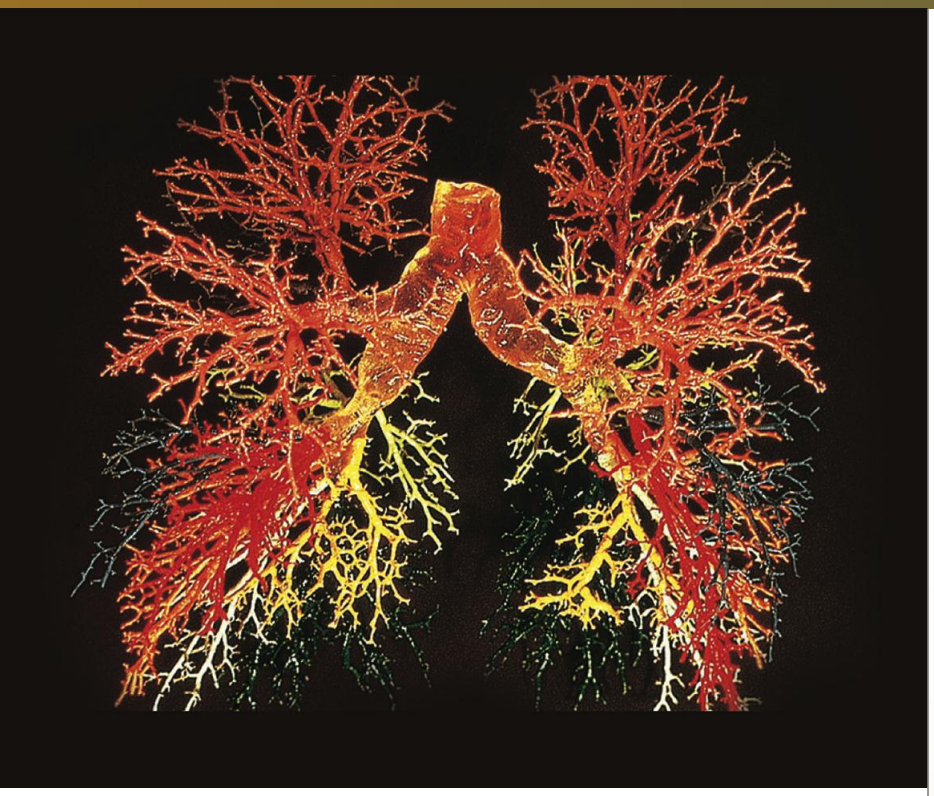
CHAPTER 13

Respiratory Physiology



Resin cast of the pulmonary arteries and bronchi.

In the previous chapter, you learned that the major role of the circulatory system is to deliver nutrients and oxygen to the tissues and to remove carbon dioxide and other waste products of metabolism. In this chapter, you will learn how the **respiratory system** is intimately associated with the circulatory system and is responsible for taking up oxygen from the environment and delivering it to the blood, as well as eliminating carbon dioxide from the blood.

Respiration has two meanings: (1) utilization of oxygen in the metabolism of organic molecules by cells, termed *internal* or *cellular respiration,* as described in Chapter 3; and (2) the exchange of oxygen and carbon dioxide between an organism and the external environment, called *pulmonary physiology.* The adjective **pulmonary** refers to the lungs. 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. Unicellular and some very small organisms can exchange oxygen and carbon dioxide directly with the external environment, but this is not possible for most cells of a complex organism like a human being. Therefore, the evolution of large animals required the development of specialized structures for the exchange of oxygen and carbon dioxide with the external environment. In humans and other mammals, the respiratory system

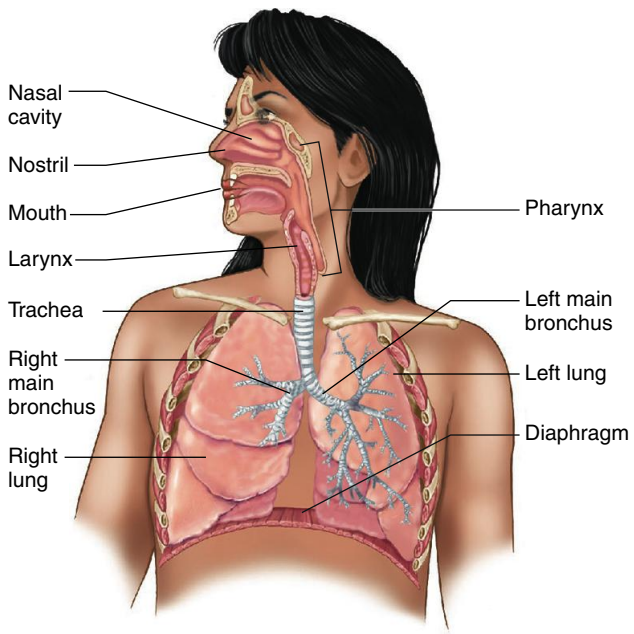
includes the oral and nasal cavities, the lungs, the series of tubes leading to the lungs, and the chest structures responsible for moving air into and out of the lungs during breathing.

As you read about the structure, function, and control of the respiratory system, you will encounter numerous examples of the general principles of physiology that were outlined in Chapter 1. The general principle of physiology that physiological processes are governed by the laws of chemistry and physics is demonstrated when describing the binding of oxygen and carbon dioxide to hemoglobin, the handling by the blood of acid produced by metabolism, and the factors that control the inflation and deflation of the lungs. The diffusion of gases is an excellent example of the general principle of physiology that controlled exchange of materials occurs between compartments and across cellular membranes. You will learn how the functional units of the lung, the alveoli, are elegant examples of the general principle of physiology that structure is a determinant of—and has coevolved with—function. Finally, the central nervous system control of respiration is yet another example of the general principle of physiology that homeostasis is essential for health and survival. ■

13.1 Organization of the Respiratory System

There are two lungs, the right and left, each divided into lobes. The lungs consist mainly of tiny air-containing sacs called **alveoli** (singular, **alveolus**), which number approximately 300 million in an adult. The alveoli are the sites of gas exchange with the blood. The **airways** are the tubes through which air flows from the external environment to the alveoli and back.

Inspiration (inhalation) is the movement of air from the external environment through the airways into the alveoli during breathing. **Expiration** (exhalation) is air movement in the opposite direction. An inspiration and expiration constitute a **respiratory cycle.** During the entire respiratory cycle, the right ventricle of the heart pumps blood through the pulmonary arteries and arterioles and into the capillaries surrounding each alveolus. In a healthy adult at rest, approximately 4 L of fresh air enters and leaves the alveoli per minute, while 5 L of blood, the cardiac output, flows through the pulmonary capillaries. During heavy exercise, the airflow can increase 20-fold, and the blood flow five- to sixfold.

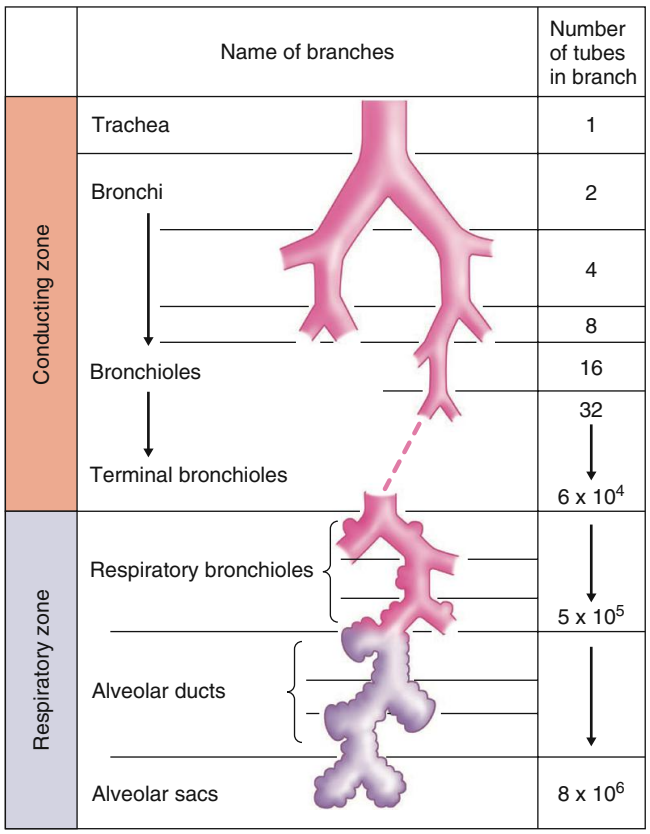


AP|R **Figure 13.1** Organization of the respiratory system. The ribs have been removed in front, and the lungs are shown in a way that makes visible the major airways within them. *Not shown:* The pharynx continues posteriorly to the esophagus.

The Airways and Blood Vessels

During inspiration, air passes through the nose or the mouth (or both) into the **pharynx,** a passage common to both air and food (**Figure 13.1**). 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 collectively 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; their names are summarized in

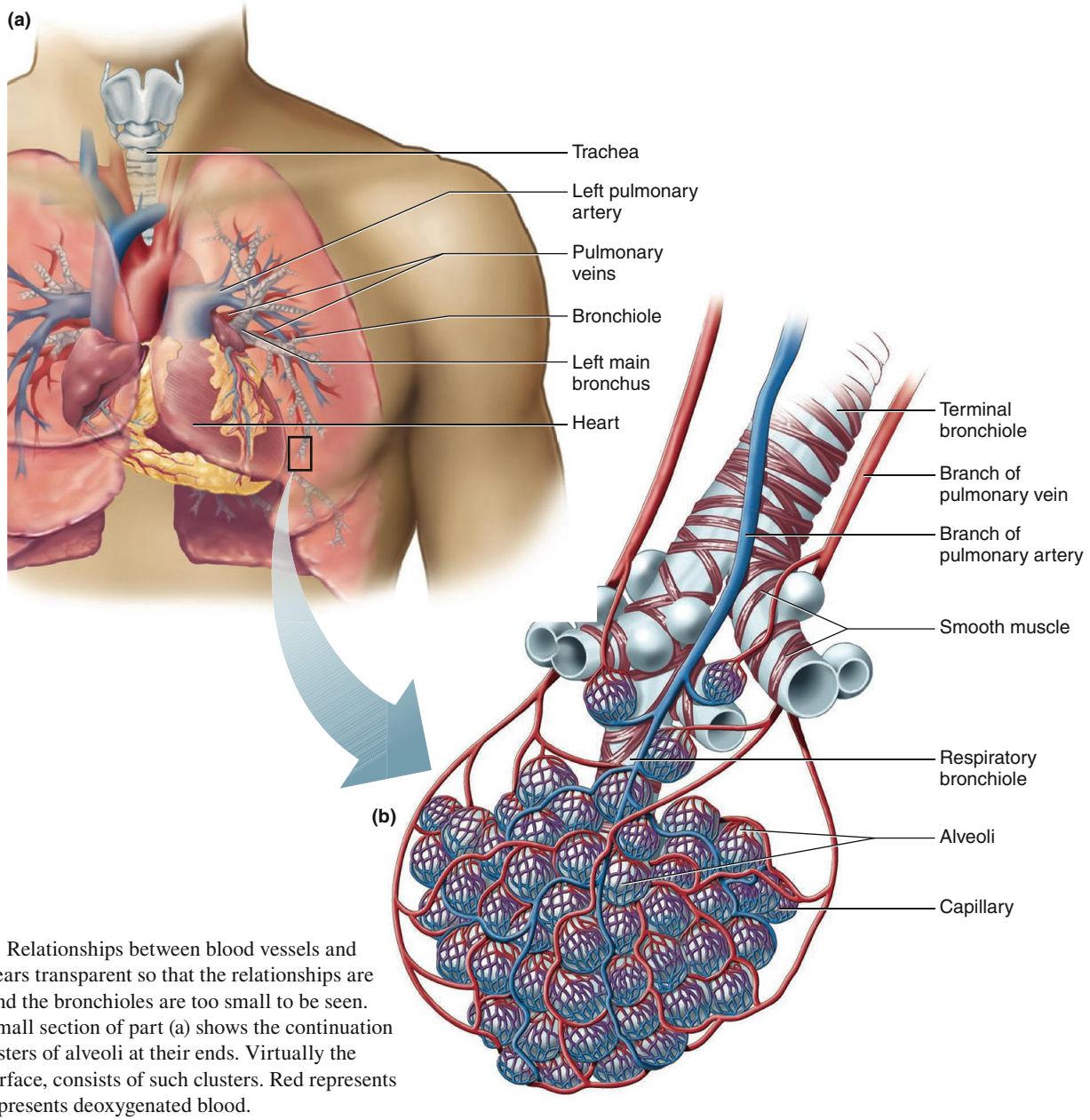


AP|R **Figure 13.2** Airway branching. Asymmetries in branching patterns between the right and left bronchial trees are not depicted. The diameters of the airways and alveoli are not drawn to scale.

Figure 13.2. The walls of the trachea and bronchi contain rings of cartilage, which give them their cylindrical shape and support them. The first airway branches that no longer contain cartilage are termed **bronchioles,** which branch into the smaller, terminal bronchioles. Alveoli first begin to appear attached to the walls of the **respiratory bronchioles.** The number of alveoli increases in the alveolar ducts (see Figure 13.2), and the airways then end in grapelike clusters called **alveolar sacs** that consist entirely of alveoli (**Figure 13.3**). The bronchioles are surrounded by smooth muscle, which contracts or relaxes to alter bronchiolar radius, in much the same way that the radius of small blood vessels (arterioles) is controlled, as you learned in Chapter 12.

The airways beyond the larynx can be divided into two zones. The **conducting zone** extends from the top of the trachea to the end of the terminal bronchioles. This zone contains no alveoli and does not exchange gases with the blood. The **respiratory zone** extends from the respiratory bronchioles down. This zone contains alveoli and is the region where gases exchange with the blood.

The oral and nasal cavities trap airborne particles in nasal hairs and mucus. The epithelial surfaces of the airways, to the end of the respiratory bronchioles, contain cilia that constantly beat upward toward the pharynx. They also contain glands and individual epithelial cells that secrete mucus, and macrophages, which can phagocytize inhaled pathogens. 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 so-called mucous escalator is important in keeping the lungs clear of particulate matter and the many bacteria that enter the body on dust particles. Ciliary activity and number



AP|R **Figure 13.3** Relationships between blood vessels and airways. (a) The lung appears transparent so that the relationships are visible. The airways beyond the bronchioles are too small to be seen. (b) An enlargement of a small section of part (a) shows 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. Red represents oxygenated blood; blue represents deoxygenated blood.

can be decreased by many noxious agents, including the smoke from chronic smoking of tobacco products. This is why smokers often cough up mucus that the cilia would normally have cleared.

