>
</tr>
</tbody>
</table>
Exchange of Gases in Alveoli and Tissues

We have now completed our discussion of the lung mechanics that produce alveolar ventilation, but this is only the first step in the respiratory process. Oxygen must move across the alveolar membranes into the pulmonary capillaries, be transported by the blood to the tissues, leave the tissue capillaries and enter the extracellular fluid, and finally cross plasma membranes to gain entry into cells. Carbon dioxide must follow a similar path in reverse.

In the steady state, the volume of oxygen that leaves the tissue capillaries and is consumed by the body cells per unit time is exactly equal to the volume of oxygen added to the blood in the lungs during the same time period. Similarly, in the steady state, the rate at which carbon dioxide is produced by the body cells and enters the systemic blood is identical to the rate at which carbon dioxide leaves the blood in the lungs and is expired. Note that these statements apply to the steady state; transiently, oxygen utilization in the tissues can differ from oxygen uptake in the lungs and carbon dioxide production can differ from elimination in the lungs, but within a short time these imbalances automatically produce changes in diffusion gradients in the lungs and tissues that reestablish steady-state balances.

The amounts of oxygen consumed by cells and carbon dioxide produced, however, are not necessarily identical to each other. The balance depends primarily upon which nutrients are being used for energy. The ratio of CO₂ produced/O₂ consumed is known as the respiratory quotient (RQ). On a mixed diet, the RQ is approximately 0.8; that is, 8 molecules of CO₂ are produced for every 10 molecules of O₂ consumed. (The RQ is 1 for carbohydrate, 0.7 for fat, and 0.8 for protein.)

For purposes of illustration, Figure 15–18 presents typical exchange values during 1 min for a person at rest, assuming a cellular oxygen consumption of 250 ml/min, a carbon dioxide production of 200 ml/min, an alveolar ventilation rate of 4000 ml/min, and a cardiac output of 5000 ml/min.

Since only 21 percent of the atmospheric air is oxygen, the total oxygen entering the alveoli per min in our illustration is 21 percent of 4000 ml, or 840 ml/min. Of this inspired oxygen, 250 ml crosses the alveoli into the pulmonary capillaries, and the rest is subsequently exhaled. Note that blood entering the lungs already contains a large quantity of oxygen, to which the new 250 ml is added. The blood then flows from the lungs to the left heart and is pumped by the left ventricle through the tissue capillaries, where 250 ml of oxygen leaves the blood to be taken up and utilized by cells. Thus, the quantities of oxygen added to the blood in the lungs and removed in the tissues are identical.

The story reads in reverse for carbon dioxide: There is already a good deal of carbon dioxide in systemic arterial blood; to this is added an additional 200 ml, the amount produced by the cells, as blood flows through tissue capillaries. This 200 ml leaves the blood as blood flows through the lungs, and is expired.

Blood pumped by the heart carries oxygen and carbon dioxide between the lungs and tissues by bulk flow, but diffusion is responsible for the net movement of these molecules between the alveoli and blood, and between the blood and the cells of the body. Understanding the mechanisms involved in these diffusional exchanges depends upon some basic chemical and physical properties of gases, which we will now discuss.

Partial Pressures of Gases

Gas molecules undergo continuous random motion. These rapidly moving molecules exert a pressure, the magnitude of which is increased by anything that increases the rate of movement. The pressure a gas exerts is proportional to (1) the temperature (because heat increases the speed at which molecules move) and (2) the concentration of the gas—that is, the number of molecules per unit volume.

As stated by Dalton’s law, in a mixture of gases, the pressure exerted by each gas is independent of the pressure exerted by the others. This is because gas molecules are normally so far apart that they do not interfere with each other. Since each gas in a mixture behaves as though no other gases are present, the total pressure of the mixture is simply the sum of the individual pressures. These individual pressures, termed partial pressures, are denoted by a P in front of the symbol for the gas. For example, the partial pressure of oxygen is represented by P₂O₅. The partial pressure of a gas is directly proportional to its concentration. Net diffusion of a gas will occur from a region where its partial pressure is high to a region where it is low.

Atmospheric air consists primarily of nitrogen (approximately 79 percent) and oxygen (approximately 21 percent), with very small quantities of water vapor, carbon dioxide, and inert gases. The sum of the partial pressures of all these gases is termed atmospheric pressure, or barometric pressure. It varies in different parts of the world as a result of differences in altitude (it also varies with local weather conditions), but at sea level it is 760 mmHg. Since the partial pressure of any gas in a mixture is the fractional concentration of that gas times the total pressure of all the gases, the P₂O₅ of atmospheric air is 0.21 × 760 mmHg = 160 mmHg at sea level.
Diffusion of Gases in Liquids  When a liquid is exposed to air containing a particular gas, molecules of the gas will enter the liquid and dissolve in it. Henry’s law states that the amount of gas dissolved will be directly proportional to the partial pressure of the gas with which the liquid is in equilibrium. A corollary is that, at equilibrium, the partial pressures of the gas molecules in the liquid and gaseous phases must be identical. Suppose, for example, that a closed container contains both water and gaseous oxygen. Oxygen molecules from the gas phase constantly bombard the surface of the water, some entering the water and dissolving. Since the number of molecules striking the surface is directly proportional to the $P_{O_2}$ of the gas phase, the number of molecules entering the water and dissolving in it is also directly proportional to the $P_{O_2}$. As long as the $P_{O_2}$ in the gas phase is higher than the $P_{O_2}$ in the liquid, there will be a net diffusion of oxygen into the liquid. Diffusion equilibrium will be reached only when the $P_{O_2}$ in the liquid is equal to the $P_{O_2}$ in the gas phase, and there will be no further net diffusion between the two phases.

Conversely, if a liquid containing a dissolved gas at high partial pressure is exposed to a lower partial pressure of that same gas in a gas phase, there will be a net diffusion of gas molecules out of the liquid into the gas phase until the partial pressures in the two phases become equal.

The exchanges between gas and liquid phases described in the last two paragraphs are precisely the phenomena occurring in the lungs between alveolar air and pulmonary capillary blood. In addition, within a liquid, dissolved gas molecules also diffuse from a region of higher partial pressure to a region of lower partial pressure, an effect that underlies the exchange of gases between cells, extracellular fluid, and capillary blood throughout the body.

Why must the diffusion of gases into or within liquids be presented in terms of partial pressures rather than “concentrations,” the values used to deal with the diffusion of all other solutes? The reason is that the concentration of a gas in a liquid is proportional not only to the partial pressure of the gas but also to the solubility of the gas in the liquid; the more soluble the
gas, the greater will be its concentration at any given partial pressure. Thus, if a liquid is exposed to two different gases having the same partial pressures, at equilibrium the partial pressures of the two gases will be identical in the liquid but the concentrations of the gases in the liquid will differ, depending upon their solubilities in that liquid.

With these basic gas properties as the foundation, we can now discuss the diffusion of oxygen and carbon dioxide across alveolar and capillary walls, and plasma membranes. The partial pressures of these gases in air and in various sites of the body are given in Figure 15–19 for a resting person at sea level. We start our discussion with the alveolar $P_{O_2}$ and pulmonary vein $P_{O_2}$, not exactly the same, is described later in the text. Note also that the $P_{O_2}$ in the systemic arteries is shown as identical to that in the pulmonary veins; for reasons involving the anatomy of the blood flow to the lungs, the systemic arterial value is actually slightly less, but we have ignored this for the sake of clarity.

**FIGURE 15–19**
Partial pressures of carbon dioxide and oxygen in inspired air at sea level and various places in the body. The reason that the alveolar $P_{O_2}$ and pulmonary vein $P_{O_2}$ are not exactly the same is described later in the text. Note also that the $P_{O_2}$ in the systemic arteries is shown as identical to that in the pulmonary veins; for reasons involving the anatomy of the blood flow to the lungs, the systemic arterial value is actually slightly less, but we have ignored this for the sake of clarity.

Alveolar Gas Pressures
Normal alveolar gas pressures are $P_{O_2} = 105$ mmHg and $P_{CO_2} = 40$ mmHg. (We do not deal with nitrogen, even though it is the most abundant gas in the alveoli, because nitrogen is biologically inert under normal conditions and does not undergo any net exchange in the alveoli.) Compare these values with the gas pressures in the air being breathed: $P_{O_2} = 160$ mmHg and $P_{CO_2} = 0.3$ mmHg, a value so low that we will simply assume it to be zero. The alveolar $P_{O_2}$ is lower than atmospheric $P_{O_2}$ because some of the oxygen in the air entering the alveoli leaves them to enter the pulmonary capillaries. Alveolar $P_{CO_2}$ is higher than atmospheric $P_{CO_2}$ because carbon dioxide enters the alveoli from the pulmonary capillaries.

The factors that determine the precise value of alveolar $P_{O_2}$ are (1) the $P_{O_2}$ of atmospheric air, (2) the rate of alveolar ventilation, and (3) the rate of total-body oxygen consumption. Although there are equations for calculating the alveolar gas pressures from these variables, we will describe the interactions in a qualitative manner (Table 15–5). To start, we will assume that only one of the factors changes at a time.

First, a decrease in the $P_{O_2}$ of the inspired air (at high altitude, for example) will decrease alveolar $P_{O_2}$. A decrease in alveolar ventilation will do the same thing (Figure 15–20) since less fresh air is entering the
alveoli per unit time. Finally, an increase in the cells’ consumption of oxygen will also lower alveolar \( P_O_2 \) because a larger fraction of the oxygen in the entering fresh air will leave the alveoli to enter the blood and be used by the tissues (recall that in the steady state, the volume of oxygen entering the blood in the lungs per unit time is always equal to the volume utilized by the tissues). This discussion has been in terms of things that lower alveolar \( P_O_2 \); just reverse the direction of change of the three factors to see how to increase \( P_O_2 \).

The story for \( P_CO_2 \) is analogous, again assuming that only one factor changes at a time. There is normally essentially no carbon dioxide in inspired air and so we can ignore that factor. A decreased alveolar ventilation will increase the alveolar \( P_CO_2 \) (Figure 15–20) because there is less inspired fresh air to dilute the carbon dioxide entering the alveoli from the blood. An increased production of carbon dioxide will also increase the alveolar \( P_CO_2 \) because more carbon dioxide will be entering the alveoli from the blood per unit time (recall that in the steady state the volume of carbon dioxide entering the alveoli per unit time is always equal to the volume produced by the tissues). Just reverse the direction of changes in this paragraph to cause a decrease in alveolar \( P_CO_2 \).

For simplicity we allowed only one factor to change at a time, but if more than one factor changes, the effects will either add to or subtract from each other. For example, if oxygen consumption and alveolar ventilation both increase at the same time, their opposing effects on alveolar \( P_O_2 \) will tend to cancel each other out.