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*** (***CF***), the most common lethal genetic disease among Caucasians, in which the mucous layer becomes thick and dehydrated, obstructing the airways. CF is caused by an autosomal recessive mutation in an epithelial chloride channel called the **CF transmembrane conductance regulator** (**CFTR**) protein. This results in problems with ion and water movement across cell membranes, which leads to thickened secretions and a high incidence of lung infection. It is usually treated with (1) therapy to improve clearance of mucus from the lung and (2) the aggressive use of antibiotics to prevent pneumonia. Although the treatment of CF has improved over the past few decades, median life expectancy is still only about 35 years. Ultimately, lung transplantation may be required. In addition to the lungs, other organs are usually affected—particularly in the secretory organs associated with the gastrointestinal tract (for example, the exocrine pancreas, as described in Chapter 15).

Constriction of bronchioles in response to irritation helps to prevent particulate matter and irritants from entering the sites of gas exchange. Another protective mechanism against infection is provided by macrophages that are present in the airways and alveoli. These cells engulf and destroy inhaled particles and bacteria that have reached the alveoli. Macrophages, like the ciliated epithelium of the airways, are injured by tobacco smoke and air pollutants. The physiology of the conducting zone is summarized in **Table 13.1**.

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 (see Figure 13.3). As you learned in Chapter 12, the pulmonary circulation has a very low resistance to the flow of blood compared to the systemic circulation, and for this reason the pressures within all pulmonary blood vessels are low. This is an important adaptation that minimizes accumulation of fluid in the interstitial spaces of the lungs (see Figure 12.45 for a description of Starling forces and the movement of fluid across capillaries).

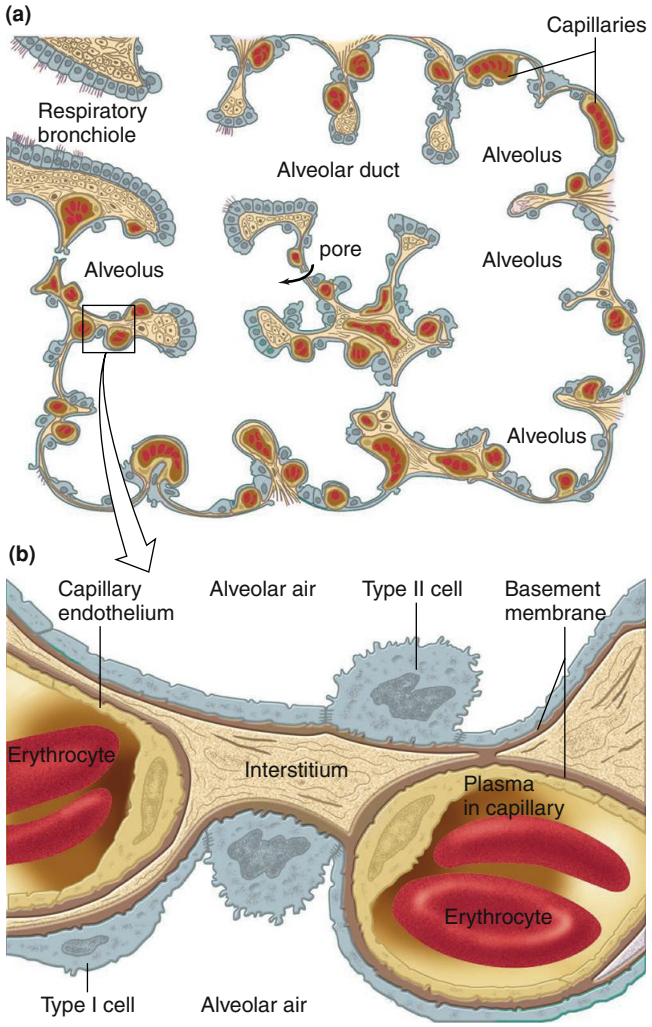
Site of Gas Exchange: The Alveoli

The alveoli are tiny, hollow sacs with open ends that are continuous with the lumens of the airways (**Figure 13.4a**). Typically, a single alveolar wall separates the air in two adjacent alveoli. Most of the air-facing surfaces 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 13.4b**) that produce a detergent-like substance called surfactant that, as we will see, is important for preventing the collapse of the alveoli.

The alveolar walls contain capillaries and a very small interstitial space, which consists of interstitial fluid and a loose meshwork of connective tissue (see Figure 13.4b). In many places, the interstitial space is absent altogether, and the basement membranes of the alveolar-surface epithelium and the capillary-wall endothelium fuse. Because of this unique anatomical arrangement, 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 the 7 μm diameter of an average red blood cell). The total surface area

TABLE 13.1 Functions of the Conducting Zone of the Airways

Provides a low-resistance pathway for airflow. Resistance is physiologically regulated by changes in contraction of bronchiolar smooth muscle and by physical forces acting upon the airways.
Defends against microbes, toxic chemicals, and other foreign matter. Cilia, mucus, and macrophages perform this function.
Warms and moistens the air.
Participates in sound production (vocal cords).



AP|R **Figure 13.4** (a) Cross section through an area of the respiratory zone. There are 18 alveoli in this figure, only four of which are labeled. Two often share a common wall. (b) Schematic enlargement of a portion of an alveolar wall.

PHYSIOLOGICAL INQUIRY

- What consequences would result if inflammation caused a buildup of fluid in the alveoli and interstitial spaces?

Answer can be found at end of chapter.

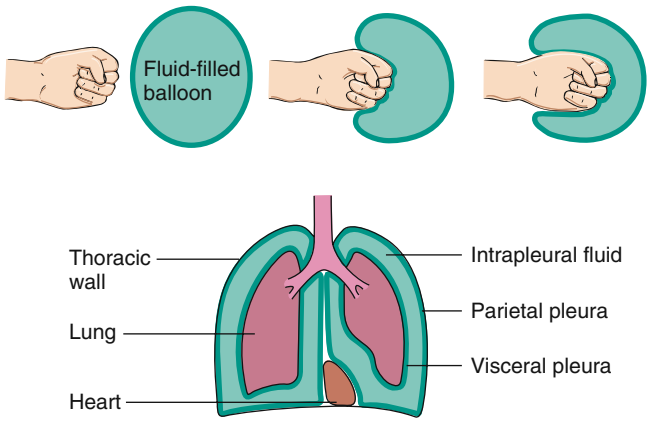
of alveoli in contact with capillaries is roughly the size of a tennis court. This extensive area and the thinness of the barrier permit the rapid exchange of large quantities of oxygen and carbon dioxide by diffusion. These are excellent examples of two of the general principles of physiology—that physiological processes require the transfer and balance of matter (in this case, oxygen and carbon dioxide) and energy between compartments; and that structure (in this case, the thinness of the diffusion barrier and the enormous surface area for gas exchange) is a determinant of—and has coevolved with—function (the transfer of oxygen and carbon dioxide between the alveolar air and the blood in the pulmonary capillaries).

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

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 bounded at the neck by muscles and connective tissue and completely separated from the abdomen by a large, dome-shaped sheet of skeletal muscle called the **diaphragm** (see Figure 13.1). 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 that are collectively called the **intercostal muscles.** The thoracic wall also contains large amounts of connective tissue with elastic properties.

Each lung is surrounded by a completely closed sac, the **pleural sac,** consisting of a thin sheet of cells called **pleura.** The pleural sac of one lung is separate from that of the other lung. The relationship between a lung and its pleural sac can be visualized by imagining what happens when you push a fist into a fluid-filled balloon. The arm shown in **Figure 13.5** represents the major bronchus leading to the lung, the fist is the lung, and the balloon



AP|R **Figure 13.5** 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, the volume of intrapleural fluid is greatly exaggerated. It normally consists of an extremely thin layer of fluid between the pleural membrane lining the inner surface of the thoracic wall (the parietal pleura) and the membrane lining the outer surface of the lungs (the visceral pleura).

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 but are separated by a thin layer of fluid. Unlike the hand and balloon, the pleural surface coating the lung known as the **visceral pleura** is firmly attached to the lung by connective tissue. Similarly, the outer layer, called the **parietal pleura,** is attached to and lines the interior thoracic wall and diaphragm. The two layers of pleura in each sac are very close but 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. As we will see in the next section, changes in the hydrostatic pressure of the intrapleural fluid—the **intrapleural pressure** ($\boldsymbol{P_{ip}}$)—cause the lungs and thoracic wall to move in and out together during normal breathing.

A way to visualize the apposition of the two pleural surfaces is to put a small drop of water between two glass microscope slides. The two slides can easily slide over each other but are very difficult to pull apart.

13.2 Ventilation and Lung Mechanics

This section highlights that physiological processes are dictated by the laws of chemistry and physics, one of the general principles of physiology described in Chapter 1. Understanding the forces that control the inflation and deflation of the lung and the flow of air between the lung and the environment requires some knowledge of several fundamental physical laws. Furthermore, understanding of these forces is necessary to appreciate several pathophysiological events, such as the collapse of a lung due to an air leak into the chest cavity. We begin with an overview of these physical processes and the steps involved in respiration (**Figure 13.6**) before examining each step in detail.

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. Bulk flow can be described by the equation

$$F = \Delta P/R \qquad \textbf{(13–1)}$$

Flow (F) is proportional to the pressure difference (ΔP) between two points and inversely proportional to the resistance (R). (Notice that this equation is the same one used to describe the movement of blood through blood vessels, described in Chapter 12.) For airflow into or out of the lungs, the relevant pressures are the gas pressure in the alveoli—the **alveolar pressure** ($\boldsymbol{P_{alv}}$)—and the gas pressure at the nose and mouth, normally **atmospheric pressure** ($\boldsymbol{P_{atm}}$), which is the pressure of the air surrounding the body:

$$F = (P_{alv} - P_{atm})/R \qquad \textbf{(13–2)}$$

A very important point must be made here: All pressures in the respiratory system, as in the cardiovascular system, are given *relative to atmospheric pressure,* which is 760 mmHg at sea level but which decreases in proportion to an increase in altitude. For example, the alveolar pressure between breaths is said to be 0 mmHg, which means that it is the same as atmospheric pressure at any given altitude. From equation 13–2, when there is no airflow,

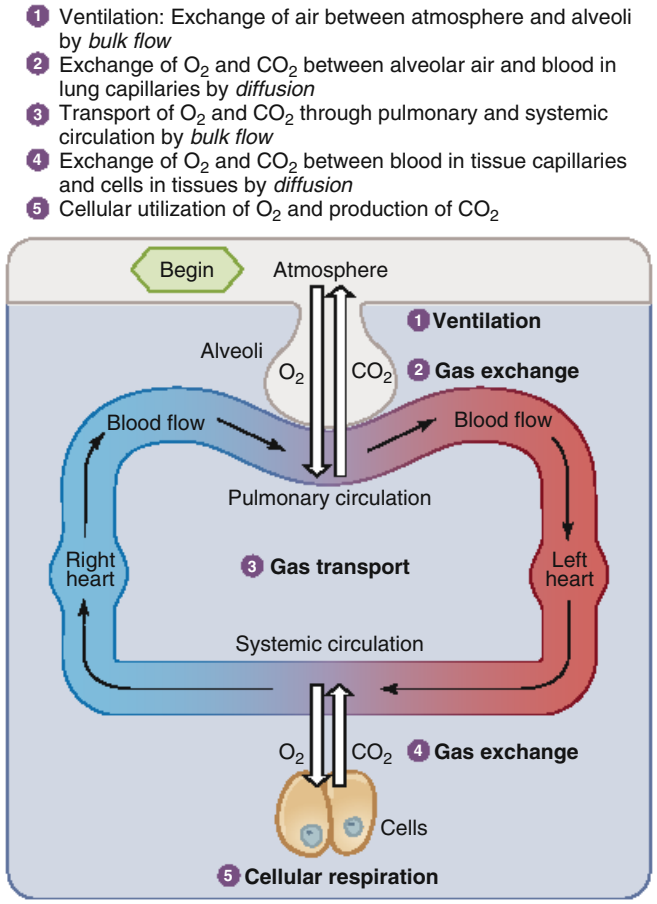
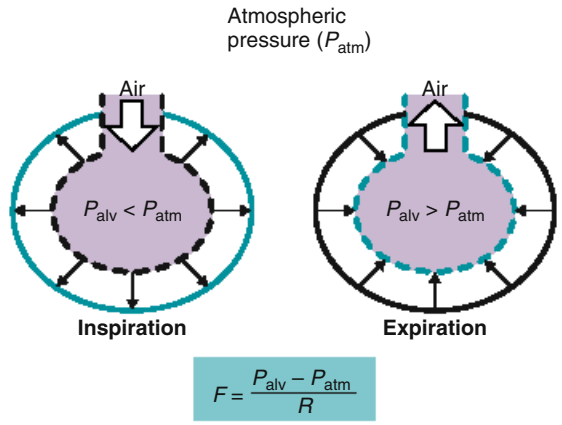


Figure 13.6 The steps of respiration.



AP|R Figure 13.7 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 ($P_{alv} - P_{atm}$) and inversely proportional to airway resistance (R). Black lines show lung's position at beginning of inspiration or expiration, and blue lines show position at end of inspiration or expiration.

$F = 0$; therefore, $P_{alv} - P_{atm} = 0$, and $P_{alv} = P_{atm}$. That is, when there is no airflow and the airway is open to the atmosphere, the pressure in the alveoli is equal to the pressure in the atmosphere.

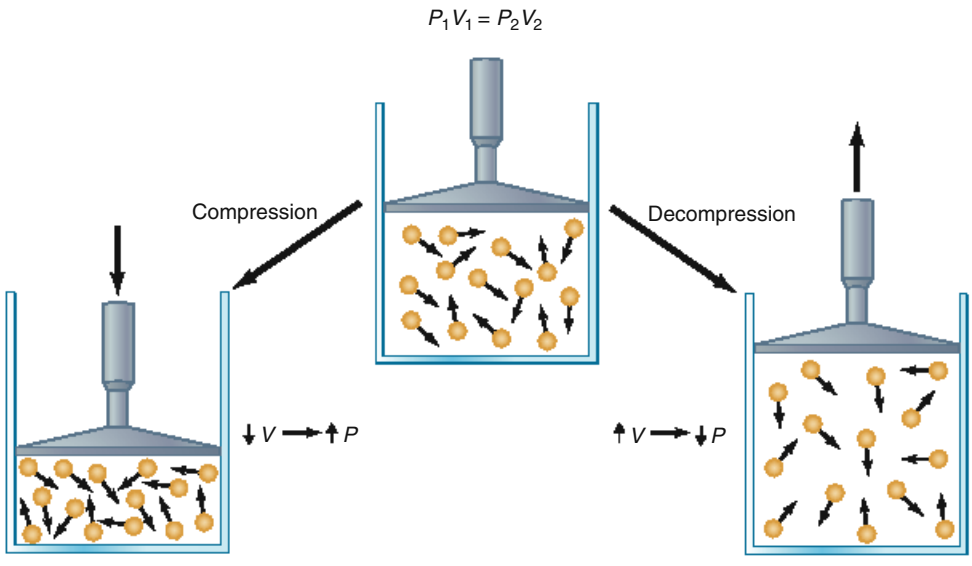
During ventilation, air moves into and out of the lungs because the alveolar pressure is alternately less than and greater than atmospheric pressure (**Figure 13.7**). In accordance with equation 13–2 describing airflow, a negative value reflects an inward-directed pressure gradient and a positive value indicates an outward-directed gradient. Therefore, when P_{alv} is less than P_{atm}, $P_{alv} - P_{atm}$ is negative and airflow is inward (inspiration). When P_{alv} is greater than P_{atm}, $P_{alv} - P_{atm}$ is positive and airflow is outward (expiration). These alveolar pressure changes are caused, as we will see, by changes in the dimensions of the chest wall and lungs.

To understand how a change in lung dimensions causes a change in alveolar pressure, you need to learn one more basic physical principle described by **Boyle's law,** which is represented by the equation $P_1V_1 = P_2V_2$ (**Figure 13.8**). At constant temperature, the relationship between the pressure (P) exerted by a fixed number of gas molecules and the volume (V) of their container is as follows:

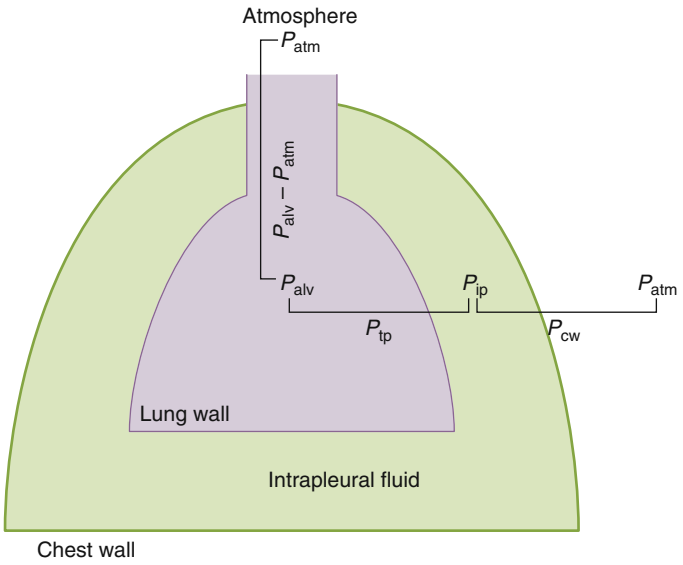
An increase in the volume of the container decreases the pressure of the gas, whereas a decrease in the container volume increases the pressure. In other words, in a closed system, the pressure of a gas and the volume of its container are inversely proportional.

It is essential to recognize the correct sequence of events that determine the inspiration and then expiration of a breath. 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 airflow 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,



AP|R Figure 13.8 Boyle's law: The pressure exerted by a constant number of gas molecules (at a constant temperature) is inversely proportional to the volume of the container. As the container is compressed, the pressure in the container increases. When the container is decompressed, the pressure inside decreases.



AP|R **Figure 13.9** Pressure differences involved in ventilation. Transpulmonary pressure ($P_{tp} = P_{alv} - P_{ip}$) is a determinant of lung size. Intrapleural pressure (P_{ip}) at rest is a balance between the tendency of the lung to collapse and the tendency of the chest wall to expand. P_{cw} represents the transmural pressure across the chest wall ($P_{ip} - P_{atm}$). $P_{alv} - P_{atm}$ is the driving pressure gradient for airflow into and out of the lungs. (The volume of intrapleural fluid is greatly exaggerated for visual clarity.)

depends on other factors. The first of these is the difference in pressure between the inside and outside of the lung, termed the **transpulmonary pressure** (P_{tp}). The second is how stretchable the lungs are, which determines how much they expand for a given change in P_{tp}. The rest of this section and the next three sections focus 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 surrounding the lungs (P_{ip}). Thus,

$$\text{Transpulmonary pressure} = P_{alv} - P_{ip}$$
$$P_{tp} = P_{alv} - P_{ip} \qquad \textbf{(13–3)}$$

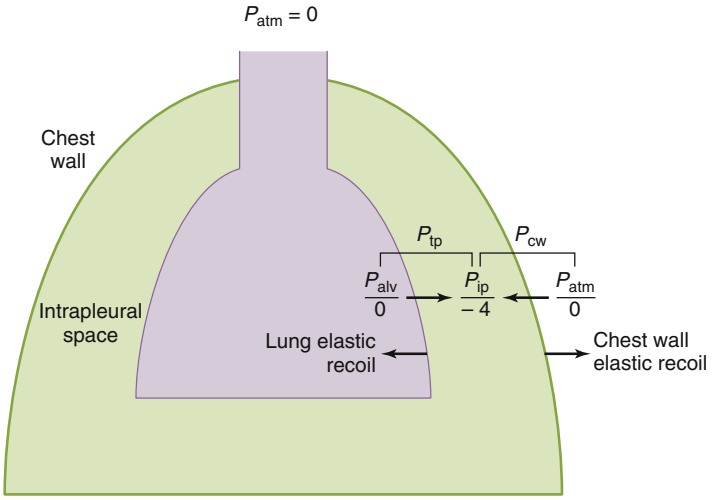
Compare this equation to equation 13–2 (the equation that describes airflow into or out of the lungs), as it will be essential to distinguish these equations from each other (**Figure 13.9**).

Transpulmonary pressure is the **transmural pressure** that governs the static properties of the lungs. *Transmural* means "across a wall" and, by convention, is represented by the pressure in the inside of the structure (P_{in}) minus the pressure outside the structure (P_{out}). Inflation of a balloonlike structure like the lungs requires an increase in the transmural pressure such that P_{in} increases relative to P_{out}.

Table 13.2 and Figure 13.9 show the major transmural pressures of the respiratory system. The transmural pressure acting on the lungs (P_{tp}) is $P_{alv} - P_{ip}$ and, on the chest wall, (P_{cw}) is $P_{ip} - P_{atm}$. The muscles of the chest wall contract and cause the chest wall to expand during inspiration; simultaneously, the diaphragm contracts downward, further enlarging the thoracic cavity. As the volume of the thoracic cavity expands, P_{ip} decreases. P_{tp} becomes more positive as a result and the lungs expand. As this occurs, P_{alv} becomes more negative compared to P_{atm} (due to Boyle's law), and air flows inward (inspiration, equation 13–2). Therefore, the transmural pressure across the lungs (P_{tp}) is increased to fill them with air by actively decreasing the pressure surrounding the lungs (P_{ip}) relative to the pressure inside the lungs (P_{alv}). When the respiratory muscles relax, elastic recoil of the lungs drives passive expiration back to the starting point.

How Is a Stable Balance of Transmural Pressures Achieved Between Breaths?

Figure 13.10 illustrates the transmural pressures of the respiratory system at rest—that is, at the end of an unforced expiration when the respiratory muscles are relaxed and there is no airflow. By definition, if there is no airflow and the airways are open to the



AP|R **Figure 13.10** Alveolar (P_{alv}), intrapleural (P_{ip}), transpulmonary (P_{tp}), and trans-chest-wall (P_{cw}) pressures (mmHg) at the end of an unforced expiration—that is, between breaths when there is no airflow. The transpulmonary pressure ($P_{alv} - P_{ip}$) exactly opposes the elastic recoil of the lung, and the lung volume remains stable. Similarly, trans-chest-wall pressure ($P_{ip} - P_{atm}$) is balanced by the outward elastic recoil of the chest wall. Notice that the transmural pressure is the pressure inside the wall minus the pressure outside the wall. (The volume of intrapleural fluid is greatly exaggerated for clarity.)

TABLE 13.2 Two Important Transmural Pressures of the Respiratory System

Transmural Pressure	$P_{in} - P_{out}$*	Value at Rest	Explanatory Notes
Transpulmonary (P_{tp})	$P_{alv} - P_{ip}$	$0 - [-4] = 4$ mmHg	Pressure difference holding lungs open (opposes inward elastic recoil of the lung)
Chest wall (P_{cw})	$P_{ip} - P_{atm}$	$-4 - 0 = -4$ mmHg	Pressure difference holding chest wall in (opposes outward elastic recoil of the chest wall)

*P_{in} is pressure inside the structure, and P_{out} is pressure surrounding the structure.

atmosphere, P_{alv} must equal P_{atm} (see equation 13–2). Because the lungs always have air in them, the transmural pressure of the lungs (P_{tp}) must always be positive; therefore, $P_{alv} > P_{ip}$. At rest, when there is no airflow and $P_{alv} = 0$, P_{ip} must be negative, providing the force that keeps the lungs open and the chest wall in.

What are the forces that cause P_{ip} to be negative? The first, the **elastic recoil** of the lungs, is defined as the tendency of an elastic structure to oppose stretching or distortion. Even at rest, the lungs contain air, and their natural tendency is to collapse because of elastic recoil. The lungs are held open by the positive P_{tp}, which, at rest, exactly opposes elastic recoil. Secondly, the chest wall also has elastic recoil, and, at rest, its natural tendency is to expand. At rest, these opposing transmural pressures balance each other out.

As the lungs tend to collapse and the thoracic wall tends to expand, they move ever so slightly away from each other. This causes an infinitesimal enlargement of the fluid-filled intrapleural space between them. But fluid cannot expand the way air can, so even this tiny enlargement of the intrapleural space—so small that the pleural surfaces still remain in contact with each other—decreases the intrapleural pressure to 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. Again, imagine trying to pull apart two glass slides that have a drop of water between them. The fluid pressure generated between the slides will be lower than atmospheric pressure.

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 enters the intrapleural space through the wound, a phenomenon called ***pneumothorax,*** and the intrapleural pressure increases from −4 mmHg to 0 mmHg. That is, P_{ip} increases from 4 mmHg lower than P_{atm} to a P_{ip} value equal to P_{atm}. The transpulmonary pressure acting to hold the lung open is eliminated, and the lung collapses (**Figure 13.11**).

At the same time, the chest wall moves outward because its elastic recoil is also no longer opposed. Also notice in Figure 13.11 that a pneumothorax can result when a hole is made in the lung such that a significant amount of air leaks from inside the lung to the pleural space. This can occur, for example, when high airway pressure is applied during artificial ventilation of a premature infant whose lung surface tension is high and whose lungs are fragile. The thoracic cavity is divided into right and left sides by the mediastinum—the central part of the thorax containing the heart, trachea, esophagus and other structures—so a pneumothorax is usually unilateral.

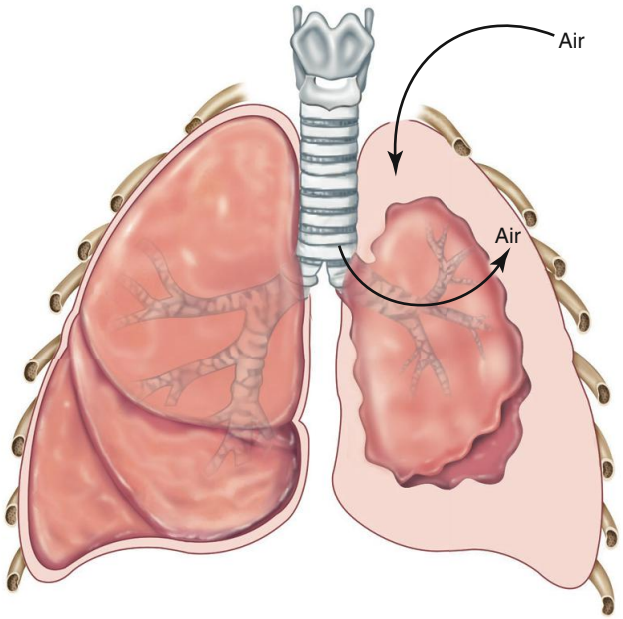


Figure 13.11 Pneumothorax. The lung collapses as air enters from the pleural cavity either from inside the lung or from the atmosphere through the thoracic wall. The combination of lung elastic recoil and surface tension causes collapse of the lung when pleural and airway pressures equalize.

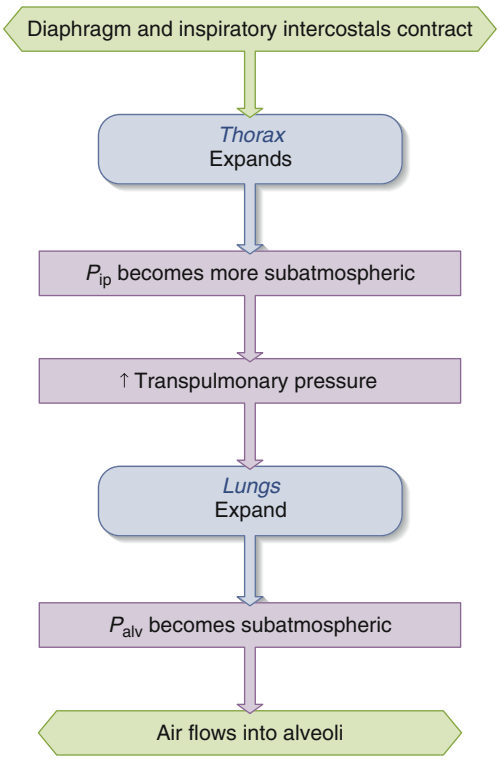
PHYSIOLOGICAL INQUIRY

- How can a collapsed lung be re-expanded in a patient with a pneumothorax? (*Hint:* What changes in P_{ip} and P_{tp} would be needed to re-expand the lung?)