This last example emphasizes that, at any particular atmospheric \( P_O_2 \), it is the ratio of oxygen consumption to alveolar ventilation (that is, \( O_2 \) consumption/alveolar ventilation) that determines alveolar \( P_O_2 \)—the higher the ratio, the lower the alveolar \( P_O_2 \). Similarly, alveolar \( P_CO_2 \) is determined by a ratio, in this case the ratio of carbon dioxide production to alveolar ventilation (that is, \( CO_2 \) production/alveolar ventilation); the higher the ratio, the higher the alveolar \( P_CO_2 \).

Two terms that denote the adequacy of ventilation—that is, the relationship between metabolism and alveolar ventilation—can now be defined. Physiologists state these definitions in terms of carbon dioxide rather than oxygen. Hypoventilation exists when there is an increase in the ratio of carbon dioxide production to alveolar ventilation. In other words, a person is said to be hypoventilating if his alveolar ventilation cannot keep pace with his carbon dioxide production. The result is that alveolar \( P_CO_2 \) increases above the normal value of 40 mmHg. Hyperventilation exists when there is a decrease in the ratio of carbon dioxide production to alveolar ventilation—that is, when alveolar ventilation is actually too great for the amount of carbon dioxide being produced. The result is that alveolar \( P_CO_2 \) decreases below the normal value of 40 mmHg.
Note that “hyperventilation” is not synonymous with “increased ventilation.” Hyperventilation represents increased ventilation relative to metabolism. Thus, for example, the increased ventilation that occurs during moderate exercise is not hyperventilation since, as we shall see, in this situation the increase in production of carbon dioxide is exactly proportional to the increased ventilation.

**Alveolar-Blood Gas Exchange**

The blood that enters the pulmonary capillaries is, of course, systemic venous blood pumped to the lungs via the pulmonary arteries. Having come from the tissues, it has a relatively high $P_{CO_2}$ (46 mmHg in a normal person at rest) and a relatively low $P_{O_2}$ (40 mmHg) (Figure 15–19 and Table 15–6). The differences in the partial pressures of oxygen and carbon dioxide on the two sides of the alveolar-capillary membrane result in the net diffusion of oxygen from alveoli to blood and of carbon dioxide from blood to alveoli. As this diffusion occurs, the capillary blood $P_{O_2}$ rises and its $P_{CO_2}$ falls. The net diffusion of these gases ceases when the capillary partial pressures become equal to those in the alveoli.

In a normal person, the rates at which oxygen and carbon dioxide diffuse are so rapid and the blood flow through the capillaries so slow that complete equilibration is reached well before the end of the capillaries (Figure 15–21). Only during the most strenuous exercise, when blood flows through the lung capillaries very rapidly, is there insufficient time for complete equilibration.

Thus, the blood that leaves the pulmonary capillaries to return to the heart and be pumped into the systemic arteries has essentially the same $P_{O_2}$ and $P_{CO_2}$ as alveolar air. (They are not exactly the same, for reasons given later.) Accordingly, the factors described in the previous section—atmospheric $P_{O_2}$, cellular oxygen consumption and carbon dioxide production, and alveolar ventilation—determine the alveolar gas pressures, which then determine the systemic arterial gas pressures.

Given that diffusion between alveoli and pulmonary capillaries normally achieves complete equilibration, the more capillaries participating in this process, the more total oxygen and carbon dioxide can be exchanged. Many of the pulmonary capillaries at the apex (top) of each lung are normally closed at rest. During exercise, these capillaries open and receive blood, thereby enhancing gas exchange. The mechanism by which this occurs is a simple physical one; the pulmonary circulation at rest is at such a low blood pressure that the pressure in these apical capillaries is inadequate to keep them open, but the increased cardiac output of exercise raises pulmonary vascular pressures, which opens these capillaries.

The diffusion of gases between alveoli and capillaries may be impaired in a number of ways, resulting in inadequate oxygen diffusion into the blood, particularly during exercise when the time for equilibration is reduced. For one thing, the surface area of the alveoli in contact with pulmonary capillaries may be decreased. In lung infections or pulmonary edema, for example, some of the alveoli may become filled with fluid. Diffusion may also be impaired if the alveolar walls become severely thickened with connective tissue, as, for example, in the disease (of unknown cause) called diffuse interstitial fibrosis. Pure diffusion problems of these types are restricted to oxygen and do not affect elimination of carbon dioxide, which is much more diffusible than oxygen.
Matching of Ventilation and Blood Flow in Alveoli

However, the major disease-induced cause of inadequate oxygen movement between alveoli and pulmonary capillary blood is not diffusion problems but the mismatching of the air supply and blood supply in individual alveoli.

The lungs are composed of approximately 300 million alveoli, each capable of receiving carbon dioxide from, and supplying oxygen to, the pulmonary capillary blood. To be most efficient, the right proportion of alveolar air flow (ventilation) and capillary blood flow (perfusion) should be available to each alveolus. Any mismatching is termed ventilation-perfusion inequality.

The major effect of ventilation-perfusion inequality is to lower the $P_{O_2}$ of systemic arterial blood. Indeed, largely because of gravitational effects on ventilation and perfusion there is enough ventilation-perfusion inequality in normal people to lower the arterial $P_{O_2}$ about 5 mmHg. This is the major explanation of the fact, given earlier, that the $P_{O_2}$ of blood in the pulmonary veins and systemic arteries is normally 5 mmHg less than that of average alveolar air.

In disease states, regional changes in lung compliance, airway resistance, and vascular resistance can cause marked ventilation-perfusion inequalities. The extremes of this phenomenon are easy to visualize: (1) There may be ventilated alveoli with no blood supply at all, or (2) there may be blood flowing through areas of lung that have no ventilation (this is termed a shunt). But the inequality need not be all-or-none to be quite significant.

Carbon dioxide elimination is also impared by ventilation-perfusion inequality but, for complex reasons, not nearly to the same degree as oxygen uptake. Nevertheless, severe ventilation-perfusion inequalities in disease states can lead to some elevation of arterial $P_{CO_2}$.

There are several local homeostatic responses within the lungs to minimize the mismatching of ventilation and blood flow. One of the most important operates on the blood vessels to alter blood-flow distribution. If an alveolus is receiving too little air relative to its blood supply, the $P_{O_2}$ in the alveolus and its surrounding area will be low. This decreased $P_{O_2}$ causes vasoconstriction of the small pulmonary blood vessels. (Note that this local effect of low oxygen on pulmonary blood vessels is precisely the opposite of that exerted on systemic arterioles.) The net adaptive effect is to supply less blood to poorly ventilated areas and more blood to well-ventilated areas.

Gas Exchange in the Tissues

As the systemic arterial blood enters capillaries throughout the body, it is separated from the interstitial fluid by only the thin capillary wall, which is highly permeable to both oxygen and carbon dioxide. The interstitial fluid in turn is separated from intracellular fluid by the plasma membranes of the cells, which are also quite permeable to oxygen and carbon dioxide. Metabolic reactions occurring within cells are constantly consuming oxygen and producing carbon dioxide. Therefore, as shown in Figure 15–19, intracellular $P_{O_2}$ is lower and $P_{CO_2}$ higher than in blood. The lowest $P_{O_2}$ of all—less than 5 mmHg—is in the mitochondria, the site of oxygen utilization. As a result, there is a net diffusion of oxygen from blood into cells (and, within the cells, into the mitochondria), and a net diffusion of carbon dioxide from cells into blood. In this manner, as blood flows through systemic capillaries, its $P_{O_2}$ decreases and its $P_{CO_2}$ increases. This accounts for the systemic venous blood values shown in Figure 15–19 and Table 15–6.

The mechanisms that enhance diffusion of oxygen and carbon dioxide between cells and blood when a tissue increases its metabolic activity were discussed in Chapter 14.

In summary, the supply of new oxygen to the alveoli and the consumption of oxygen in the cells create $P_{O_2}$ gradients that produce net diffusion of oxygen from alveoli to blood in the lungs and from blood to cells in the rest of the body. Conversely, the production of carbon dioxide by cells and its elimination from the alveoli via expiration create $P_{CO_2}$ gradients that produce net diffusion of carbon dioxide from cells to blood in the rest of the body and from blood to alveoli in the lungs.

Transport of Oxygen in Blood

Table 15–7 summarizes the oxygen content of systemic arterial blood (we shall henceforth refer to systemic arterial blood simply as arterial blood). Each liter normally contains the number of oxygen molecules equivalent to 200 ml of pure gaseous oxygen at atmospheric pressure. The oxygen is present in two forms: (1) dissolved in the plasma and erythrocyte water and (2) reversibly combined with hemoglobin molecules in the erythrocytes.

As predicted by Henry’s law, the amount of oxygen dissolved in blood is directly proportional to the $P_{O_2}$ of the blood. Because oxygen is relatively insoluble in water, only 3 ml can be dissolved in 1 L of blood at the normal arterial $P_{O_2}$ of 100 mmHg. The other 197 ml of oxygen in a liter of arterial blood, more than 98 percent of the oxygen content in the liter, is transported in the erythrocytes reversibly combined with hemoglobin.

Each hemoglobin molecule is a protein made up of four subunits bound together. Each subunit consists of a molecular group known as heme and a polypeptide attached to the heme. [Hemoglobin is not the only
heme-containing protein in the body; others are the cytochromes and myoglobin (Chapters 4 and 11). The four polypeptides of a hemoglobin molecule are collectively called globin. Each of the four heme groups in a hemoglobin molecule (Figure 15–22) contains one atom of iron (Fe), to which oxygen binds. Since each iron atom can bind one molecule of oxygen, a single hemoglobin molecule can bind four molecules of oxygen. However, for simplicity, the equation for the reaction between oxygen and hemoglobin is usually written in terms of a single polypeptide-heme chain of a hemoglobin molecule:

\[ \text{O}_2 + \text{Hb} \rightleftharpoons \text{HbO}_2 \]  

(15-7)

Thus this chain can exist in one of two forms—deoxyhemoglobin (Hb) and oxyhemoglobin (HbO2). In a blood sample containing many hemoglobin molecules, the fraction of all the hemoglobin in the form of oxyhemoglobin is expressed as the percent hemoglobin saturation:

\[
\text{Percent saturation} = \frac{\text{O}_2 \text{ bound to Hb}}{\text{Maximal capacity of Hb to bind O}_2} \times 100
\]

(15-8)

For example, if the amount of oxygen bound to hemoglobin is 40 percent of the maximal capacity of hemoglobin to bind oxygen, the sample is said to be 40 percent saturated. The denominator in this equation is also termed the oxygen-carrying capacity of the blood.

What factors determine the percent hemoglobin saturation? By far the most important is the blood \( P_{O_2} \). Before turning to this subject, however, it must be stressed that the total amount of oxygen carried by hemoglobin in blood depends not only on the percent saturation of hemoglobin but also on how much hemoglobin there is in each liter of blood. For example, if a person’s blood contained only half as much hemoglobin per liter as normal, then at any given percent saturation the oxygen content of the blood would be only half as much.

**Effect of \( P_{O_2} \) on Hemoglobin Saturation**

From inspection of Equation 15-7 and the law of mass action, one can see that raising the blood \( P_{O_2} \) should increase the combination of oxygen with hemoglobin. The experimentally determined quantitative relationship between these variables is shown in Figure 15–23,
which is called an oxygen-hemoglobin dissociation curve. (The term “dissociate” means “to separate,” in this case oxygen from hemoglobin; it could just as well have been called an oxygen-hemoglobin association curve.) The curve is S-shaped because, as stated earlier, each hemoglobin molecule contains four subunits; each subunit can combine with one molecule of oxygen, and the reactions of the four subunits occur sequentially, with each combination facilitating the next one. (This combination of oxygen with hemoglobin is an example of cooperativity, as described in Chapter 4. The explanation in this case is as follows. The globin units of deoxyhemoglobin are tightly held by electrostatic bonds in a conformation with a relatively low affinity for oxygen. The binding of oxygen to a heme molecule breaks some of these bonds between the globin units, leading to a conformation change such that the remaining oxygen-binding sites are more exposed. Thus, the binding of one oxygen molecule to deoxyhemoglobin increases the affinity of the remaining sites on the same hemoglobin molecule, and so on.)

Note that the curve has a steep slope between 10 and 60 mmHg $P_{O_2}$ and a relatively flat portion (or plateau) between 70 and 100 mmHg $P_{O_2}$. Thus, the extent to which oxygen combines with hemoglobin increases very rapidly as the $P_{O_2}$ increases from 10 to 60 mmHg, so that at a $P_{O_2}$ of 60 mmHg, 90 percent of the total hemoglobin is combined with oxygen. From this point on, a further increase in $P_{O_2}$ produces only a small increase in oxygen binding.

The importance of this plateau at higher $P_{O_2}$ values is as follows. Many situations, including high altitude and pulmonary disease, are characterized by a moderate reduction in alveolar and therefore arterial $P_{O_2}$. Even if the $P_{O_2}$ fell from the normal value of 100 to 60 mmHg, the total quantity of oxygen carried by hemoglobin would decrease by only 10 percent since hemoglobin saturation is still close to 90 percent at a $P_{O_2}$ of 60 mmHg. The plateau therefore provides an excellent safety factor in the supply of oxygen to the tissues.

The plateau also explains another fact: In a normal person at sea level, raising the alveolar (and therefore the arterial) $P_{O_2}$ either by hyperventilating or by breathing 100 percent oxygen adds very little additional oxygen to the blood. A small additional amount dissolves, but because hemoglobin is already almost completely saturated with oxygen at the normal arterial $P_{O_2}$ of 100 mmHg, it simply cannot pick up any more oxygen when the $P_{O_2}$ is elevated beyond this point. But this applies only to normal people at sea level. If the person initially has a low arterial $P_{O_2}$ because of lung disease or high altitude, then there would be a great deal of deoxyhemoglobin initially present in the arterial blood. Therefore, raising the alveolar and thereby the arterial $P_{O_2}$ would result in significantly more oxygen transport.

We now retrace our steps and reconsider the movement of oxygen across the various membranes, this time including hemoglobin in our analysis. It is essential to recognize that the oxygen bound to hemoglobin does not contribute directly to the $P_{O_2}$ of the blood. Only dissolved oxygen does so. Therefore, oxygen diffusion is governed only by the dissolved portion, a fact that permitted us to ignore hemoglobin in discussing transmembrane partial pressure gradients. However, the presence of hemoglobin plays a critical role in determining the total amount of oxygen that will diffuse, as illustrated by a simple example (Figure 15–24).

Two solutions separated by a semipermeable membrane contain equal quantities of oxygen, the gas pressures are equal, and no net diffusion occurs. Addition of hemoglobin to compartment B destroys this equilibrium because much of the oxygen combines with hemoglobin. Despite the fact that the total quantity of oxygen in compartment B is still the same, the number of dissolved oxygen molecules has decreased. Therefore, the $P_{O_2}$ of compartment B is less than that of A, and so there is a net diffusion of oxygen from A to B. At the new equilibrium, the oxygen pressures are once again equal, but almost all the oxygen is in compartment B and is combined with hemoglobin.

Let us now apply this analysis to capillaries of the lungs and tissues (Figure 15–25). The plasma and erythrocytes entering the lungs have a $P_{O_2}$ of 40 mmHg. As we can see from Figure 15–23, hemoglobin

![FIGURE 15–24](image_url)
saturation at this $P_{O_2}$ is 75 percent. The alveolar $P_{O_2}$—105 mmHg—is higher than the blood $P_{O_2}$ and so oxygen diffuses from the alveoles into the plasma. This increases plasma $P_{O_2}$ and induces diffusion of oxygen into the erythrocytes, elevating erythrocyte $P_{O_2}$ and causing increased combination of oxygen and hemoglobin. The vast preponderance of the oxygen diffusing into the blood from the alveoli does not remain dissolved but combines with hemoglobin. Therefore, the blood $P_{O_2}$ normally remains less than the alveolar $P_{O_2}$ until hemoglobin is virtually 100 percent saturated. Thus the diffusion gradient favoring oxygen movement into the blood is maintained despite the very large transfer of oxygen.

In the tissue capillaries, the procedure is reversed. Because the mitochondria of the cells all over the body are utilizing oxygen, the cellular $P_{O_2}$ is less than the $P_{O_2}$ of the surrounding interstitial fluid. Therefore, oxygen is continuously diffusing into the cells. This causes the interstitial fluid $P_{O_2}$ to always be less than the $P_{O_2}$ of the blood flowing through the tissue capillaries, and so net diffusion of oxygen occurs from the plasma within the capillary into the interstitial fluid. Accordingly, plasma $P_{O_2}$ becomes lower than erythrocyte $P_{O_2}$ and oxygen diffuses out of the erythrocyte into the plasma. The lowering of erythrocyte $P_{O_2}$ causes the dissociation of oxygen from hemoglobin, thereby liberating oxygen, which then diffuses out of the erythrocyte. The net result is a transfer, purely by diffusion, of large quantities of oxygen from hemoglobin to plasma to interstitial fluid to the mitochondria of tissue cells.

To repeat, in most tissues under resting conditions, hemoglobin is still 75 percent saturated as the blood leaves the tissue capillaries. This fact underlies an important automatic mechanism by which cells can obtain more oxygen whenever they increase their activity. An exercising muscle consumes more oxygen, thereby lowering its tissue $P_{O_2}$. This increases the blood-to-tissue $P_{O_2}$ gradient and hence the diffusion of oxygen from blood to cell. In turn, the resulting reduction in erythrocyte $P_{O_2}$ causes additional dissociation of hemoglobin and oxygen. In this manner, an exercising muscle can extract almost all the oxygen from its blood supply, not just the usual 25 percent. Of course, an increased blood flow to the muscles (active hyperemia) also contributes greatly to the increased oxygen supply.

**Carbon Monoxide and Oxygen Carriage** Carbon monoxide is a colorless, odorless gas that is a product of the incomplete combustion of hydrocarbons, such as gasoline. It is one of the most common causes of sickness and death due to poisoning, both intentional and accidental. Its most striking pathophysiological characteristic is its extremely high affinity—250 times that of oxygen—for the oxygen-binding sites in hemoglobin. For this reason, it reduces the amount of oxygen that combines with hemoglobin in pulmonary capillaries by competing for these sites. It
exerts a second deleterious effect: It alters the hemoglobin molecule so as to shift the oxygen-hemoglobin dissociation curve to the left, thus decreasing the unloading of oxygen from hemoglobin in the tissues. As we shall see later, the situation is worsened by the fact that persons suffering from carbon monoxide poisoning do not show any reflex increase in their ventilation.

**Effects of Blood **$P_{CO_2}$**, H$^+$ Concentration, Temperature, and DPG Concentration on Hemoglobin Saturation**

At any given $P_{O_2}$, a variety of other factors influence the degree of hemoglobin saturation: blood $P_{CO_2}$, $H^+$ concentration, temperature, and the concentration of a substance—2,3-diphosphoglycerate (DPG) (also known as bisphosphoglycerate, BPG)—produced by the erythrocytes. As illustrated in Figure 15–26, an increase in any of these factors causes the dissociation curve to shift to the right, which means that, at any given $P_{O_2}$, hemoglobin has less affinity for oxygen. In contrast, a decrease in any of these factors causes the dissociation curve to shift to the left, which means that, at any given $P_{O_2}$, hemoglobin has a greater affinity for oxygen.

The effects of increased $P_{CO_2}$, $H^+$ concentration, and temperature are continuously exerted on the blood in tissue capillaries, because each of these factors is higher in tissue-capillary blood than in arterial blood: The $P_{CO_2}$ is increased because of the carbon dioxide entering the blood from the tissues. For reasons to be described later, the $H^+$ concentration is elevated because of the elevated $P_{CO_2}$ and the release of metabolically produced acids such as lactic acid. The temperature is increased because of the heat produced by tissue metabolism. Therefore, hemoglobin exposed to this elevated blood $P_{CO_2}$, $H^+$ concentration, and temperature as it passes through the tissue capillaries has its affinity for oxygen decreased, and therefore hemoglobin gives up even more oxygen than it would have if the decreased tissue-capillary $P_{O_2}$ had been the only operating factor.

The more active a tissue is, the greater its $P_{CO_2}$, $H^+$ concentration, and temperature. At any given $P_{O_2}$, this causes hemoglobin to release more oxygen during passage through the tissue’s capillaries and provides the more active cells with additional oxygen. Here is another local mechanism that increases oxygen delivery to tissues that have increased metabolic activity.

What is the mechanism by which these factors influence hemoglobin’s affinity for oxygen? Carbon dioxide and hydrogen ions do so by combining with the globin portion of hemoglobin and altering the conformation of the hemoglobin molecule. Thus, these effects are a form of allosteric modulation (Chapter 4).

An elevated temperature also decreases hemoglobin’s affinity for oxygen by altering its molecular configuration.

Erythrocytes contain large quantities of DPG, which is present in only trace amounts in other mammalian cells. DPG, which is produced by the erythrocytes
during glycolysis, binds reversibly with hemoglobin, allosterically causing it to have a lower affinity for oxygen (Figure 15–26). The net result is that whenever DPG levels are increased, there is enhanced unloading of oxygen from hemoglobin as blood flows through the tissues. Such an increase in DPG concentration is triggered by a variety of conditions associated with inadequate oxygen supply to the tissues and helps to maintain oxygen delivery. Examples include anemia and exposure to high altitude.