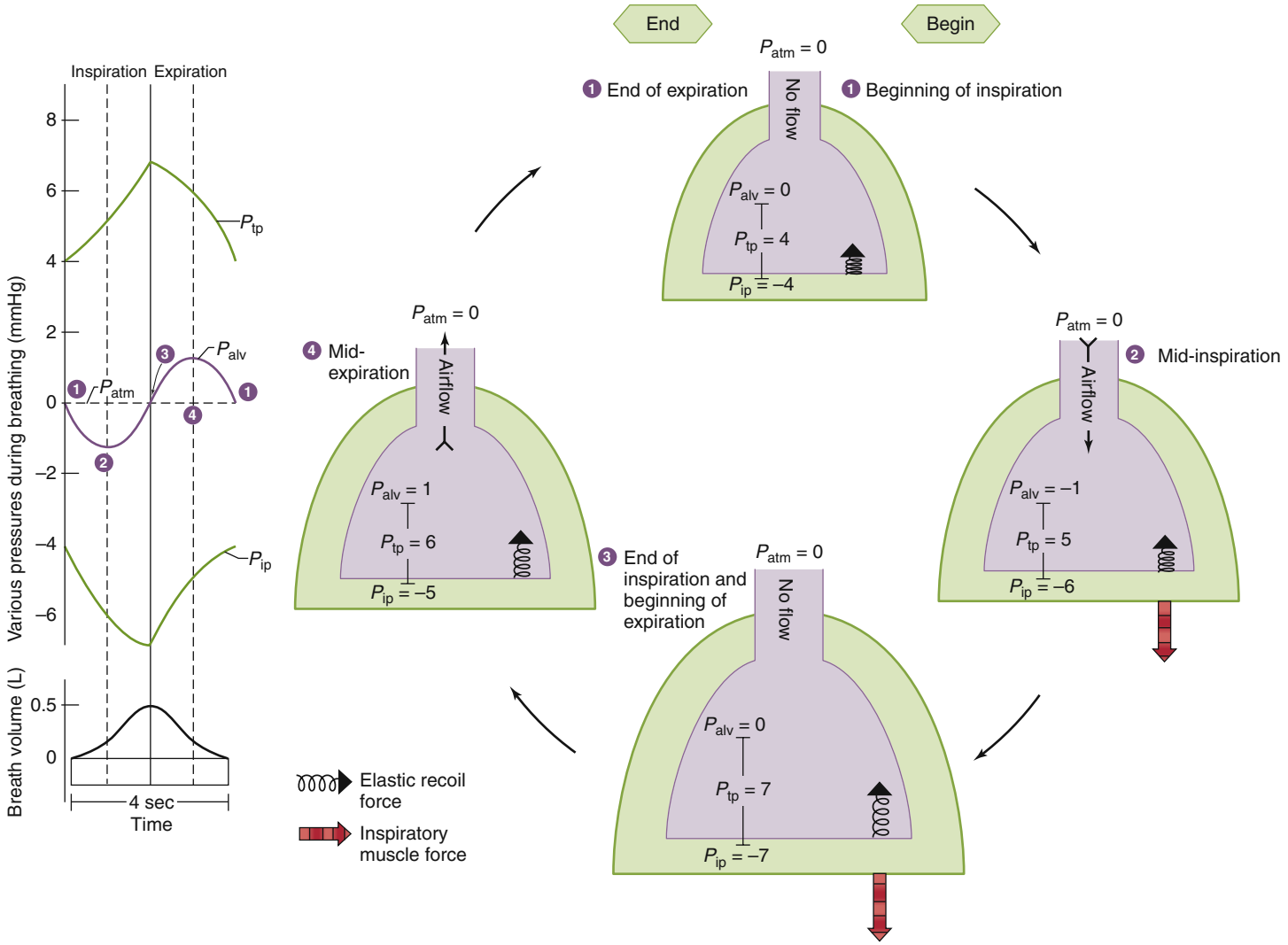
Answer can be found at end of chapter.

Inspiration

Figure 13.12 and **Figure 13.13** summarize the events that occur during normal inspiration at rest. Inspiration is initiated by the neurally induced contraction of the diaphragm and the external intercostal muscles located between the ribs (**Figure 13.14**). The diaphragm is the most important inspiratory muscle that acts



AP|R **Figure 13.12** Sequence of events during inspiration. Figure 13.13 illustrates these events quantitatively.



AP|R **Figure 13.13** Summary of alveolar (P_{alv}), intrapleural (P_{ip}), and transpulmonary (P_{tp}) pressure changes and airflow during a typical respiratory cycle. At the end of expiration ❶, P_{alv} is equal to P_{atm} and there is no airflow. At mid-inspiration ❷, the chest wall is expanding, lowering P_{ip} and making P_{tp} more positive. This expands the lung, making P_{alv} negative, and results in an inward airflow. At end of inspiration ❸, the chest wall is no longer expanding but has yet to start passive recoil. Because lung size is not changing and the airway is open to the atmosphere, P_{alv} is equal to P_{atm} and there is no airflow. As the respiratory muscles relax, the lungs and chest wall start to passively collapse due to elastic recoil. At mid-expiration ❹, the lung is collapsing, thus compressing alveolar gas. As a result, P_{alv} is positive relative to P_{atm} and airflow is outward. The cycle starts over again at the end of expiration. Notice that throughout a typical respiratory cycle with a normal tidal volume, P_{ip} is negative relative to P_{atm}. In the graph on the left, the difference between P_{alv} and P_{ip} ($P_{alv} - P_{ip}$) at any point along the curves is equivalent to P_{tp}. For clarity, the chest-wall elastic recoil (as in Figure 13.10) is not shown.

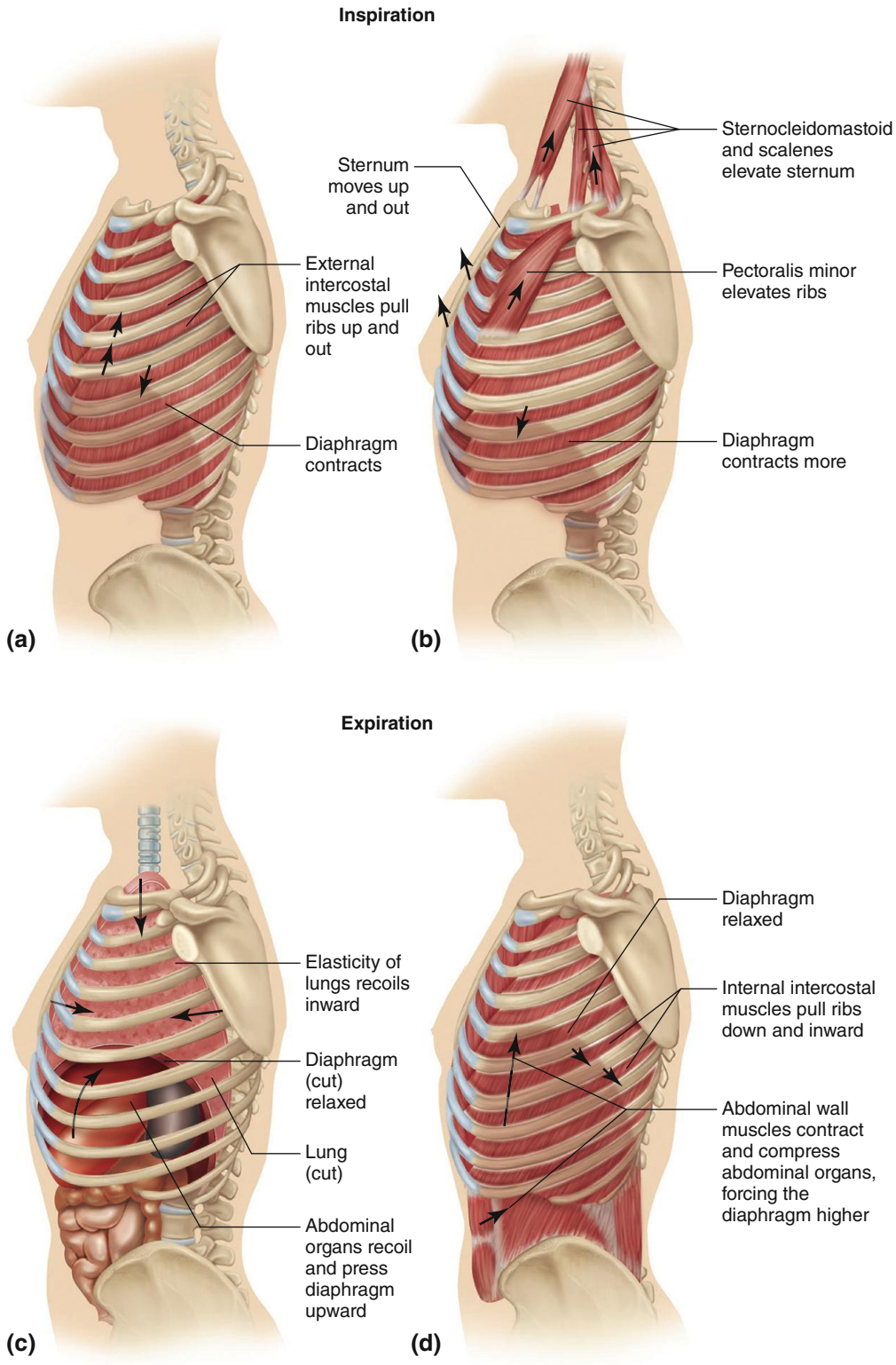
PHYSIOLOGICAL INQUIRY

- How do the changes in P_{tp} between each step (❶–❹) explain whether the volume of the lung is increasing or decreasing?

Answer can be found at end of chapter.

during normal quiet breathing. When activation of the motor neurons within the **phrenic nerves** innervating the diaphragm causes it to contract, its dome moves downward into the abdomen, enlarging the thorax (see Figure 13.14). Simultaneously, activation of the motor neurons in the intercostal 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. Also notice in Figure 13.14 that there are several other sets of muscles that participate in the expansion of the thoracic cavity, which become important during a maximal inspiration.

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. 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



AP|R **Figure 13.14** Muscles of respiration during inspiration and expiration. (a) Normal inspiration; (b) maximal inspiration; (c) normal, resting expiration; and (d) maximal expiration.

further. Note in Figure 13.13 that, by the end of inspiration, equilibrium *across the lungs* is once again established because 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, at the end of both inspiration and expiration when there is no airflow).

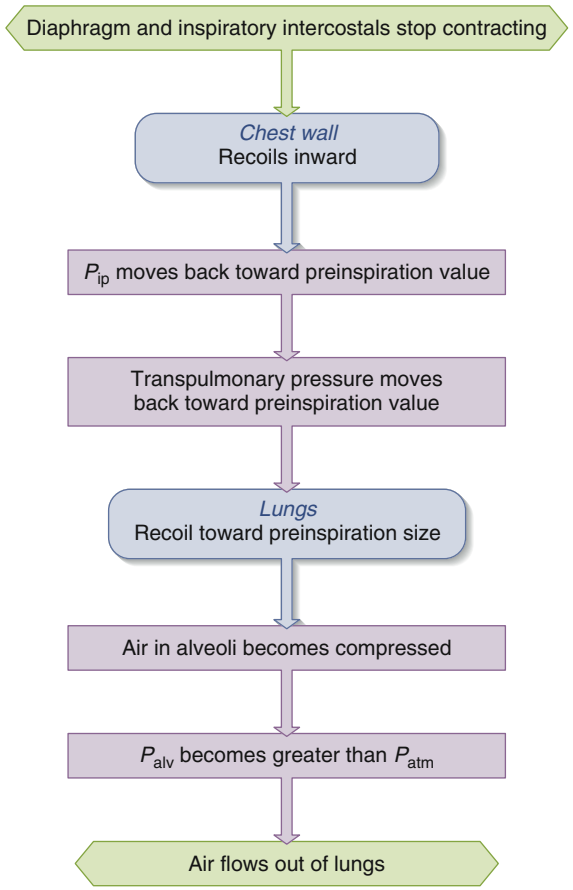
Therefore, when contraction of the inspiratory muscles actively increases the thoracic dimensions, the lungs are passively forced to enlarge. The enlargement of the lungs causes an increase in the sizes of the alveoli throughout the lungs. By Boyle's law, the pressure within the alveoli decreases to less than atmospheric (see Figure 13.13). 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 airflow ceases.

Expiration

Figure 13.13 and **Figure 13.15** summarize the sequence of events that occur during expiration. At the end of inspiration, the motor neurons to the diaphragm and inspiratory intercostal muscles decrease their firing and so these muscles relax. The diaphragm and chest wall are no longer actively pulled outward by the muscle contractions, and so they start to recoil inward to their original smaller dimensions that existed between breaths. This immediately makes the intrapleural pressure less subatmospheric, thereby *decreasing* 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 dimension.

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 13.13). Therefore, air flows from the alveoli through the airways out into the atmosphere. Expiration at rest is passive, depending only upon the relaxation of the inspiratory muscles and the elastic recoil of the stretched lungs.

Under certain conditions, such as during exercise, expiration of larger volumes is achieved by contraction of a different set of intercostal muscles and the abdominal muscles, which *actively* decrease thoracic dimensions (see Figure 13.14). The internal intercostal muscles insert on the ribs in such a way that their contraction pulls the chest wall downward and inward, thereby decreasing thoracic volume. Contraction of the abdominal muscles increases



AP|R **Figure 13.15** Sequence of events during expiration. Figure 13.13 illustrates these events quantitatively.

intra-abdominal 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, $P_{alv} - P_{ip}$. But just how much any given change in 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 (ΔV_L) produced by a given change in the transpulmonary pressure:

$$C_L = \Delta V_L / \Delta P_{tp} \qquad \textbf{(13–4)}$$

This equation indicates that the greater the lung compliance, the easier it is to expand the lungs at any given change in transpulmonary pressure (**Figure 13.16**). Compliance can be considered the inverse of stiffness. 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 (increased stiffness), 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. The less compliant the lung, the more energy is required to produce a given amount of expansion. Persons with low lung compliance due to disease tend to breathe

$$\text{Compliance} = \frac{\Delta \text{ Lung volume}}{\Delta\,(P_{alv} - P_{ip})} = \frac{\Delta\ V}{\Delta\ P_{tp}}$$

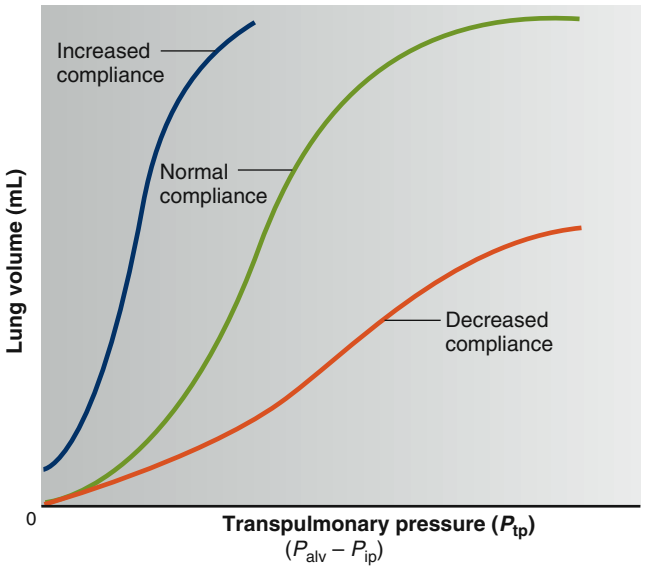


Figure 13.16 A graphic representation of lung compliance. Changes in lung volume and transpulmonary pressure are measured as a subject takes progressively larger breaths. When compliance is lower than normal (the lung is stiffer), there is a lesser increase in lung volume for any given increase in transpulmonary pressure. When compliance is increased, as in emphysema, small decreases in P_{tp} allow the lung to collapse.