Transport of Carbon Dioxide in Blood

In a resting person, metabolism generates about 200 ml of carbon dioxide per minute. When arterial blood flows through tissue capillaries, this volume of carbon dioxide diffuses from the tissues into the blood (Figure 15–27). Carbon dioxide is much more soluble in water than is oxygen, and so more dissolved carbon dioxide than dissolved oxygen is carried in blood. Even so, only a relatively small amount of blood carbon dioxide is transported in this way; only 10 percent of the carbon dioxide entering the blood remains physically dissolved in the plasma and erythrocytes.

Another 30 percent of the carbon dioxide molecules entering the blood reacts reversibly with the amino groups of hemoglobin to form carbamino hemoglobin. For simplicity, this reaction with hemoglobin is written as:

\[ \text{CO}_2 + \text{Hb} \rightleftharpoons \text{HbCO}_2 \quad (15-9) \]

**FIGURE 15–27**

Summary of CO₂ movement. Expiration of CO₂ is by bulk-flow, whereas all movements of CO₂ across membranes are by diffusion. Arrows reflect relative proportions of the fates of the CO₂. About two-thirds of the CO₂ entering the blood in the tissues ultimately is converted to HCO₃⁻ in the erythrocytes because carbonic anhydrase is located there, but most of the HCO₃⁻ then moves out of the erythrocytes into the plasma in exchange for chloride ions (the “chloride shift”). See Figure 15–28 for the fate of the hydrogen ions generated in the erythrocytes.
This reaction is aided by the fact that deoxyhemoglobin, formed as blood flows through the tissue capillaries, has a greater affinity for carbon dioxide than does oxyhemoglobin.

The remaining 60 percent of the carbon dioxide molecules entering the blood in the tissues is converted to bicarbonate:

\[
\text{Carbonic anhydrase} \\
\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{HCO}_3^- + \text{H}^+ \quad (15-10)
\]

The first reaction in Equation 15-10 is rate-limiting and is very slow unless catalyzed by the enzyme carbonic anhydrase. This enzyme is present in the erythrocytes but not in the plasma; therefore, this reaction occurs mainly in the erythrocytes. In contrast, carbonic acid dissociates very rapidly into a bicarbonate ion and a hydrogen ion without any enzyme assistance. Once formed, most of the bicarbonate moves out of the erythrocytes into the plasma via a transporter that exchanges one bicarbonate for one chloride ion (this is called the “chloride shift”).

The reactions shown in Equation 15-10 also explain why, as mentioned earlier, the H⁺ concentration in tissue capillary blood and systemic venous blood is higher than that of the arterial blood and increases as metabolic activity increases. The fate of these hydrogen ions will be discussed in the next section.

Because carbon dioxide undergoes these various fates in blood, it is customary to add up the amounts of dissolved carbon dioxide, bicarbonate, and carbon dioxide in carbamino hemoglobin and call this sum the total blood carbon dioxide.

Just the opposite events occur as systemic venous blood flows through the lung capillaries (Figure 15–27). Because the blood \( P_{\text{CO}_2} \) is higher than alveolar \( P_{\text{CO}_2} \), a net diffusion of \( \text{CO}_2 \) from blood into alveoli occurs. This loss of \( \text{CO}_2 \) from the blood lowers the blood \( P_{\text{CO}_2} \) and drives reactions 15-10 and 15-9 to the left: \( \text{HCO}_3^- \) and \( \text{H}^+ \) combine to give \( \text{H}_2\text{CO}_3 \), which then dissociates to \( \text{CO}_2 \) and \( \text{H}_2\text{O} \). Similarly, \( \text{HbCO}_2 \) generates \( \text{Hb} \) and free \( \text{CO}_2 \). Normally, as fast as \( \text{CO}_2 \) is generated from \( \text{HCO}_3^- \) and \( \text{H}^+ \) and from \( \text{HbCO}_2 \), it diffuses into the alveoli. In this manner, all the \( \text{CO}_2 \) delivered into the blood in the tissues now is delivered into the alveoli; it is eliminated from the alveoli and from the body during expiration.

Transport of Hydrogen Ions between Tissues and Lungs

To repeat, as blood flows through the tissues, a fraction of oxyhemoglobin loses its oxygen to become deoxyhemoglobin, while simultaneously a large quantity of carbon dioxide enters the blood and undergoes the reactions that generate bicarbonate and hydrogen ions. What happens to these hydrogen ions?

Deoxyhemoglobin has a much greater affinity for \( \text{H}^+ \) than does oxyhemoglobin, and so it binds (buffers) most of the hydrogen ions (Figure 15–28). Indeed, deoxyhemoglobin is often abbreviated \( \text{HbH} \) rather than \( \text{Hb} \) to denote its binding of \( \text{H}^+ \). In effect, the reaction is \( \text{HbO}_2 + \text{H}^+ \rightleftharpoons \text{HbH} + \text{O}_2 \). In this manner, only a small number of the hydrogen ions generated in the blood remains free. This explains why the acidity of venous blood (pH = 7.36) is only slightly greater than that of arterial blood (pH = 7.40).

As the venous blood passes through the lungs, all these reactions are reversed. Deoxyhemoglobin becomes converted to oxyhemoglobin and, in the process, releases the hydrogen ions it had picked up in the tissues. The hydrogen ions react with bicarbonate to give carbonic acid, which dissociates to form carbon dioxide and water, and the carbon dioxide diffuses into the alveoli to be expired. Normally all the hydrogen ions that are generated in the tissue capillaries from the reaction of carbon dioxide and water recombine with bicarbonate to form carbon dioxide and water in the pulmonary capillaries. Therefore, none of these hydrogen ions appear in the arterial blood.

But what if the person is hypoventilating or has a lung disease that prevents normal elimination of carbon dioxide? Not only would arterial \( P_{\text{CO}_2} \) rise as a result but so would arterial \( \text{H}^+ \) concentration. Increased arterial \( \text{H}^+ \) concentration due to carbon dioxide retention is termed respiratory acidosis. Conversely, hyperventilation would lower the arterial values of both \( P_{\text{CO}_2} \) and \( \text{H}^+ \) concentration, producing respiratory alkalosis.

In the course of describing the transport of oxygen, carbon dioxide, and \( \text{H}^+ \) in blood, we have presented multiple factors that influence the binding of these substances by hemoglobin. They are all summarized in Table 15–8.

One more aspect of the remarkable hemoglobin molecule should at least be mentioned—its ability to bind and transport nitric oxide. As described in Chapters 8, 14, and 20 respectively, nitric oxide is an important neurotransmitter and is also released by endothelial cells and macrophages. A present hypothesis is that as blood passes through the lungs, hemoglobin picks up and binds not only oxygen but nitric oxide synthesized there, carries it to the peripheral tissues, and releases it along with oxygen. Simultaneously, via a different binding site hemoglobin picks up and catalyzes nitric oxide produced in the peripheral tissues. Theoretically this cycle could play an important role in determining the peripheral concentration of nitric oxide and, thereby, the overall effect of this vasodilator agent. For example, by supplying net nitric
oxide to the periphery, the process could cause additional vasodilation by systemic blood vessels; this would have effects on both local blood flow and systemic arterial blood pressure.

Control of Respiration

**Neural Generation of Rhythmic Breathing**

The diaphragm and intercostal muscles are skeletal muscles and therefore do not contract unless stimulated to do so by nerves. Thus, breathing depends entirely upon cyclical respiratory muscle excitation of the diaphragm and the intercostal muscles by their motor nerves. Destruction of these nerves (as in the viral disease poliomyelitis, for example) results in paralysis of the respiratory muscles and death, unless some form of artificial respiration can be instituted.

Inspiration is initiated by a burst of action potentials in the nerves to the inspiratory muscles. Then the action potentials cease, the inspiratory muscles relax, and expiration occurs as the elastic lungs recoil. In situations when expiration is facilitated by contraction of expiratory muscles, the nerves to these muscles, which were quiescent during inspiration, begin firing during expiration.

By what mechanism are nerve impulses to the respiratory muscles alternately increased and decreased? Control of this neural activity resides primarily in neurons in the medulla oblongata, the same area of brain that contains the major cardiovascular control centers. (For the rest of this chapter we shall refer to the medulla oblongata simply as the medulla.) In several nuclei of the medulla, neurons called medullary inspiratory neurons discharge in synchrony with inspiration and cease discharging during expiration. They provide, through either direct or interneuronal connections, the rhythmic input to the motor neurons innervating the inspiratory muscles. The alternating cycles of firing and quiescence in the medullary inspiratory neurons are generated by a cooperative interaction between synaptic input from other medullary neurons and intrinsic pacemaker potentials in the inspiratory neurons themselves.

The medullary inspiratory neurons receive a rich synaptic input from neurons in various areas of the pons, the part of the brainstem just above the medulla. This input modulates the output of the medullary inspiratory neurons and may help terminate inspiration by inhibiting them. It is likely that an area of the lower pons called the apneustic center is the major source of this output, whereas an area of the upper pons called the pneumotaxic center modulates the activity of the apneustic center.
Another cutoff signal for inspiration comes from pulmonary stretch receptors, which lie in the airway smooth-muscle layer and are activated by a large lung inflation. Action potentials in the afferent nerve fibers from the stretch receptors travel to the brain and inhibit the medullary inspiratory neurons. (This is known as the Hering-Breuer inflation reflex.) Thus, feedback from the lungs helps to terminate inspiration. However, this pulmonary stretch-receptor reflex plays a role in setting respiratory rhythm only under conditions of very large tidal volumes, as in rigorous exercise.

One last point about the medullary inspiratory neurons should be made: They are quite sensitive to depression by drugs such as barbiturates and morphine, and death from an overdose of these drugs is often due directly to a cessation of ventilation.

**Control of Ventilation by \( P_{O_2} \), \( P_{CO_2} \), and \( H^+ \) Concentration**

Respiratory rate and tidal volume are not fixed but can be increased or decreased over a wide range. For simplicity, we shall describe the control of ventilation without discussing whether rate or depth makes the greater contribution to the change.

There are many inputs to the medullary inspiratory neurons, but the most important for the automatic control of ventilation at rest are from peripheral chemoreceptors and central chemoreceptors.

The **peripheral chemoreceptors**, located high in the neck at the bifurcation of the common carotid arteries and in the thorax on the arch of the aorta (Figure 15–29), are called the carotid bodies and aortic bodies. In both locations they are quite close to, but distinct from, the arterial baroreceptors described in Chapter 14 and are in intimate contact with the arterial blood. The peripheral chemoreceptors are composed of specialized receptor cells that are stimulated mainly by a decrease in the arterial \( P_{O_2} \), and an increase in the arterial \( H^+ \) concentration (Table 15–9). These cells communicate synaptically with neuron terminals from which afferent nerve fibers pass to the brainstem. There they provide excitatory synaptic input to the medullary inspiratory neurons.

The **central chemoreceptors** are located in the medulla and, like the peripheral chemoreceptors, provide excitatory synaptic input to the medullary inspiratory neurons. They are stimulated by an increase in the \( H^+ \) concentration of the brain’s extracellular fluid. As we shall see, such changes result mainly from changes in blood \( P_{CO_2} \).

**Control by \( P_{O_2} \)** Figure 15–30 illustrates an experiment in which healthy subjects breathe low \( P_{O_2} \) gas mixtures for several minutes. (The experiment is per-formed in a way that keeps arterial \( P_{CO_2} \) constant so that the pure effects of changing only \( P_{O_2} \) can be studied.) Little increase in ventilation is observed until the oxygen content of the inspired air is reduced enough to lower arterial \( P_{O_2} \) to 60 mmHg. Beyond this point, any further reduction in arterial \( P_{O_2} \) causes a marked reflex increase in ventilation.

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**TABLE 15–9 Major Stimuli for the Central and Peripheral Chemoreceptors**

<table>
<thead>
<tr>
<th>Category</th>
<th>Stimulus Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral chemoreceptors</strong></td>
<td>decreased ( P_{O_2} ), increased ( H^+ ) concentration</td>
<td>lower arterial ( P_{O_2} )</td>
</tr>
<tr>
<td><strong>Central chemoreceptors</strong></td>
<td>increased ( P_{CO_2} ), associated changes in ( H^+ )</td>
<td>reduced arterial ( P_{CO_2} ), via associated changes in ( H^+ )</td>
</tr>
</tbody>
</table>
This reflex is mediated by the peripheral chemoreceptors (Figure 15–31). The low arterial $P_\text{O}_2$ increases the rate at which the receptors discharge, resulting in an increased number of action potentials traveling up the afferent nerve fibers and stimulating the medullary inspiratory neurons. The resulting increase in ventilation provides more oxygen to the alveoli and minimizes the drop in alveolar and arterial $P_\text{O}_2$ produced by the low $P_\text{O}_2$ gas mixture.

It may seem surprising that we are so insensitive to smaller reductions of arterial $P_\text{O}_2$, but look again at the oxygen-hemoglobin dissociation curve (see Figure 15–23). Total oxygen transport by the blood is not really reduced very much until the arterial $P_\text{O}_2$ falls below about 60 mmHg. Therefore, increased ventilation would not result in very much more oxygen being added to the blood until that point is reached.

To reiterate, the peripheral chemoreceptors respond to decreases in arterial $P_\text{O}_2$, as occurs in lung disease or exposure to high altitude. However, the peripheral chemoreceptors are not stimulated in situations in which there are modest reductions in the oxygen content of the blood but no change in arterial $P_\text{O}_2$. An example of this is anemia, where there is a decrease in the amount of hemoglobin present in the blood (Chapter 14) but no decrease in arterial $P_\text{O}_2$, because the concentration of dissolved oxygen in the blood is normal.

This same analysis holds true when oxygen content is reduced moderately by the presence of carbon monoxide, which as described earlier reduces the amount of oxygen combined with hemoglobin by competing for these sites. Since carbon monoxide does not affect the amount of oxygen that can dissolve in blood, the arterial $P_\text{O}_2$ is unaltered, and no increase in peripheral chemoreceptor output occurs.

**Control by $P_\text{CO}_2$.** Figure 15–32 illustrates an experiment in which subjects breathe air to which variable quantities of carbon dioxide have been added. The presence of carbon dioxide in the inspired air causes an elevation of alveolar $P_\text{CO}_2$ and thereby an elevation of arterial $P_\text{CO}_2$. Note that even a very small increase in arterial $P_\text{CO}_2$ causes a marked reflex increase in ventilation. Experiments like this have documented that small increases in arterial $P_\text{CO}_2$ are resisted by the reflex mechanisms controlling ventilation to a much greater degree than are equivalent decreases in arterial $P_\text{O}_2$.

Of course we don’t usually breathe bags of gas containing carbon dioxide. What is the physiological role of this reflex? If a defect in the respiratory system (emphysema, for example) causes a retention of carbon dioxide in the body, the increase in arterial $P_\text{CO}_2$
stimulates ventilation, which promotes the elimination of carbon dioxide. Conversely, if arterial $P_{CO_2}$ decreases below normal levels for whatever reason, this removes some of the stimulus for ventilation, thereby reducing ventilation and allowing metabolically produced carbon dioxide to accumulate and return the $P_{CO_2}$ to normal. In this manner, the arterial $P_{CO_2}$ is stabilized near the normal value of 40 mmHg.

The ability of changes in arterial $P_{CO_2}$ to control ventilation reflexly is largely due to associated changes in $H^+$ concentration (Equation 15-10). As summarized in Figure 15–33, the pathways that mediate these reflexes are initiated by both the peripheral and central chemoreceptors. The peripheral chemoreceptors are stimulated by the increased arterial $H^+$ concentration resulting from the increased $P_{CO_2}$. At the same time, because carbon dioxide diffuses rapidly across the membranes separating capillary blood and brain tissue, the increase in arterial $P_{CO_2}$ causes a rapid increase in brain extracellular fluid $P_{CO_2}$. This increased $P_{CO_2}$ increases brain extracellular-fluid $H^+$ concentration, which stimulates the central chemoreceptors. Inputs from both the peripheral and central chemoreceptors stimulate the medullary inspiratory neurons to increase ventilation. The end result is a return of arterial and brain extracellular fluid $P_{CO_2}$ and $H^+$ concentration toward normal. Of the two sets of receptors involved in this reflex response to elevated $P_{CO_2}$, the central chemoreceptors are the more important, accounting for about 70 percent of the increased ventilation.

It should also be noted that the effects of increased $P_{CO_2}$ and decreased $P_{O_2}$ not only exist as independent inputs to the medulla but manifest synergistic interactions as well. Acute ventilatory response to combined low $P_{O_2}$ and high $P_{CO_2}$ is considerably greater than the sum of the individual responses.

Throughout this section, we have described the stimulatory effects of carbon dioxide on ventilation via reflex input to the medulla, but very high levels of carbon dioxide actually inhibit ventilation and may be lethal. This is because such concentrations of carbon dioxide act directly on the medulla to inhibit the respiratory neurons by an anesthesia-like effect. Other symptoms caused by very high blood $P_{CO_2}$ include severe headaches, restlessness, and dulling or loss of consciousness.

**Control by Changes in Arterial $H^+$ Concentration That Are Not Due to Altered Carbon Dioxide**

We have seen that retention or excessive elimination of carbon dioxide causes respiratory acidosis and respiratory alkalosis, respectively. There are, however, many normal and pathological situations in which a change in arterial $H^+$ concentration is due to some cause other than a primary change in $P_{CO_2}$. These are termed **metabolic acidosis** when $H^+$ concentration is increased and **metabolic alkalosis** when it is decreased. In such cases, the peripheral chemoreceptors play the major role in altering ventilation.

For example, addition of lactic acid to the blood, as in strenuous exercise, causes hyperventilation almost entirely by stimulation of the peripheral chemoreceptors (Figures 15–34 and 15–35). The central chemoreceptors are only minimally stimulated in this case because brain $H^+$ concentration is increased to only a small extent, at least early on, by the hydrogen ions generated from the lactic acid. This is because hydrogen ions penetrate the blood-brain barrier very slowly. In contrast, as described earlier, carbon dioxide penetrates the blood-brain barrier easily and changes brain $H^+$ concentration.

The converse of the above situation is also true: When arterial $H^+$ concentration is lowered by any means other than by a reduction in $P_{CO_2}$ (for example, by loss of hydrogen ions from the stomach in vomiting), ventilation is reflexly depressed because of decreased peripheral chemoreceptor output.

The adaptive value such reflexes have in regulating arterial $H^+$ concentration is shown in Figure 15–35. The hyperventilation induced by a metabolic acidosis reduces arterial $P_{CO_2}$, which lowers arterial $H^+$ concentration back toward normal. Similarly, hyperventilation induced by a metabolic alkalosis results in an elevated arterial $P_{CO_2}$ and a restoration of $H^+$ concentration toward normal.
Breathing gas mixture containing CO₂

↑ Alveolar $P_{CO_2}$

↑ Arterial $P_{CO_2}$

↑ Brain extracellular fluid $P_{CO_2}$

↑ Arterial $[H^+]$

↑ Brain extracellular fluid $[H^+]$

Peripheral chemoreceptors

↑ Firing

(Reflex via medullary respiratory neurons)

Respiratory muscles

↑ Contractions

↑ Ventilation

Return of alveolar and arterial $P_{CO_2}$ toward normal

Return of brain extracellular fluid $P_{CO_2}$ toward normal

Return of arterial $[H^+]$ toward normal

Return of brain extracellular fluid $[H^+]$ toward normal

FIGURE 15–33

Pathways by which increased arterial $P_{CO_2}$ stimulates ventilation. Note that the peripheral chemoreceptors are stimulated by an increase in $H^+$ concentration, whereas they are also stimulated by a decrease in $P_{O_2}$ (Figure 15–31).
Respiration

CHAPTER FIFTEEN

Notice that when a change in arterial H⁺ concentration due to some acid unrelated to carbon dioxide influences ventilation via the peripheral chemoreceptors, \( P_{CO_2} \) is displaced from normal. This is a reflex that regulates arterial H⁺ concentration at the expense of changes in arterial \( P_{CO_2} \).

Figure 15–36 summarizes the control of ventilation by \( P_{O_2} \), \( P_{CO_2} \), and H⁺ concentration.

Control of Ventilation during Exercise

During exercise, the alveolar ventilation may increase as much as twentyfold. On the basis of our three variables—\( P_{O_2} \), \( P_{CO_2} \), and H⁺ concentration—it might seem easy to explain the mechanism that induces this increased ventilation. Unhappily, such is not the case, and the major stimuli to ventilation during exercise, at least that of moderate degree, remain unclear.

Increased \( P_{CO_2} \) as the Stimulus? It would seem logical that, as the exercising muscles produce more carbon dioxide, blood \( P_{CO_2} \) would increase. This is true, however, only for systemic venous blood but not for systemic arterial blood. Why doesn’t arterial \( P_{CO_2} \) increase during exercise? Recall two facts from the section on alveolar gas pressures: (1) alveolar \( P_{CO_2} \) sets arterial \( P_{CO_2} \), and (2) alveolar \( P_{CO_2} \) is determined by the ratio of carbon dioxide production to alveolar ventilation. During moderate exercise, the alveolar ventilation increases in exact proportion to the increased carbon dioxide production, and so alveolar and therefore arterial \( P_{CO_2} \) do not change. Indeed, for reasons described below, in very strenuous exercise the alveolar ventilation increases relatively more than carbon dioxide production. In other words, during severe exercise the person hyperventilates, and thus alveolar and systemic arterial \( P_{CO_2} \) actually decrease (Figure 15–37)!