PHYSIOLOGICAL INQUIRY

- Premature infants with inadequate surfactant have decreased lung compliance (respiratory distress syndrome of the newborn). If surfactant is not available to administer for therapy, what would you suggest could be done to inflate the lung?

Answer can be found at end of chapter.

shallowly and at a higher frequency to inspire an adequate volume of air. This minimizes the work of breathing.

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. Therefore, a thickening of the lung tissues decreases lung compliance. However, an equally if not more important determinant of lung compliance is the surface tension at the air–water interfaces within the alveoli.

The inner surface of the alveolar cells is moist, so the alveoli can be pictured as air-filled sacs lined with a layer of liquid. 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 tends to shrink and resists further stretching. Therefore, 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 if the alveoli were 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 the detergent-like substance mentioned earlier, known as **surfactant,** which markedly reduces the cohesive forces between water molecules on the alveolar surface. The net result is that surfactant lowers the surface tension, which increases lung compliance and makes it easier to expand the lungs.

Surfactant is a mixture of both lipids and proteins, but its major component is a phospholipid that inserts its hydrophilic end into the water layer lining the alveoli; its hydrophobic ends form 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.

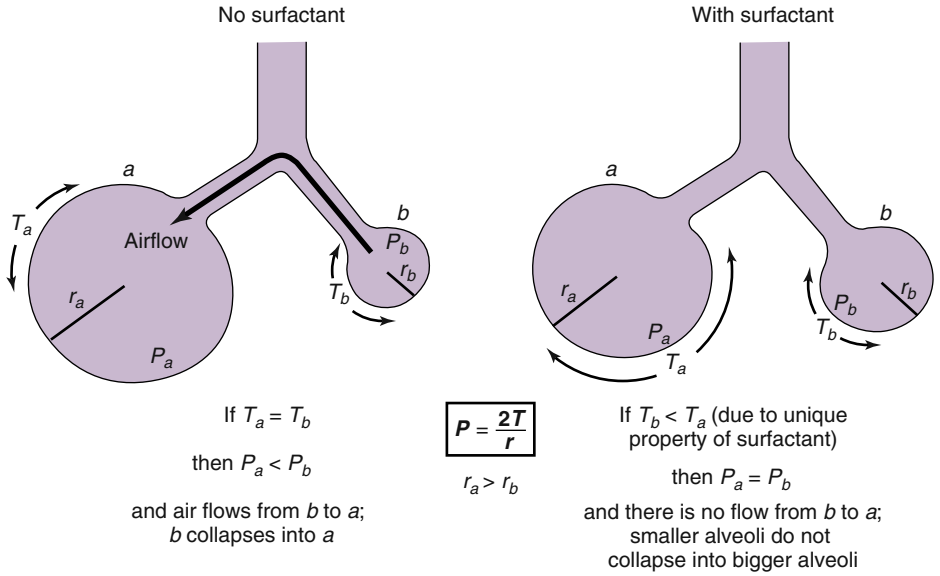


Figure 13.17 Stabilizing effect of surfactant. P is pressure inside the alveoli, T is a surface tension, and r is the radius of the alveolus. The Law of Laplace is described by the equation in the box.

The **Law of Laplace** describes the relationship between pressure (P), surface tension (T), and the radius (r) of an alveolus, shown in **Figure 13.17**:

$$P = 2T/r \qquad \textbf{(13–5)}$$

As the radius of an alveolus decreases, the pressure inside it increases. Now imagine two alveoli next to each other sharing an alveolar duct (see Figure 13.17). The radius of alveolus a (r_a) is greater than the radius of alveolus b (r_b). If surface tension (T) were equivalent between these two alveoli, alveolus b would have a higher pressure than alveolus a by the Law of Laplace. If P_b is higher than P_a, air would flow from alveolus b into alveolus a, and alveolus b would collapse. Therefore, small alveoli would be unstable and would collapse into large alveoli. Another important property of surfactant is that it stabilizes alveoli of different sizes by altering surface tension, depending on the surface area of the alveolus. As an alveolus gets smaller, the molecules of surfactant on its inside surface are less spread out, thus reducing surface tension. The decrease in surface tension helps to maintain a pressure in smaller alveoli equal to that in larger ones. This gives stability to alveoli of different sizes. **Table 13.3** summarizes some of the important aspects of pulmonary surfactant.

A striking example of what occurs when surfactant is deficient is the disease known as ***respiratory distress syndrome of the newborn.*** This is a leading cause of death in premature infants, in whom the surfactant-synthesizing cells may be too immature to function adequately. Respiratory movements in the fetus do not require surfactant because the lungs are filled with amniotic fluid, and the fetus receives oxygen from the maternal blood through the placenta. Because of low lung compliance, the affected newborn infant can inspire only by the most strenuous efforts, which may ultimately cause complete exhaustion, inability to breathe, lung collapse, and death. Before the development of newer treatments over the past 30 years, almost half of infants with this condition died. Current therapy includes assisted breathing with a mechanical ventilator and the administration of natural or synthetic surfactant given through the infant's trachea. These improved methods of treatment have markedly reduced mortality, and most infants treated adequately now survive.

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 is inversely proportional to the resistance to flow of the airways (see equation 13–2). 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 radius of the tube—airway resistance is inversely proportional to the fourth power of the airway radii.

TABLE 13.3 Some Important Facts About Pulmonary Surfactant

Pulmonary surfactant is a mixture of phospholipids and protein.
It is secreted by type II alveolar cells.
It lowers the surface tension of the water layer at the alveolar surface, which increases lung compliance, thereby making it easier for the lungs to expand.
Its effect is greater in smaller alveoli, thereby reducing the surface tension of small alveoli below that of larger alveoli. This stabilizes the alveoli.
A deep breath increases its secretion by stretching the type II cells. Its concentration decreases when breaths are small.
Production in the fetal lung occurs in late gestation and is stimulated by the increase in cortisol (glucocorticoid) secretion that occurs then.

Airway resistance to airflow is normally so small that very small pressure differences produce large volumes of airflow. As we have seen in Figure 13.13, the average atmosphere-to-alveoli pressure difference during a normal breath when at rest is only about 1 mmHg; yet approximately 500 mL of air is moved by this tiny difference.

Physical, neural, and chemical factors affect airway radii and therefore resistance. 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 transpulmonary pressure increases during inspiration (see Figure 13.13), airway radius becomes larger and airway resistance lower 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; in turn, they help pull the airways open even more than between breaths. This is termed **lateral traction.** Both transpulmonary pressure and lateral traction act in the same direction, decreasing airway resistance during inspiration.

Such physical factors also explain why the airways become narrower and airway resistance increases during a forced expiration. The increase in intrapleural pressure compresses the small conducting airways and decreases their radii. Therefore, because of increased airway resistance, there is a limit to how much one can increase the airflow rate during a forced expiration no matter how intense the effort. The harder one pushes, the greater the compression of the airways, further limiting expiratory airflow.

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 by an effect on beta-adrenergic receptors, whereas the leukotrienes, members of the eicosanoid family produced in the lungs during inflammation, contract the muscle.

Why are we concerned with all the physical and chemical factors that *can* influence airway resistance when airway resistance is normally so low that it poses no impediment to airflow? The reason is that, under abnormal circumstances, changes in these factors may cause significant increases in airway resistance. Asthma and chronic obstructive pulmonary disease provide important examples, as we see next.

Asthma

Asthma is a disease characterized by intermittent episodes 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, viral infections, and sensitivity to environmental factors. The underlying inflammation makes the airway smooth muscles hyperresponsive and causes them to contract strongly in response to such things as exercise (especially in cold, dry air), tobacco smoke, environmental pollutants, viruses, allergens, normally released bronchoconstrictor chemicals, and a variety of other potential triggers. In fact, the incidence of asthma is increasing in the United States, possibly due in part to environmental pollution.

The first aim of therapy for asthma is to reduce the chronic inflammation and airway hyperresponsiveness with ***anti-inflammatory drugs,*** particularly leukotriene inhibitors and inhaled glucocorticoids. The second aim is to overcome acute excessive airway smooth muscle contraction with ***bronchodilator drugs,*** which relax the airways. The latter drugs work on the airways either by relaxing airway smooth muscle or by blocking the actions of bronchoconstrictors. For example, one class of bronchodilator drugs mimics the normal action of epinephrine on beta-2 (β_2) adrenergic receptors. Another class of inhaled drugs blocks muscarinic cholinergic receptors, which have been implicated in bronchoconstriction.

Chronic Obstructive Pulmonary Disease

The term ***chronic obstructive pulmonary disease*** (***COPD***) refers to emphysema, chronic bronchitis, or 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.

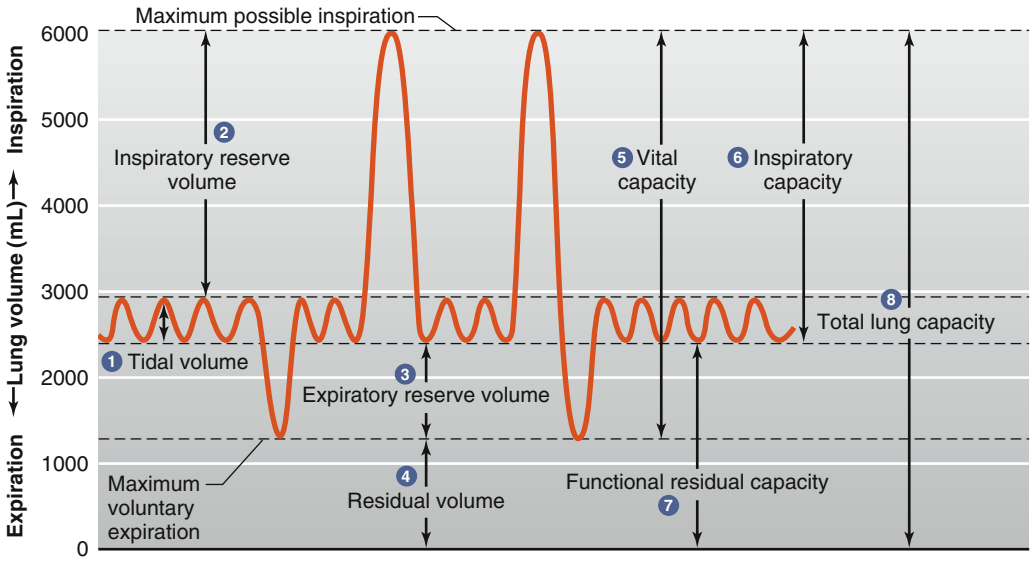
Emphysema is discussed later in this chapter; suffice it to say here that the cause of obstruction in this disease is damage to and collapse of the smaller airways.

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. Bronchitis may also be acute—for example, in response to viral infections such as those that cause upper respiratory infections. In such cases, the coughing and excess sputum and phlegm production associated with acute bronchitis typically resolve within 2 to 3 weeks.

Lung Volumes and Capacities

Normally, the volume of air entering the lungs during a single inspiration—the **tidal volume** (V_t)—is approximately equal to the volume leaving on the subsequent expiration. The tidal volume during normal quiet breathing—the resting tidal volume—is approximately 500 mL depending on body size. As illustrated in **Figure 13.18**, the maximal amount of air that can be increased above this value during deepest inspiration—the **inspiratory reserve volume** (**IRV**)—is about 3000 mL—that is, six times greater than resting tidal volume.

After expiration of a resting tidal volume, the lungs still contain a large volume of air. As described earlier, this is the resting position of the lungs and chest wall when there is no contraction of the respiratory muscles; this amount of air—the **functional residual capacity** (**FRC**)—averages about 2400 mL. 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; 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—the **expiratory reserve volume** (**ERV**)—is about 1200 mL. Even after a maximal active expiration, approximately 1200 mL of air still remains in the lungs—the **residual volume** (**RV**). Therefore, the lungs are never completely emptied of air.



Respiratory Volumes and Capacities for an Average Young Adult Male		
Measurement	Typical Value*	Definition
Respiratory Volumes		
1 Tidal volume (TV)	500 mL	Amount of air inhaled or exhaled in one breath
2 Inspiratory reserve volume (IRV)	3000 mL	Amount of air in excess of tidal inspiration that can be inhaled with maximum effort
3 Expiratory reserve volume (ERV)	1200 mL	Amount of air in excess of tidal expiration that can be exhaled with maximum effort
4 Residual volume (RV)	1200 mL	Amount of air remaining in the lungs after maximum expiration; keeps alveoli inflated between breaths and mixes with fresh air on next inspiration
Respiratory Capacities		
5 Vital capacity (VC)	4700 mL	Amount of air that can be exhaled with maximum effort after maximum inspiration (ERV + TV + IRV); used to assess strength of thoracic muscles as well as pulmonary function
6 Inspiratory capacity (IC)	3500 mL	Maximum amount of air that can be inhaled after a normal tidal expiration (TV + IRV)
7 Functional residual capacity (FRC)	2400 mL	Amount of air remaining in the lungs after a normal tidal expiration (RV + ERV)
8 Total lung capacity (TLC)	5900 mL	Maximum amount of air the lungs can contain (RV + VC)
*Typical value at rest		

Figure 13.18 Lung volumes and capacities recorded on a spirometer, an apparatus for measuring inspired and expired volumes. When the subject inspires, the pen moves up; with expiration, it moves down. The capacities are the sums of two or more lung volumes. The lung volumes are the four distinct components of total lung capacity. Note that residual volume, total lung capacity, and functional residual capacity cannot be measured with a spirometer.

The **vital capacity** (**VC**) is the maximal volume of air a person can expire after a maximal inspiration. Under these conditions, the person is expiring both the resting tidal volume and the inspiratory reserve volume just inspired, plus the expiratory reserve volume (see Figure 13.18). In other words, the vital capacity is the sum of these three volumes and is an important measurement when assessing pulmonary function.

A variant on this measurement is the ***forced expiratory volume in 1 sec*** (***FEV_1***), 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 sec. Healthy individuals can expire at least 80% of the vital capacity in 1 sec.

Measurement of vital capacity and FEV_1 are useful diagnostically and are known as ***pulmonary function tests.*** For example, people with ***obstructive lung diseases*** (increased airway resistance as in asthma) typically have an FEV_1 that is less than 80% 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 typically characterized by a reduced vital capacity but a normal ratio of FEV_1 to vital capacity.

Alveolar Ventilation

The total ventilation per minute—the **minute ventilation** ($\dot{V}_E$)—is equal to the tidal volume multiplied by the respiratory rate as shown in equation 13-6. (The dot above the letter V indicates per minute.)

$$\underset{(\text{mL/min})}{\text{Minute ventilation}} = \underset{(\text{mL/breath})}{\text{Tidal volume}} \times \underset{(\text{breaths/min})}{\text{Respiratory rate}} \quad \textbf{(13–6)}$$

$$\dot{V}_E = V_t \cdot f$$

For example, at rest, a typical healthy adult moves approximately 500 mL of air in and out of the lungs with each breath and takes 12 breaths each minute. The minute ventilation is therefore

500 mL/breath × 12 breaths/minute = 6000 mL of air per minute. However, because of dead space, not all this air is available for exchange with the blood, as we see next.

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 of 500 mL. The 500 mL of air is forced out of the alveoli and through the airways. Approximately 350 mL of this alveolar air is exhaled at the nose or mouth, but approximately 150 mL remains in the airways at the end of expiration. During the next inspiration (**Figure 13.19**), 500 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. Therefore, only 350 mL of new atmospheric air enters the alveoli during the inspiration. The end result is that 150 mL of the 500 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 called the **anatomical dead space** (V_D).

The volume of *fresh* air entering the alveoli during each inspiration equals the tidal volume *minus* the volume of air in the anatomical dead space. For the previous example,

Tidal volume (V_t) = 500 mL

Anatomical dead space (V_D) = 150 mL

Fresh air entering alveoli in one inspiration (V_A) =
500 mL − 150 mL = 350 mL

The total volume of fresh air entering the alveoli per minute is called the **alveolar ventilation** ($\dot{V}_A$)**:**

$$\begin{array}{l}\text{Alveolar} \\ \text{ventilation} \\ \text{(mL/min)}\end{array} = \left(\begin{array}{c}\text{Tidal} \\ \text{volume} \\ \text{(mL/breath)}\end{array} - \begin{array}{c}\text{Dead} \\ \text{space} \\ \text{(mL/breath)}\end{array}\right) \times \begin{array}{c}\text{Respiratory} \\ \text{rate} \\ \text{(breaths/min)}\end{array}$$

$$\dot{V}_A = (V_t - V_D) \cdot f \qquad \textbf{(13–7)}$$

Alveolar ventilation, rather than minute ventilation, is the important factor in the effectiveness of gas exchange. This generalization is demonstrated by the data in **Table 13.4**. 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 anatomical-dead-space ventilation from the minute ventilation, we find marked differences in alveolar ventilation. Subject A has no alveolar ventilation and would quickly become unconscious, whereas C has a considerably greater alveolar ventilation than B, who is breathing normally.

Another important generalization drawn from this example is that increased *depth* of breathing is far more effective in increasing alveolar ventilation than 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 percentage 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 increase in ventilation, such as exercise, reflexively call forth a relatively greater increase in breathing depth than in breathing rate.

The anatomical 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 may, for various reasons, have little or no blood supply. This volume of air is known as **alveolar dead space.** It is quite small in healthy persons but may be very large in persons with lung disease. As we shall see, local mechanisms that match air and blood flows minimize the alveolar dead space. The sum of the anatomical and alveolar dead spaces is known as the **physiological dead space.** This is also known as wasted ventilation because it is air that is inspired but does not participate in gas exchange with blood flowing through the lungs.

13.3 Exchange of Gases in Alveoli and Tissues

We have now completed the 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

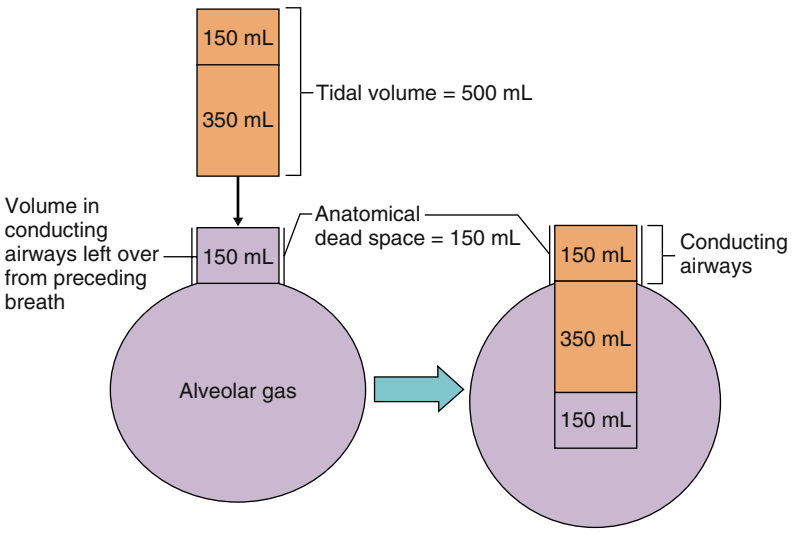


Figure 13.19 Effects of anatomical dead space on alveolar ventilation. Anatomical dead space is the volume of the conducting airways. Of a 500 mL tidal volume breath, 350 mL enters the airway involved in gas exchange. The remaining 150 mL remains in the conducting airways and does not participate in gas exchange.

PHYSIOLOGICAL INQUIRY

- What would be the effect of breathing through a plastic tube with a length of 20 cm and diameter of 4 cm? (*Hint:* Use the formula for the volume of a perfect cylinder.)

Answer can be found at end of chapter.

TABLE 13.4 Effect of Breathing Patterns on Alveolar Ventilation

Subject	Tidal Volume (mL/breath)	×	Frequency (breaths/min)	=	Minute Ventilation (mL/min)	Anatomical-Dead-Space Ventilation (mL/min)	Alveolar Ventilation (mL/min)
A	150		40		6000	150 × 40 = 6000	0
B	500		12		6000	150 × 12 = 1800	4200
C	1000		6		6000	150 × 6 = 900	5100

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, but 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 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 the same as the rate at which carbon dioxide leaves the blood in the lungs and is expired.

The amount of oxygen the cells consume and the amount of carbon dioxide they produce, however, are usually not identical. The balance depends primarily upon which nutrients are used for energy, because the enzymatic pathways for metabolizing carbohydrates, fats, and proteins generate different amounts of CO_2. The ratio of CO_2 produced to O_2 consumed is known as the **respiratory quotient** (**RQ**). The RQ is 1 for carbohydrate, 0.7 for fat, and 0.8 for protein. On a mixed diet, the RQ is approximately 0.8; that is, 8 molecules of CO_2 are produced for every 10 molecules of O_2 consumed.

Figure 13.20 presents typical exchange values during 1 min for a person at rest with an RQ of 0.8, assuming a cellular oxygen consumption of 250 mL/min, a carbon dioxide production of 200 mL/min, an alveolar ventilation of 4000 mL/min (4 L/min), and a cardiac output of 5000 mL/min (5 L/min).

Because only 21% of the atmospheric air is oxygen, the total oxygen entering the alveoli per min in our illustration is 21% 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 side of the heart and is pumped by the left ventricle through the aorta, arteries, and arterioles into the tissue capillaries, where 250 mL of oxygen leaves the blood per minute for cells to take up and utilize. Therefore, the quantities of oxygen added to the blood in the lungs and removed in the tissues are the same.

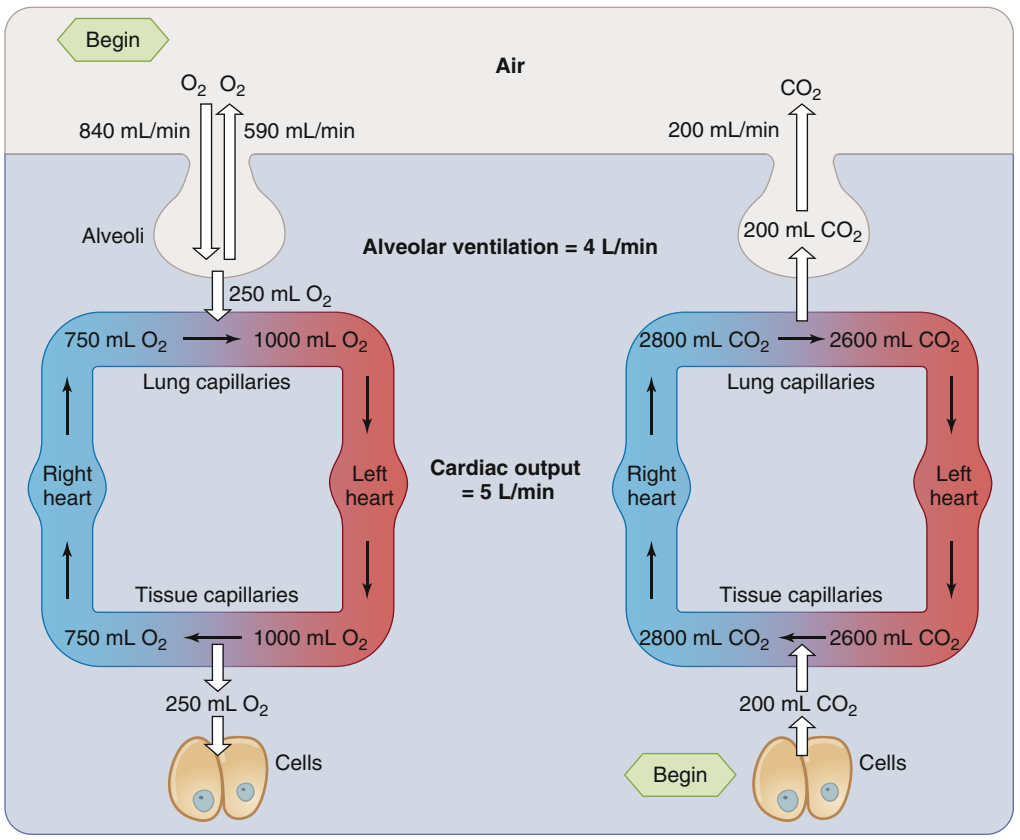


Figure 13.20 Summary of typical oxygen and carbon dioxide exchanges between atmosphere, lungs, blood, and tissues *during 1 min* in a resting individual. Note that the values in this figure for oxygen and carbon dioxide in blood are *not* the values per liter of blood but, rather, the amounts transported *per minute* in the cardiac output (5 L in this example). The volume of oxygen in 1 L of arterial blood is 200 mL O_2/L of blood—that is, 1000 mL O_2/5 L of blood.

PHYSIOLOGICAL INQUIRY

- How does this figure illustrate the general principle of physiology described in Chapter 1 that physiological processes require the transfer and balance of matter and energy?

Answer can be found at end of chapter.

The story reads in reverse for carbon dioxide. A significant amount of carbon dioxide already exists in systemic arterial blood; the cells add an additional 200 mL per minute, as blood flows through tissue capillaries. This 200 mL leaves the blood each minute 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 collide and 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 temperature (because heat increases the speed at which molecules move) and the concentration of the gas—that is, the number of molecules per unit volume.

As **Dalton's law** states, in a mixture of gases, the pressure each gas exerts is independent of the pressure the others exert. This is because gas molecules are normally so far apart that they do not affect each other. Each gas in a mixture behaves as though no other gases are present, so 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 expressed as P_{O_2}. 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. An appreciation of the importance of Dalton's law is another example of the general principle of physiology that physiological processes are dictated by the laws of chemistry and physics.

Atmospheric air consists of approximately 79% nitrogen and approximately 21% oxygen, with very small quantities of water vapor, carbon dioxide, and inert gases. The sum of the partial pressures of all these gases is called atmospheric pressure, or barometric pressure. It varies in different parts of the world as a result of local weather conditions and gravitational differences due to altitude; at sea level, it is 760 mmHg. Because 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 P_{O_2} of atmospheric air at sea level 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. Another physical law, called **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. The number of molecules striking the surface is directly proportional to the P_{O_2} of the gas phase, so 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 then 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, a net diffusion of gas molecules will occur out of the liquid into the gas phase until the partial pressures in the two phases become equal. A familiar example of this is when you first open a carbonated beverage and observe the bubbles of carbon dioxide coming out of solution (from the liquid to the gas phase).

The exchanges *between* gas and liquid phases described in the preceding 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.

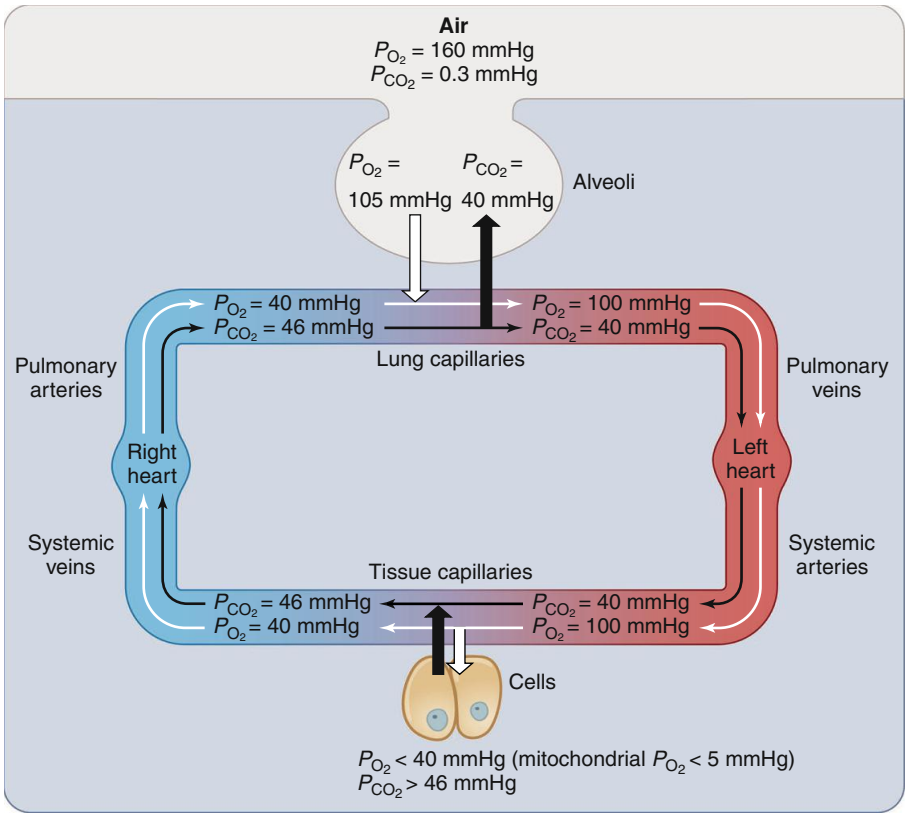
Why must the diffusion of gases into or within liquids be presented in terms of partial pressures rather than "concentrations," the values used to deal with the diffusion of all other solutes? The reason is that the concentration of a gas in a liquid is proportional not only to the partial pressure of the gas but also to the solubility of the gas in the liquid. The more soluble the gas, the greater its concentration will be at any given partial pressure. 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 for a resting person at sea level appear in **Figure 13.21**. We start our discussion with the alveolar gas pressures because their values set those of systemic arterial blood. This fact cannot be emphasized too strongly: The alveolar P_{O_2} and P_{CO_2} determine the systemic arterial P_{O_2} and P_{CO_2}. So, what determines alveolar gas pressures?