Decreased \( P_{O_2} \) as the Stimulus? The story is similar for oxygen. Although systemic venous \( P_{O_2} \) decreases during exercise, alveolar \( P_{O_2} \), and hence systemic arterial \( P_{O_2} \) usually remain unchanged (Figure 15–37). This is because cellular oxygen consumption and alveolar ventilation increase in exact proportion to each other, at least during moderate exercise.
Note in Figure 15–37 that even though the hyperventilation of very strenuous exercise lowers arterial $P_{CO_2}$, it does not produce the increase in arterial $P_{O_2}$ you would expect to occur during hyperventilation. In fact, not shown in the figure, alveolar $P_{O_2}$ does increase during severe exercise, as expected, but for a variety of reasons, the increase in alveolar $P_{O_2}$ is not accompanied by an increase in arterial $P_{O_2}$. (Indeed, in highly conditioned athletes the arterial $P_{O_2}$ may decrease somewhat during strenuous exercise and may also contribute to stimulation of ventilation at that time.)

This is a good place to remind you of an important point made in Chapter 14: In normal individuals, ventilation is not the limiting factor in endurance exercise—cardiac output is. Ventilation can, as has just been seen, increase enough to maintain arterial $P_{O_2}$.

**Increased H⁺ Concentration as the Stimulus?**

Since the arterial $P_{CO_2}$ does not change during moderate exercise and decreases in severe exercise, there is no accumulation of excess H⁺ resulting from carbon dioxide accumulation. However, during strenuous
exercise, there is an increase in arterial H⁺ concentration (Figure 15–37), but for quite a different reason, namely, generation and release of lactic acid into the blood. This change in H⁺ concentration is responsible, in part, for stimulating the hyperventilation of severe exercise.

Other Factors A variety of other factors play some role in stimulating ventilation during exercise. These include (1) reflex input from mechanoreceptors in joints and muscles; (2) an increase in body temperature; (3) inputs to the respiratory neurons via branches from axons descending from the brain to motor neurons supplying the exercising muscles; (4) an increase in the plasma epinephrine concentration; (5) an increase in the plasma potassium concentration (because of movement out of the exercising muscles); and (6) a conditioned (learned) response mediated by neural input to the respiratory centers. The operation of this last factor can be seen in Figure 15–38: There is an abrupt increase—within seconds—in ventilation at the onset of exercise and an equally abrupt decrease at the end; these changes occur too rapidly to be explained by alteration of chemical constituents of the blood or altered body temperature.

Figure 15–39 summarizes various factors that influence ventilation during exercise. The possibility that oscillatory changes in arterial $P_{O_2}$, $P_{CO_2}$, or H⁺ concentration occur, despite unchanged average levels of these variables, and play a role has been proposed but remains unproven.

Other Ventilatory Responses

Protective Reflexes A group of responses protect the respiratory system from irritant materials. Most familiar are the cough and the sneeze reflexes, which originate in receptors located between airway epithelial cells. The receptors for the sneeze reflex are in the nose or pharynx, and those for cough are in the larynx, trachea, and bronchi. When the receptors initiating a cough are stimulated, the medullary respiratory neurons reflexly cause a deep inspiration and a violent expiration. In this manner, particles and secretions are moved from smaller to larger airways, and aspiration of materials into the lungs is also prevented.

The cough reflex is inhibited by alcohol, which may contribute to the susceptibility of alcoholics to choking and pneumonia.

Another example of a protective reflex is the immediate cessation of respiration that is frequently triggered when noxious agents are inhaled. Chronic smoking causes a loss of this reflex.

Voluntary Control of Breathing Although we have discussed in detail the involuntary nature of most respiratory reflexes, it is quite obvious that considerable voluntary control of respiratory movements exists. Voluntary control is accomplished by descending
pathways from the cerebral cortex to the motor neurons of the respiratory muscles. This voluntary control of respiration cannot be maintained when the involuntary stimuli, such as an elevated $P_{CO_2}$ or $H^+$ concentration, become intense. An example is the inability to hold one’s breath for very long.

The opposite of breath-holding—deliberate hyperventilation—lowers alveolar and arterial $P_{CO_2}$ and increases $P_{O_2}$. Unfortunately, swimmers sometimes voluntarily hyperventilate immediately before underwater swimming to be able to hold their breath longer. We say “unfortunately” because the low $P_{CO_2}$ may still permit breath-holding at a time when the exertion is lowering the arterial $P_{O_2}$ to levels that can cause unconsciousness and lead to drowning.

Besides the obvious forms of voluntary control, respiration must also be controlled during such complex actions as speaking and singing.

**Reflexes from J Receptors** In the lungs, either in the capillary walls or the interstitium, are a group of receptors called J receptors. They are normally dormant but are stimulated by an increase in lung interstitial pressure caused by the collection of fluid in the interstitium. Such an increase occurs during the vascular congestion caused by either occlusion of a pulmonary vessel (pulmonary embolus) or left ventricular heart failure (Chapter 14), as well as by strong exercise in healthy people. The main reflex effects are rapid breathing (tachypnea) and a dry cough. In addition, neural input from J receptors gives rise to sensations of pressure in the chest and dyspnea—the feeling that breathing is labored or difficult.

**Hypoxia**

Hypoxia is defined as a deficiency of oxygen at the tissue level. There are many potential causes of hypoxia, but they can be classed in four general categories: (1) hypoxic hypoxia (also termed hypoxemia), in which the arterial $P_{O_2}$ is reduced; (2) anemic hypoxia, in which the arterial $P_{O_2}$ is normal but the total oxygen content of the blood is reduced because of inadequate numbers of erythrocytes, deficient or abnormal hemoglobin, or competition for the hemoglobin molecule by carbon monoxide; (3) ischemic hypoxia (also called hypoperfusion hypoxia), in which blood flow to the tissues is too low; and (4) histotoxic hypoxia, in which the quantity of oxygen reaching the tissues is normal but the cell is unable to utilize the oxygen because a toxic agent—cyanide, for example—has interfered with the cell’s metabolic machinery.

The primary causes of hypoxic hypoxia in disease are listed in Table 15–10. Exposure to the reduced $P_{O_2}$ of high altitude also causes hypoxic hypoxia but is, of course, not a “disease.” The brief summaries in Table 15–10 provide a review of many of the key aspects of respiratory physiology and pathophysiology described in this chapter.
The pathophysiology of emphysema, a major cause of hypoxia, offers an excellent review of many basic principles of respiratory physiology. **Emphysema** is characterized by destruction of the alveolar walls, as well as atrophy and collapse of the lower airways—those from the terminal bronchioles on down. The lungs actually undergo self-destruction by proteolytic enzymes secreted by leukocytes in the lungs in response to a variety of factors. Cigarette smoking is by far the most important of these factors; it exerts its action by stimulating the release of the proteolytic enzymes and by destroying other enzymes that normally protect the lung against the proteolytic enzymes.

As a result of alveolar-wall loss, adjacent alveoli fuse to form fewer but larger alveoli, and there is a loss of the pulmonary capillaries that were originally in the walls. The merging of alveoli, often into huge balloon-like structures, reduces the total surface area available for diffusion, and this impairs gas exchange. Moreover, even more important, because the destructive changes are not uniform throughout the lungs, some areas may receive large amounts of air and little blood, while others have just the opposite pattern; the result is marked ventilation-perfusion inequality.

In addition to problems in gas exchange, emphysema is associated with a marked increase in airway resistance, which greatly increases the work of breathing and, if severe enough, may cause hypoventilation. This is why emphysema is classified, as noted earlier in this chapter, as a "chronic obstructive pulmonary disease." The airway obstruction in emphysema is due to collapse of the lower airways. To understand this, recall that two physical factors passively holding the airways open are the transpulmonary pressure and the lateral traction of connective-tissue fibers attached to the airway exteriors. Both of these factors are diminished in emphysema because of the destruction of the lung elastic tissues, and so the airways collapse.

In summary, patients with emphysema suffer from increased airway resistance, decreased total area available for diffusion, and ventilation-perfusion inequality. The result, particularly of the ventilation-perfusion inequality, is always some degree of hypoxia. What happens to arterial $P_{CO_2}$ in emphysema? Certainly the ventilation-perfusion inequality should cause it to increase, but the fact is that many patients with emphysema have a normal arterial $P_{CO_2}$. The reason is that the hypoxia and any tendency for arterial $P_{CO_2}$ to increase will stimulate ventilation, and this increased ventilation can bring arterial $P_{CO_2}$ back virtually to normal. In other words, any tendency for the arterial $P_{CO_2}$ to increase due to the ventilation-perfusion inequality may be compensated by the increased ventilation. Such increased ventilation, however, does not occur in many people with emphysema, probably because the increased airway resistance prevents it, and indeed may make it very difficult to maintain even a normal ventilation; in such people, the arterial $P_{CO_2}$ rises above normal.

**Acclimatization to High Altitude**

Atmospheric pressure progressively decreases as altitude increases. Thus, at the top of Mt. Everest (approximately 29,000 ft, or 9000 m), the atmospheric pressure is 253 mmHg (recall that it is 760 mmHg at sea

<table>
<thead>
<tr>
<th>TABLE 15–10 Causes of a Decreased Arterial $P_{O_2}$ (Hypoxic Hypoxia) in Disease</th>
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| 1. *Hypventilation* may be caused (a) by a defect anywhere along the respiratory control pathway, from the medulla through the respiratory muscles, (b) by severe thoracic cage abnormalities, and (c) by major obstruction of the upper airway. The hypoxemia of hypventilation is always accompanied by an increased arterial $P_{CO_2}$.
| 2. *Diffusion impairment* results from thickening of the alveolar membranes or a decrease in their surface area. In turn, it causes failure of equilibration of blood $P_{O_2}$ with alveolar $P_{O_2}$. Often it is apparent only during exercise. Arterial $P_{CO_2}$ is either normal, since carbon dioxide diffuses more readily than oxygen, or *reduced*, if the hypoxemia reflexly stimulates ventilation.
| 3. A *shunt* is (a) an anatomic abnormality of the cardiovascular system that causes mixed venous blood to bypass ventilated alveoli in passing from the right heart to the left heart, or (b) an intrapulmonary defect in which mixed venous blood perfuses unventilated alveoli (ventilation/perfusion = 0). Arterial $P_{CO_2}$ generally does not rise since the effect of the shunt on arterial $P_{CO_2}$ is counterbalanced by the increased ventilation reflexly stimulated by the hypoxemia.
| 4. *Ventilation-perfusion inequality* is by far the most common cause of hypoxemia. It occurs in chronic obstructive lung diseases and many other lung diseases. Arterial $P_{CO_2}$ may be normal or increased, depending upon how much ventilation is reflexly stimulated. |
level). The air is still 21 percent oxygen, which means that the $P_{O_2}$ is 53 mmHg ($0.21 \times 253$ mmHg). Obviously, the alveolar and arterial $P_{O_2}$ must decrease as one ascends unless pure oxygen is breathed. The highest villages permanently inhabited by people are in the Andes at 19,000 ft (5700 m). These villagers work quite normally, and the only major precaution they take is that the women come down to lower altitudes during late pregnancy.

The effects of oxygen deprivation vary from one individual to another, but most people who ascend rapidly to altitudes above 10,000 ft experience some degree of mountain sickness. This disorder consists of breathlessness, headache, nausea, vomiting, insomnia, fatigue, and impairment of mental processes. Much more serious is the appearance, in some individuals, of life-threatening pulmonary edema, the leakage of fluid from the pulmonary capillaries into the alveolar walls and eventually the airspaces, themselves. Brain edema can also occur.

Over the course of several days, the symptoms of mountain sickness disappear, although maximal physical capacity remains reduced. Acclimatization to high altitude is achieved by the compensatory mechanisms given in Table 15–11.

Finally, it should be noted that the responses to high altitude are essentially the same as the responses to hypoxia from any other cause. Thus, a person with severe hypoxia from lung disease may show many of the same changes—increased hematocrit, for example—as a high-altitude sojourner.

### Nonrespiratory Functions of the Lungs

The lungs have a variety of functions in addition to their roles in gas exchange and regulation of H$^+$ concentration. Most notable are the influences they have on the arterial concentrations of a large number of biologically active substances. Many substances (neurotransmitters and paracrine agents, for example) released locally into interstitial fluid may diffuse into capillaries and thus make their way into the systemic venous system. The lungs partially or completely remove some of these substances from the blood and thereby prevent them from reaching other locations in the body via the arteries. The cells that perform this function are the endothelial cells lining the pulmonary capillaries.

In contrast, the lungs may also produce and add new substances to the blood. Some of these substances play local regulatory roles within the lungs, but if produced in large enough quantity, they may diffuse into the pulmonary capillaries and be carried to the rest of the body. For example, inflammatory responses (Chapter 20) in the lung may lead, via excessive release of potent chemicals such as histamine, to profound alterations of systemic blood pressure or flow. In at least one case, the lungs contribute a hormone, angiotensin II, to the blood (Chapter 16).

Finally, the lungs also act as a “sieve” that traps and dissolves small blood clots generated in the systemic circulation, thereby preventing them from reaching the systemic arterial blood where they could occlude blood vessels in other organs.

### Organization of the Respiratory System

I. The respiratory system comprises the lungs, the airways leading to them, and the chest structures responsible for movement of air into and out of them.
   a. The conducting zone of the airways consists of the trachea, bronchi, and terminal bronchioles.
   b. The respiratory zone of the airways consists of the alveoli, which are the sites of gas exchange, and those airways to which alveoli are attached.
   c. The alveoli are lined by type I cells and some type II cells, which produce surfactant.
   d. The lungs and interior of the thorax are covered by pleura; between the two pleural layers is an extremely thin layer of intrapleural fluid.

II. The lungs are elastic structures whose volume depends upon the pressure difference across the lungs—the transpulmonary pressure—and how stretchable the lungs are.
Summary of Steps Involved in Respiration

I. The steps involved in respiration are summarized in Figure 15–6. In the steady state, the net volumes of oxygen and carbon dioxide exchanged in the lungs per unit time are equal to the net volumes exchanged in the tissues. Typical volumes per minute are 250 ml for oxygen consumption and 200 ml for carbon dioxide production.

Ventilation and Lung Mechanics

I. Bulk flow of air between the atmosphere and alveoli is proportional to the difference between the atmospheric and alveolar pressures and inversely proportional to the airway resistance: \( F = \frac{(P_{\text{atm}} - P_{\text{alv}})}{R} \).

II. Between breaths at the end of an unforced expiration \( P_{\text{atm}} = P_{\text{alv}} \), no air is flowing, and the dimensions of the lungs and thoracic cage are stable as the result of opposing elastic forces. The lungs are stretched and are attempting to recoil, whereas the chest wall is compressed and attempting to move outward. This creates a subatmospheric intrapleural pressure and hence a transpulmonary pressure that opposes the forces of elastic recoil.

III. During inspiration, the contractions of the diaphragm and inspiratory intercostal muscles increase the volume of the thoracic cage.
   a. This makes intrapleural pressure more subatmospheric, increases transpulmonary pressure, and causes the lungs to expand to a greater degree than between breaths.
   b. This expansion initially makes alveolar pressure subatmospheric, which creates the pressure difference between atmosphere and alveoli to drive air flow into the lungs.

IV. During expiration, the inspiratory muscles cease contracting, allowing the elastic recoil of the chest wall and lungs to return them to their original between-breath size.
   a. This initially compresses the alveolar air, raising alveolar pressure above atmospheric pressure and driving air out of the lungs.
   b. In forced expirations, the contraction of expiratory intercostal muscles and abdominal muscles actively decreases chest dimensions.

V. Lung compliance is determined by the elastic connective tissues of the lungs and the surface tension of the fluid lining the alveoli. The latter is greatly reduced, and compliance increased, by surfactant, produced by the type II cells of the alveoli.

VI. Airway resistance determines how much air flows into the lungs at any given pressure difference between atmosphere and alveoli. The major determinant of airway resistance is the radii of the airways.

VII. The vital capacity is the sum of resting tidal volume, inspiratory reserve volume, and expiratory reserve volume. The volume expired during the first second of a forced vital capacity (FVC) measurement is the FEV₁ and normally averages 80 percent of FVC.

Exchange of Gases in Alveoli and Tissues

I. Exchange of gases in lungs and tissues is by diffusion, as a result of differences in partial pressures. Gases diffuse from a region of higher partial pressure to one of lower partial pressure.

II. Normal alveolar gas pressure for oxygen is 105 mmHg and for carbon dioxide is 40 mmHg.
   a. At any given inspired \( P_{O_2} \), the ratio of oxygen consumption to alveolar ventilation determines alveolar \( P_{O_2} \)—the higher the ratio, the lower the alveolar \( P_{O_2} \).
   b. The higher the ratio of carbon dioxide production to alveolar ventilation, the higher the alveolar \( P_{CO_2} \).

III. The average value at rest for systemic venous \( P_{O_2} \) is 40 mmHg and for \( P_{CO_2} \) is 46 mmHg.

IV. As systemic venous blood flows through the pulmonary capillaries, there is net diffusion of oxygen from alveoli to blood and of carbon dioxide from blood to alveoli. By the end of each pulmonary capillary, the blood gas pressures have become equal to those in the alveoli.

V. Inadequate gas exchange between alveoli and pulmonary capillaries may occur when the alveolocapillary surface area is decreased, when the alveolar walls thicken, or when there are ventilation-perfusion inequalities.

VI. Significant ventilation-perfusion inequalities cause the systemic arterial \( P_{O_2} \) to be reduced. An important mechanism for opposing mismatching is that a low local \( P_{O_2} \) causes local vasoconstriction, thereby diverting blood away from poorly ventilated areas.

VII. In the tissues, net diffusion of oxygen occurs from blood to cells, and net diffusion of carbon dioxide from cells to blood.

Transport of Oxygen in the Blood

I. Each liter of systemic arterial blood normally contains 200 ml of oxygen, more than 98 percent bound to hemoglobin and the rest dissolved.

II. The major determinant of the degree to which hemoglobin is saturated with oxygen is blood \( P_{O_2} \).
   a. Hemoglobin is almost 100 percent saturated at the normal systemic arterial \( P_{O_2} \) of 100 mmHg. The fact that saturation is already more than 90 percent at a \( P_{O_2} \) of 60 mmHg permits relatively normal uptake of oxygen by the blood even when alveolar \( P_{O_2} \) is moderately reduced.
   b. Hemoglobin is 75 percent saturated at the normal systemic venous \( P_{O_2} \) of 40 mmHg. Thus, only 25 percent of the oxygen has dissociated from hemoglobin and entered the tissues.

III. The affinity of hemoglobin for oxygen is decreased by an increase in \( P_{CO_2} \), hydrogen-ion concentration, and temperature. All these conditions exist in the tissues and facilitate the dissociation of oxygen from hemoglobin.
IV. The affinity of hemoglobin for oxygen is also decreased by binding DPG, which is synthesized by the erythrocytes. DPG increases in situations associated with inadequate oxygen supply and helps maintain oxygen release in the tissues.

**Transport of Carbon Dioxide in Blood**

I. When carbon dioxide molecules diffuse from the tissues into the blood, 10 percent remains dissolved in plasma and erythrocytes, 30 percent combines in the erythrocytes with deoxyhemoglobin to form carbamino compounds, and 60 percent combines in the erythrocytes with water to form carbonic acid, which then dissociates to yield bicarbonate and hydrogen ions. Most of the bicarbonate then moves out of the erythrocytes into the plasma in exchange for chloride ions.

II. As venous blood flows through lung capillaries, blood $P_{CO_2}$ decreases because of diffusion of carbon dioxide out of the blood into the alveoli, and the above reactions are reversed.

**Transport of Hydrogen Ions between Tissues and Lungs**

I. Most of the hydrogen ions generated in the erythrocytes from carbonic acid during blood passage through tissue capillaries bind to deoxyhemoglobin because deoxyhemoglobin, formed as oxygen unloads from oxyhemoglobin, has a high affinity for hydrogen ions.

II. As the blood flows through the lung capillaries, hydrogen ions bound to deoxyhemoglobin are released and combine with bicarbonate to yield carbon dioxide and water.

**Control of Respiration**

I. Breathing depends upon cyclical inspiratory muscle excitation by the nerves to the diaphragm and intercostal muscles. This neural activity is triggered by the medullary inspiratory neurons.

II. The most important inputs to the medullary inspiratory neurons for the involuntary control of ventilation are from the peripheral chemoreceptors—the carotid and aortic bodies—and the central chemoreceptors.

III. Ventilation is reflexly stimulated, via the peripheral chemoreceptors, by a decrease in arterial $P_{O_2}$, but only when the decrease is large.

IV. Ventilation is reflexly stimulated, via both the peripheral and central chemoreceptors, when the arterial $P_{CO_2}$ goes up even a slight amount. The stimulus for this reflex is not the increased $P_{CO_2}$ itself, but the concomitant increased hydrogen-ion concentration in arterial blood and brain extracellular fluid.