Alveolar Gas Pressures

Typical alveolar gas pressures are $P_{O_2} = 105$ mmHg and $P_{CO_2} = 40$ mmHg. (*Note:* 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 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, the latter value so low that we will simply treat it as 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 equations exist for calculating the alveolar gas pressures from



AP|R **Figure 13.21** Partial pressures of carbon dioxide and oxygen in inspired air at sea level and in 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 through the lungs, the systemic arterial value is actually slightly less, but we have ignored this for the sake of clarity.

these variables, we will describe the interactions in a qualitative manner (**Table 13.5**). 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, such as would occur at high altitude, will decrease alveolar P_{O_2}. A decrease in alveolar ventilation will do the same thing (**Figure 13.22**) because less fresh air is entering the alveoli per unit time. Finally, an increase in the oxygen consumption in the cells during, for example, strenuous physical activity, results in a decrease in the oxygen content of the blood returning to the lungs compared to the resting state. This will increase the concentration gradient of oxygen from the lungs to the pulmonary capillaries resulting in an increase in oxygen diffusion. If alveolar ventilation does not change, this will 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 for use 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 factors that lower alveolar P_{O_2}; just reverse the direction of change of the three factors to see how to increase alveolar P_{O_2}.

The situation for alveolar 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 decrease the amount of carbon dioxide exhaled, thereby increasing the alveolar P_{CO_2} (see Figure 13.22). Increased production of carbon dioxide will also increase the alveolar P_{CO_2} because more carbon dioxide will be diffusing into 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 the changes to see how to decrease alveolar P_{CO_2}.

For simplicity, we assumed only one factor would 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, and alveolar P_{O_2} will not change.

This last example emphasizes that, at any particular atmospheric P_{O_2}, it is the *ratio* of oxygen consumption to 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 the ratio of carbon dioxide production to alveolar ventilation—the higher the ratio, the higher the alveolar P_{CO_2}.

TABLE 13.5 Effects of Various Conditions on Alveolar Gas Pressures

Condition	Alveolar P_{O_2}	Alveolar P_{CO_2}
Breathing air with low P_{O_2}	Decreases	No change*
↑ Alveolar ventilation and unchanged metabolism	Increases	Decreases
↓ Alveolar ventilation and unchanged metabolism	Decreases	Increases
↑ Metabolism and unchanged alveolar ventilation	Decreases	Increases
↓ Metabolism and unchanged alveolar ventilation	Increases	Decreases
Proportional increases in metabolism and alveolar ventilation	No change	No change

*Breathing air with low P_{O_2} has no direct effect on alveolar P_{CO_2}. However, as described later in the text, people in this situation will reflexively increase their ventilation, and that will lower P_{CO_2}.

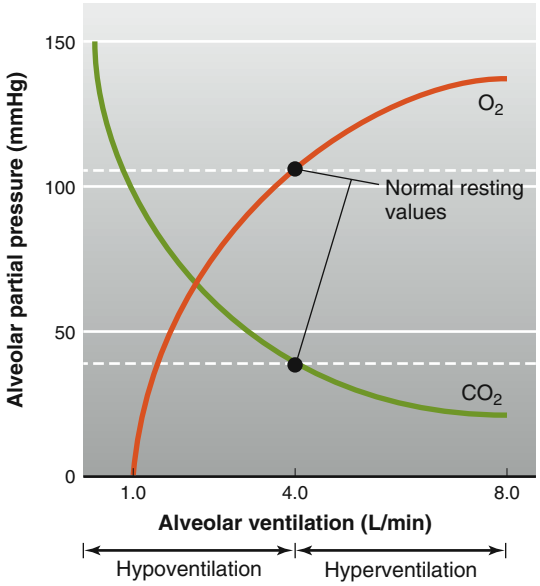


Figure 13.22 Effects of increasing or decreasing alveolar ventilation on alveolar partial pressures in a person having a constant metabolic rate (cellular oxygen consumption and carbon dioxide production). Note that alveolar P_{O_2} approaches zero when alveolar ventilation is about 1 L/min. At this point, all the oxygen entering the alveoli crosses into the blood, leaving virtually no oxygen in the alveoli.

We can now define two terms that denote the adequacy of ventilation—that is, the relationship between metabolism and alveolar ventilation. These definitions are stated 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 hypoventilating if the alveolar ventilation cannot keep pace with the carbon dioxide production. The result is that alveolar P_{CO_2} increases above the normal value. ***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.

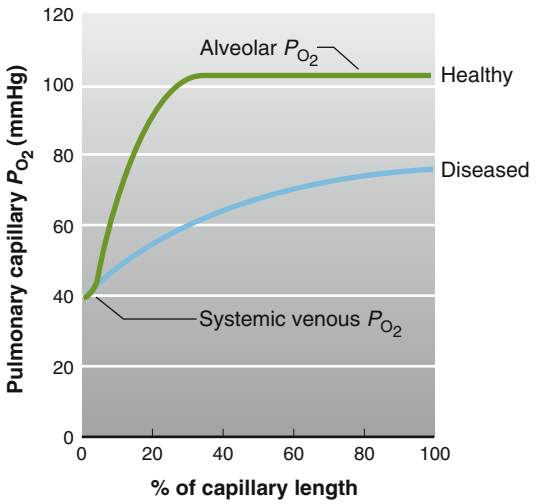
Note that "hyperventilation" is not synonymous with "increased ventilation." Hyperventilation represents increased ventilation *relative to metabolism*. For example, the increased ventilation that occurs during moderate exercise is not hyperventilation because, as we will see, the increase in production of carbon dioxide in this situation is proportional to the increased ventilation.

Gas Exchange Between Alveoli and Blood

The blood that enters the pulmonary capillaries is systemic venous blood pumped by the right ventricle to the lungs through the pulmonary arteries. Having come from the tissues, it has a relatively high P_{CO_2} (46 mmHg in a healthy person at rest) and a relatively low P_{O_2} (40 mmHg) (see Figure 13.21 and **Table 13.6**). 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. (For simplicity, we are ignoring the small diffusion barrier provided by the interstitial space.) As this diffusion occurs, the P_{O_2} in the pulmonary capillary blood increases and the P_{CO_2} decreases. The net diffusion of these gases ceases when the capillary partial pressures become equal to those in the alveoli.

In a healthy person, the rates at which oxygen and carbon dioxide diffuse are high enough and the blood flow through the capillaries slow enough that complete equilibrium is reached well before the blood reaches the end of the capillaries (**Figure 13.23**).

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.



AP|R **Figure 13.23** Equilibration of blood P_{O_2} with an alveolus with a P_{O_2} of 105 mmHg along the length of a pulmonary capillary. Note that in an abnormal alveolar-diffusion barrier (diseased), the blood is not fully oxygenated.

PHYSIOLOGICAL INQUIRY

- What is the effect of strenuous exercise on P_{O_2} at the end of a capillary in a normal region of the lung? In a region of the lung with diffusion limitation due to disease?

Answers can be found at end of chapter.

TABLE 13.6 Normal Gas Pressure

	Venous Blood	Arterial Blood	Alveoli	Atmosphere
P_{O_2}	40 mmHg	100 mmHg*	105 mmHg*	160 mmHg
P_{CO_2}	46 mmHg	40 mmHg	40 mmHg	0.3 mmHg

*The reason that the arterial P_{O_2} and alveolar P_{O_2} are not exactly the same is described later in this chapter.

The diffusion of gases between alveoli and capillaries may be impaired in a number of ways (see Figure 13.23), resulting in inadequate oxygen diffusion into the blood. For one thing, the total surface area of all of the alveoli in contact with pulmonary capillaries may be decreased. In ***pulmonary edema,*** some of the alveoli may become filled with fluid. (As described in Section C of Chapter 12, edema is the accumulation of fluid in tissues; in the alveoli, this increases the diffusion barrier for gases.) Diffusion may also be impaired if the alveolar walls become severely thickened with connective tissue (fibrotic), as, for example, in the disease called ***diffuse interstitial fibrosis.*** In this disease, fibrosis may arise from infection, autoimmune disease, hypersensitivity to inspired substances, exposure to toxic airborne chemicals, and many other causes. Typical symptoms of these types of diffusion diseases are shortness of breath and poor oxygenation of blood. Pure diffusion problems of these types are restricted to oxygen and usually do not affect the elimination of carbon dioxide, which diffuses more rapidly than oxygen.

Matching of Ventilation and Blood Flow in Alveoli

The major disease-induced cause of inadequate oxygen movement between alveoli and pulmonary capillary blood is not a problem with diffusion but, instead, is due to 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 correct proportion of alveolar airflow (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 decrease 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 healthy people to decrease the arterial P_{O_2} about 5 mmHg. One effect of upright posture is to increase the filling of blood vessels at the bottom of the lung due to gravity, which contributes to a difference in blood-flow distribution in the lung. 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 about 5 mmHg less than that of average alveolar air (see Table 13.6).

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 (dead space or wasted ventilation) due to a blood clot, for example; or (2) there may be blood flowing through areas of lung that have no ventilation (this is termed a ***shunt***) due to collapsed alveoli, for example. However, the inequality need not be all-or-none to be significant.

Carbon dioxide elimination is also impaired by ventilation–perfusion inequality but not nearly to the same degree as oxygen uptake. Although the reasons for this are complex, small increases in arterial P_{CO_2} lead to increases in alveolar ventilation, which usually prevent further increases in arterial P_{CO_2}. Nevertheless, severe ventilation–perfusion inequalities in disease states can lead to an increase in arterial P_{CO_2}.

There are several local homeostatic responses within the lungs that minimize the mismatching of ventilation and blood flow and thereby maximize the efficiency of gas exchange (**Figure 13.24**). Probably the most important of these is a direct effect of low oxygen on pulmonary blood vessels. A decrease in ventilation within a group of alveoli—which might occur, for example, from a mucus plug blocking the small airways—leads to a decrease in alveolar P_{O_2} and the area around it, including the arterioles. A decrease in P_{O_2} in these alveoli and nearby arterioles leads to vasoconstriction, diverting blood flow away from the poorly ventilated area. This local adaptive effect, unique to the pulmonary arterial blood vessels, ensures that blood flow is directed away from diseased areas of the lung toward areas that are well ventilated. Another factor to improve the match between ventilation and perfusion can occur if there is a local decrease in blood flow within a lung region due to, for example, a small blood clot in a pulmonary arteriole. A local decrease in blood flow brings less systemic CO_2 to that area, resulting in a local decrease in P_{CO_2}. This causes local bronchoconstriction, which diverts airflow away to areas of the lung with better perfusion.

The net adaptive effects of vasoconstriction and bronchoconstriction are to (1) supply less blood flow to poorly ventilated areas, thus diverting blood flow to well-ventilated areas; and (2) redirect air away from diseased or damaged alveoli and toward healthy alveoli. These factors greatly improve the efficiency of pulmonary gas exchange, but they are not perfect even in the

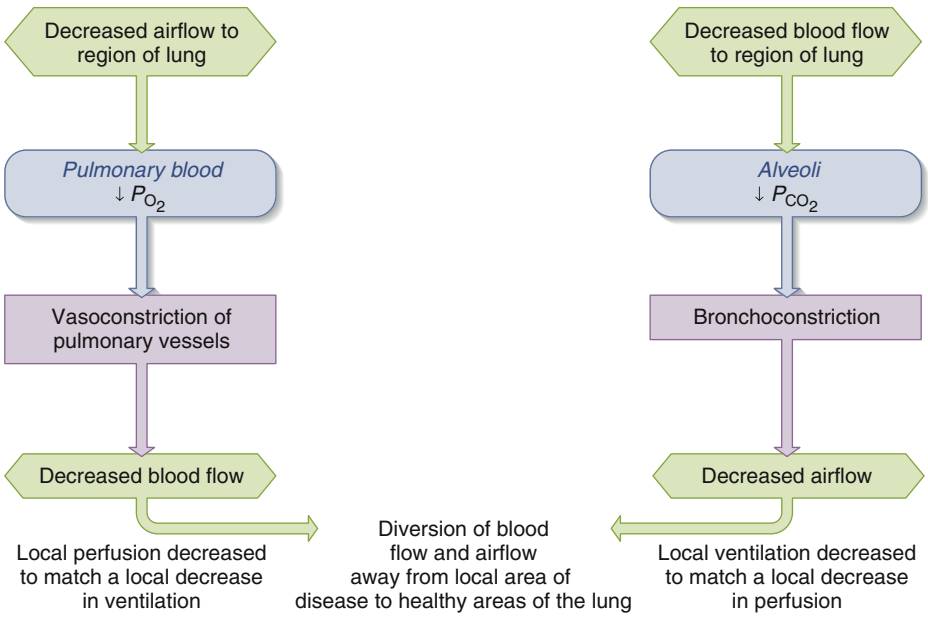


Figure 13.24 Local control of ventilation–perfusion matching.

healthy lung. There is always a small mismatch of ventilation and perfusion, which, as just described, leads to the normal alveolar-arterial O_2 gradient of about 5 mmHg.

Gas Exchange Between Tissues and Blood

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 the 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 13.21, intracellular P_{O_2} is lower and P_{CO_2} higher than in arterial blood. The lowest P_{O_2} of all—less than 5 mmHg—is in the mitochondria, the site of oxygen utilization. As a result, a net diffusion of oxygen occurs from blood into cells and, within the cells, into the mitochondria, and a net diffusion of carbon dioxide occurs 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 13.21 and Table 13.6.

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.

13.4 Transport of Oxygen in Blood

Table 13.7 summarizes the oxygen content of systemic arterial blood, referred to 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 cytosol 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 the solubility of oxygen in water is relatively low, 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% of the oxygen content in the liter—is transported in the erythrocytes, reversibly combined with hemoglobin.