V. Ventilation is also stimulated, mainly via the peripheral chemoreceptors, by an increase in arterial hydrogen-ion concentration resulting from causes other than an increase in $P_{CO_2}$. The result of this reflex is to restore hydrogen-ion concentration toward normal by lowering $P_{CO_2}$.

VI. Ventilation is reflexly inhibited by an increase in arterial $P_{O_2}$ and by a decrease in arterial $P_{CO_2}$ or hydrogen-ion concentration.

VII. During moderate exercise, ventilation increases in exact proportion to metabolism, but the signals causing this are not known. During very strenuous exercise, ventilation increases more than metabolism.

a. The proportional increases in ventilation and metabolism during moderate exercise cause the arterial $P_{O_2}$, $P_{CO_2}$, and hydrogen-ion concentration to remain unchanged.

b. Arterial hydrogen-ion concentration increases during very strenuous exercise because of increased lactic acid production. This accounts for some of the hyperventilation seen in that situation.

VIII. Ventilation is also controlled by reflexes originating in airway receptors and by conscious intent.

**Hypoxia**

I. The causes of hypoxic hypoxia are listed in Table 15–10.

II. During exposure to hypoxia, as at high altitude, oxygen supply to the tissues is maintained by the five responses listed in Table 15–11.

**Nonrespiratory Functions of the Lungs**

I. The lungs influence arterial blood concentrations of biologically active substances by removing some from systemic venous blood and adding others to systemic arterial blood.

II. The lungs also act as sieves that dissolve small clots formed in the systemic tissues.

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**KEY TERMS**

- respiration (two definitions)
- respiratory system
- pulmonary
- alveoli (alveolus)
- airway
- inspiration
- expiration
- respiratory cycle
- pharynx
- larynx
- vocal cords
- trachea
- bronchi (bronchus)
- bronchiole
- conducting zone
- respiratory zone
- type I alveolar cell
- type II alveolar cell
- thorax
- diaphragm
- intercostal muscle
- pleural sac
- pleura
- intrapleural fluid
- intrapleural pressure ($P_{Ip}$)
- ventilation
- alveolar pressure ($P_{alv}$)
- atmospheric pressure ($P_{atm}$)
- Boyle’s law
- transpulmonary pressure
- elastic recoil
- lung compliance ($C_{L}$)
- surface tension
- surfactant
- lateral tension
- tidal volume
- inspiratory reserve volume
- functional residual capacity
- expiratory reserve volume
- residual volume
- vital capacity
- minute ventilation
- anatomic dead space
- alveolar ventilation
- alveolar dead space
- physiologic dead space
- respiratory quotient (RQ)
- Dalton’s law
1. List the functions of the respiratory system.

2. At rest, how many liters of air and blood flow through the lungs per minute?

3. Describe four functions of the conducting portion of the airways.

4. Which respiration steps occur by diffusion and which by bulk flow?

5. What are normal values for intrapleural pressure, alveolar pressure, and transpulmonary pressure at the end of an unforced expiration?

6. Between breaths at the end of an unforced expiration, in what directions are the lungs and chest wall tending to move? What prevents them from doing so?

7. State typical values for oxygen consumption, carbon dioxide production, and cardiac output at rest. How much oxygen (in milliliters per liter) is present in systemic venous and systemic arterial blood?

8. Write the equation relating air flow into or out of the lungs to atmospheric pressure, alveolar pressure, and airway resistance.

9. Describe the sequence of events that cause air to move into the lungs during inspiration and out of the lungs during expiration. Diagram the changes in intrapleural pressure and alveolar pressure.

10. What factors determine lung compliance? Which is most important?

11. How does surfactant increase lung compliance?

12. How is airway resistance influenced by airway radii?

13. List the physical factors that alter airway resistance.

14. Contrast the causes of increased airway resistance in asthma, emphysema, and chronic bronchitis.

15. What distinguishes lung capacities, as a group, from lung volumes?

16. State the formula relating minute ventilation, tidal volume, and respiratory rate. Give representative values for each at rest.

17. State the formula for calculating alveolar ventilation. What is an average value for alveolar ventilation?

18. The partial pressure of a gas is dependent upon what two factors?

19. State the alveolar partial pressures for oxygen and carbon dioxide in a normal person at rest.

20. What factors determine alveolar partial pressures?

21. What is the mechanism of gas exchange between alveoli and pulmonary capillaries? In a normal person at rest, what are the gas pressures at the end of the pulmonary capillaries, relative to those in the alveoli?

22. Why does thickening of alveolar membranes impair oxygen movement but have little effect on carbon dioxide exchange?

23. What is the major result of ventilation-perfusion inequalities throughout the lungs? Describe one homeostatic response that minimizes mismatching.

24. What generates the diffusion gradients for oxygen and carbon dioxide in the tissues?

25. In what two forms is oxygen carried in the blood? What are the normal quantities (in milliliters per liter) for each form in arterial blood?

26. Describe the structure of hemoglobin.

27. Draw an oxygen-hemoglobin dissociation curve. Put in the points that represent systemic venous and systemic arterial blood (ignore the rightward shift of the curve in systemic venous blood). What is the adaptive importance of the plateau?

28. Would breathing pure oxygen cause a large increase in oxygen transport by the blood in a normal person? In a person with a low alveolar \( P_{CO_2} \)?

29. Describe the effects of increased \( P_{CO_2} \) on H^+ concentration, and temperature on the oxygen-hemoglobin dissociation curve. How are these effects adaptive for oxygen unloading in the tissues?

30. Describe the effects of increased DPG on the oxygen-hemoglobin dissociation curve. Under what conditions does an increase in DPG occur?

31. Draw figures showing the reactions carbon dioxide undergoes entering the blood in the tissue capillaries and leaving the blood in the alveoli. What fractions are contributed by dissolved carbon dioxide, bicarbonate, and carbamino?

32. What happens to most of the hydrogen ions formed in the erythrocytes from carbonic acid? What happens to blood H^+ concentration as blood flows through tissue capillaries?

33. What are the effects of \( P_{CO_2} \) on carbamino formation and H^+ binding by hemoglobin?

34. In what area of the brain does automatic control of rhythmic respirations reside?

35. Describe the function of the pulmonary stretch receptors.

36. What changes stimulate the peripheral chemoreceptors? The central chemoreceptors?

37. Why does moderate anemia or carbon monoxide exposure not stimulate the peripheral chemoreceptors?

38. Is respiratory control more sensitive to small changes in arterial \( P_{O_2} \) or in arterial \( P_{CO_2} \)?

39. Describe the pathways by which increased arterial \( P_{CO_2} \) stimulates ventilation. What pathway is more important?
40. Describe the pathway by which a change in arterial \( \text{H}^+ \) concentration independent of altered carbon dioxide influences ventilation. What is the adaptive value of this reflex?

41. What happens to arterial \( P_{\text{CO}_2}, P_{\text{CO}_2} \), and \( \text{H}^+ \) concentration during moderate and severe exercise? List other factors that may stimulate ventilation during exercise.

42. List four general causes of hypoxic hypoxia.

43. Describe two general ways in which the lungs can alter the concentrations of substances other than oxygen, carbon dioxide, and \( \text{H}^+ \) in the arterial blood.

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**Clinical Terms**

- cystic fibrosis
- pneumothorax
- respiratory-distress syndrome of the newborn
- asthma
- anti-inflammatory drugs
- bronchodilator drugs
- chronic obstructive pulmonary disease
- chronic bronchitis
- Heimlich maneuver
- forced expiratory volume in 1 s (FEV1)
- pulmonary function tests
- obstructive lung diseases
- restrictive lung diseases
- hypoventilation
- hyperventilation
- diffuse interstitial fibrosis
- ventilation-perfusion inequality

- shunt
- carbon monoxide
- respiratory acidosis
- respiratory alkalosis
- poliomyelitis
- metabolic acidosis
- metabolic alkalosis
- pulmonary embolus
dyspnea
hypoxia
hypoxic hypoxia
hypoxemia
anemic hypoxia
ischemic hypoxia
histotoxic hypoxia
diffusion impairment
hypercapnea
emphysema
mountain sickness

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**Thought Questions**

(Answers are given in Appendix A.)

1. At the end of a normal expiration, a person’s lung volume is 2 L, his alveolar pressure is 0 mmHg, and his intrapleural pressure is \(-4\) mmHg. He then inhales 800 ml, and at the end of inspiration the alveolar pressure is 0 mmHg and the intrapleural pressure is \(-8\) mmHg. Calculate this person’s lung compliance.

2. A patient is unable to produce surfactant. In order to inhale a normal tidal volume, will her intrapleural pressure have to be more or less subatmospheric during inspiration, relative to a normal person?

3. A 70-kg adult patient is artificially ventilated by a machine during surgery at a rate of 20 breaths/min and a tidal volume of 250 ml/breath. Assuming a normal anatomic dead space of 150 ml, is this patient receiving an adequate alveolar ventilation?

4. Why must a person floating on the surface of the water and breathing through a snorkel increase his tidal volume and/or breathing frequency if alveolar ventilation is to remain normal?

5. A normal person breathing room air voluntarily increases her alveolar ventilation twofold and continues to do so until new steady-state alveolar gas pressures for oxygen and carbon dioxide are reached. Are the new values higher or lower than normal?

6. A person breathing room air has an alveolar \( P_{\text{O}_2} \) of \( 105 \) mmHg and an arterial \( P_{\text{O}_2} \) of \( 80 \) mmHg. Could hyperventilation, say, due to respiratory muscle weakness, produce these values?

7. A person’s alveolar membranes have become thickened enough to moderately decrease the rate at which gases diffuse across them at any given partial pressure differences. Will this person necessarily have a low arterial \( P_{\text{O}_2} \) at rest? During exercise?

8. A person is breathing 100 percent oxygen. How much will the oxygen content (in milliliters per liter of blood) of the arterial blood increase compared to when the person is breathing room air?

9. Which of the following have higher values in systemic venous blood than in systemic arterial blood: plasma \( P_{\text{CO}_2} \), erythrocyte \( P_{\text{CO}_2} \), plasma bicarbonate concentration, erythrocyte bicarbonate concentration, plasma hydrogen-ion concentration, erythrocyte hydrogen-ion concentration, erythrocyte carbamino concentration, erythrocyte chloride concentration, plasma chloride concentration?

10. If the spinal cord were severed where it joins the brainstem, what would happen to respiration?

11. The peripheral chemoreceptors are denervated in an experimental animal, and the animal then breathes a gas mixture containing 10 percent oxygen. What changes occur in the animal’s ventilation? What changes occur when this denervated animal is given a mixture of air containing 21 percent oxygen and 5 percent carbon dioxide to breathe?

12. Patients with severe uncontrolled diabetes mellitus produce large quantities of certain organic acids. Can you predict the ventilation pattern in these patients and whether their arterial \( P_{\text{O}_2} \) and \( P_{\text{CO}_2} \) increase or decrease?