TABLE 13.7 Oxygen Content of Systemic Arterial Blood at Sea Level

1 liter (L) arterial blood contains		
	3 mL	O_2 physically dissolved (1.5%)
	197 mL	O_2 bound to hemoglobin (98.5%)
Total:	200 mL	O_2
Cardiac output = 5 L/min		
O_2 carried to tissues/min	=	5 L/min × 200 mL O_2/L
	=	1000 mL O_2/min

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. The four polypeptides of a hemoglobin molecule are collectively called **globin.** Each of the four heme groups in a hemoglobin molecule (**Figure 13.25**) contains one atom of iron (Fe^{2+}), to which molecular oxygen binds. Because each iron atom shown in Figure 13.25 can bind one molecule of oxygen, a single hemoglobin molecule can bind four oxygen molecules (see Figure 2.19 for the quaternary structure of hemoglobin). However, for simplicity, the equation for the reaction between oxygen and hemoglobin is usually written in terms of a single polypeptide–heme subunit of a hemoglobin molecule:

$$O_2 + Hb \rightleftharpoons HbO_2 \qquad \textbf{(13–8)}$$

Therefore, hemoglobin can exist in one of two forms—**deoxyhemoglobin** (**Hb**) and **oxyhemoglobin** (**HbO_2**). 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:**

$$\text{Percent Hb saturation} = \frac{O_2 \text{ bound to Hb}}{\text{Maximal capacity of Hb to bind } O_2} \times 100 \qquad \textbf{(13–9)}$$

For example, if the amount of oxygen bound to hemoglobin is 40% of the maximal capacity, the sample is said to be 40% 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 the blood depends not only on the

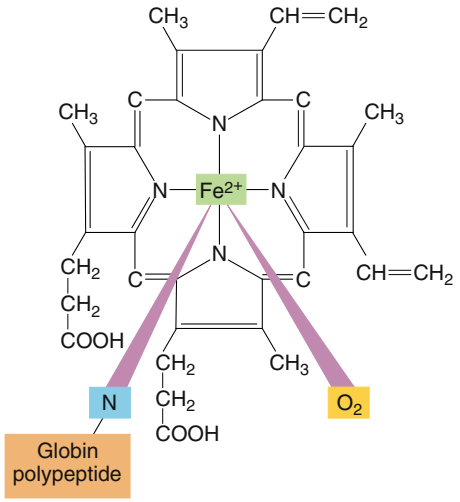


Figure 13.25 Heme in two dimensions. Oxygen binds to the iron atom (Fe^{2+}). Heme attaches to a polypeptide chain by a nitrogen atom to form one subunit of hemoglobin. Four of these subunits bind to each other to make a single hemoglobin molecule. See Figure 2.19, which shows the arrangements of polypeptide chains that make up the hemoglobin molecule.

percent saturation of hemoglobin but also on how much hemoglobin is in each liter of blood. A significant decrease in hemoglobin in the blood is called ***anemia.*** For example, if a person's blood contained only half as much hemoglobin per liter as normal, then at any given P_{O_2} and percent saturation, the oxygen content of the blood would be only half as much. The most common way in which the hemoglobin content of blood is decreased is due to a low hematocrit, for example, due to chronic blood loss and to certain dietary deficiencies resulting in inadequate production of erythrocytes in the bone marrow.

What Is the Effect of P_{O_2} on Hemoglobin Saturation?

Based on equation 13–8 and the law of mass action (see Chapter 3), it is evident that increasing the blood P_{O_2} should increase the combination of oxygen with hemoglobin. The quantitative relationship between these variables is shown in **Figure 13.26**, 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 sigmoid 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 3, and is a classic example of the general principle of physiology that physiological processes are dictated by the laws of chemistry and physics. 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 subunits, leading to a conformation change that leaves the remaining oxygen-binding sites more exposed. Therefore, the binding of one oxygen molecule to deoxyhemoglobin increases the affinity of the remaining sites on the same hemoglobin molecule, and so on.

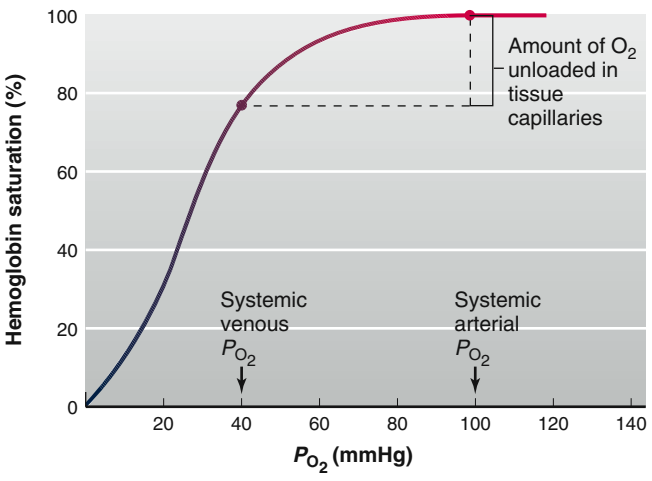


Figure 13.26 Oxygen–hemoglobin dissociation curve. This curve applies to blood at 37°C and a normal arterial H^+ concentration. At any given blood hemoglobin concentration, the *y*-axis could also have plotted oxygen content in milliliters of oxygen per liter of blood (normally about 200 mL/liter when hemoglobin is 100% saturated).

The shape of the oxygen–hemoglobin dissociation curve is extremely important in understanding oxygen exchange. 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, approximately 90% 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.

This plateau at higher P_{O_2} values has a number of important implications. In many situations, including at high altitude and with pulmonary disease, a moderate reduction occurs in alveolar and therefore arterial P_{O_2}. Even if the P_{O_2} decreased from the normal value of 100 to 60 mmHg, the total quantity of oxygen carried by hemoglobin would decrease by only 10% because hemoglobin saturation is still close to 90% at a P_{O_2} of 60 mmHg. The plateau provides an excellent safety factor so that even a moderate limitation of lung function still allows significant saturation of hemoglobin.

The plateau also explains why, in a healthy person at sea level, increasing the alveolar (and therefore the arterial) P_{O_2} either by hyperventilating or by breathing 100% oxygen does not appreciably increase the total content of oxygen in the blood. A small additional amount dissolves. 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 increased beyond this point. This applies only to healthy people at sea level. If a 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. Increasing the alveolar and thereby the arterial P_{O_2} would result in significantly more oxygen transport on hemoglobin.

The steep portion of the curve from 60 mmHg down to 20 mmHg is ideal for unloading oxygen in the tissues. That is, for a small decrease in P_{O_2} due to diffusion of oxygen from the blood to the cells, a large quantity of oxygen can be unloaded in the peripheral tissue capillaries.

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 is the major factor in determining the *total amount* of oxygen that will diffuse, as illustrated by a simple example (**Figure 13.27**). Two solutions separated by a semipermeable membrane contain equal quantities of oxygen. The gas pressures in both solutions are equal, and no net diffusion of oxygen occurs. Addition of hemoglobin to compartment B disturbs 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 has combined with hemoglobin.

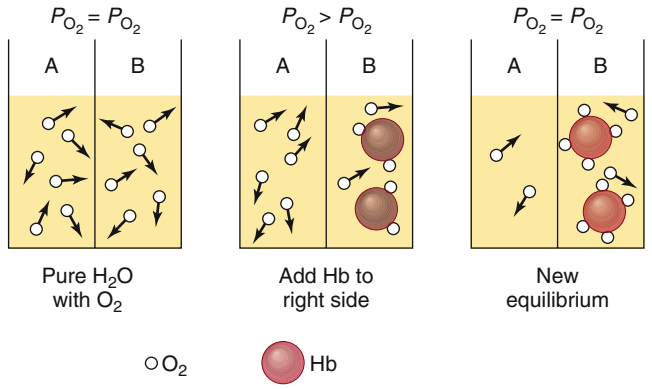


Figure 13.27 Effect of added hemoglobin on oxygen distribution between two compartments containing a fixed number of oxygen molecules and separated by a semipermeable membrane. At the new equilibrium, the P_{O_2} values are again equal to each other but lower than before the hemoglobin was added. However, the total oxygen—in other words, the oxygen dissolved plus that combined with hemoglobin—is now much higher on the right side of the membrane.

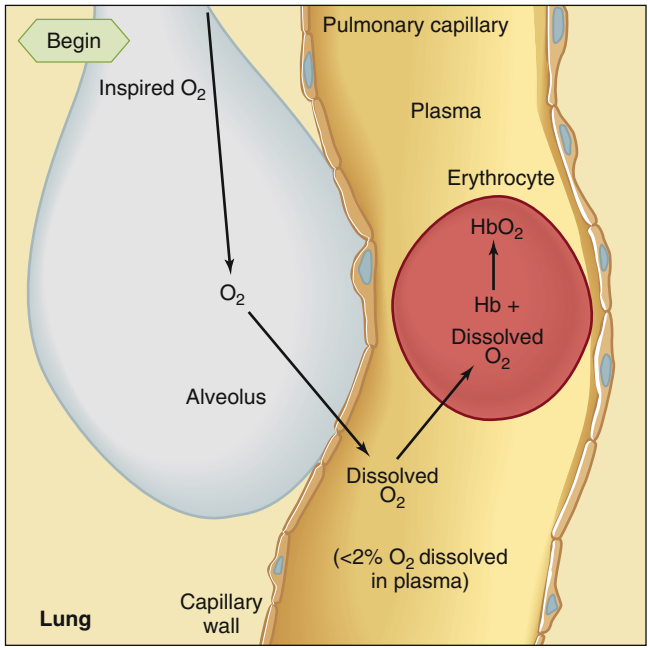
Let us now apply this analysis to capillaries of the lungs and tissues (**Figure 13.28**). The plasma and erythrocytes entering the lungs have a P_{O_2} of 40 mmHg. As we can see from Figure 13.26, hemoglobin saturation at this P_{O_2} is 75%. The alveolar P_{O_2}—105 mmHg—is higher than the blood P_{O_2} and so oxygen diffuses from the alveoli into the plasma. This increases plasma P_{O_2} and induces diffusion of oxygen into the erythrocytes, increasing erythrocyte P_{O_2} and causing increased combination of oxygen and hemoglobin. Most 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% saturated. This maintains the diffusion gradient of oxygen movement into the blood during the very large transfer of oxygen.

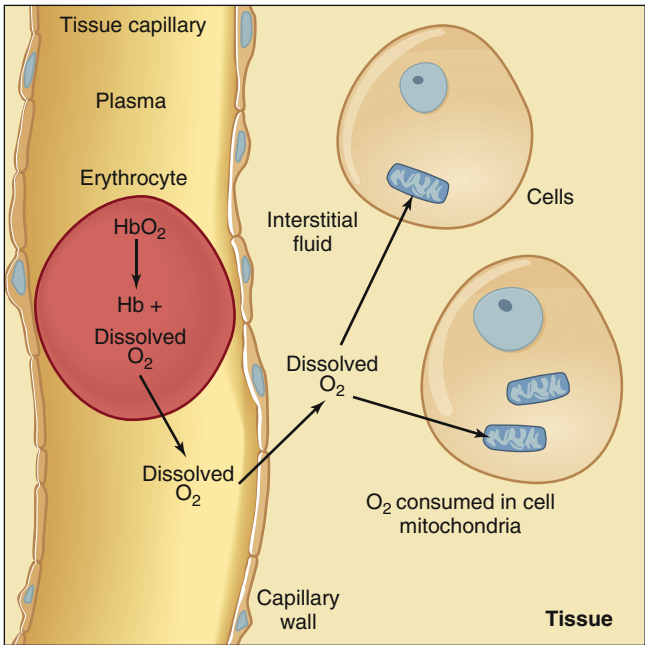
In the tissue capillaries, the process is reversed. Because the mitochondria of all cells are utilizing oxygen, the cellular P_{O_2} is less than the P_{O_2} of the surrounding interstitial fluid. Therefore, oxygen is continuously diffusing into the cells. This causes the interstitial fluid P_{O_2} to always be less than the P_{O_2} of the blood flowing through the tissue capillaries, so net diffusion of oxygen occurs from the plasma within the capillary into the interstitial fluid. As a result, plasma P_{O_2} becomes lower than erythrocyte P_{O_2}, and oxygen diffuses out of the erythrocyte into the plasma. The decrease in 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.

In most tissues under resting conditions, hemoglobin is still 75% saturated as the blood leaves the tissue capillaries. This fact underlies an important local mechanism by which cells can obtain more oxygen whenever they increase their activity. For example, an exercising muscle consumes more oxygen, thereby lowering its intracellular and interstitial P_{O_2}. This increases the blood-to-cell P_{O_2} gradient. As a result, the rate of oxygen diffusion from blood to cells increases. In turn, the resulting decrease in erythrocyte P_{O_2} causes additional dissociation of hemoglobin and oxygen. In this manner, the extraction of oxygen from blood in an exercising muscle is much greater than the usual 25%. In addition, an increased blood flow to the muscles, called active hyperemia (Chapter 12), also contributes greatly to the increased oxygen supply.

Effect of Carbon Monoxide on Oxygen Binding to Hemoglobin

Carbon monoxide is a colorless, odorless gas that is a product of the incomplete combustion of hydrocarbons, such as gasoline. It is a common cause of sickness and death due to poisoning, both intentional and accidental. Its most striking pathophysiological characteristic is its extremely high affinity—210 times that of oxygen—for the oxygen-binding sites in





AP|R **Figure 13.28** Oxygen movement in the lungs and tissues. Movement of inspired air into the alveoli is by bulk flow; all movements across membranes are by diffusion.

hemoglobin. For this reason, it reduces the amount of oxygen that combines with hemoglobin in pulmonary capillaries by competing for these sites. It also exerts a second deleterious effect: It alters the hemoglobin molecule shifting the oxygen–hemoglobin dissociation curve to the left, thereby decreasing the unloading of oxygen from hemoglobin in the tissues. As we will see later, the situation is worsened because persons suffering from carbon monoxide poisoning do not show any reflex increase in their ventilation.

Effects of CO_2 and Other Factors in the Blood and Different Isoforms on Hemoglobin Saturation

At any given P_{O_2}, other factors influence the degree of hemoglobin saturation. These include blood P_{CO_2}, H^+ concentration, temperature, the concentration of a substance produced by erythrocytes called **2,3-diphosphoglycerate** (**DPG**) (also known as bisphosphoglycerate [BPG]), and the presence of a special kind of hemoglobin usually only found in the fetal blood. As illustrated in **Figure 13.29**, an increase in DPG concentration, temperature, and acidity causes the dissociation curve to shift to the right. This means that at any given P_{O_2}, hemoglobin has less affinity for oxygen. In contrast, a decrease in DPG concentration, temperature, or acidity causes the dissociation curve to shift to the left, such 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 greater 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 increased because of the increased 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. Hemoglobin exposed to this increased blood P_{CO_2}, H^+ concentration, and temperature as it passes through the tissue capillaries has a decreased affinity for oxygen. 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 metabolically active a tissue, the greater its P_{CO_2}, H^+ concentration, and temperature will be. 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, then, is another local mechanism that increases oxygen delivery to tissues with increased metabolic activity.

What is the mechanism by which these factors influence the affinity of hemoglobin for oxygen? Carbon dioxide and H^+ do so by combining with the globin portion of hemoglobin and altering the conformation of the hemoglobin molecule. Therefore, these effects are a form of allosteric modulation (Chapter 3). Increased temperature also decreases hemoglobin's affinity for oxygen by altering its conformation.

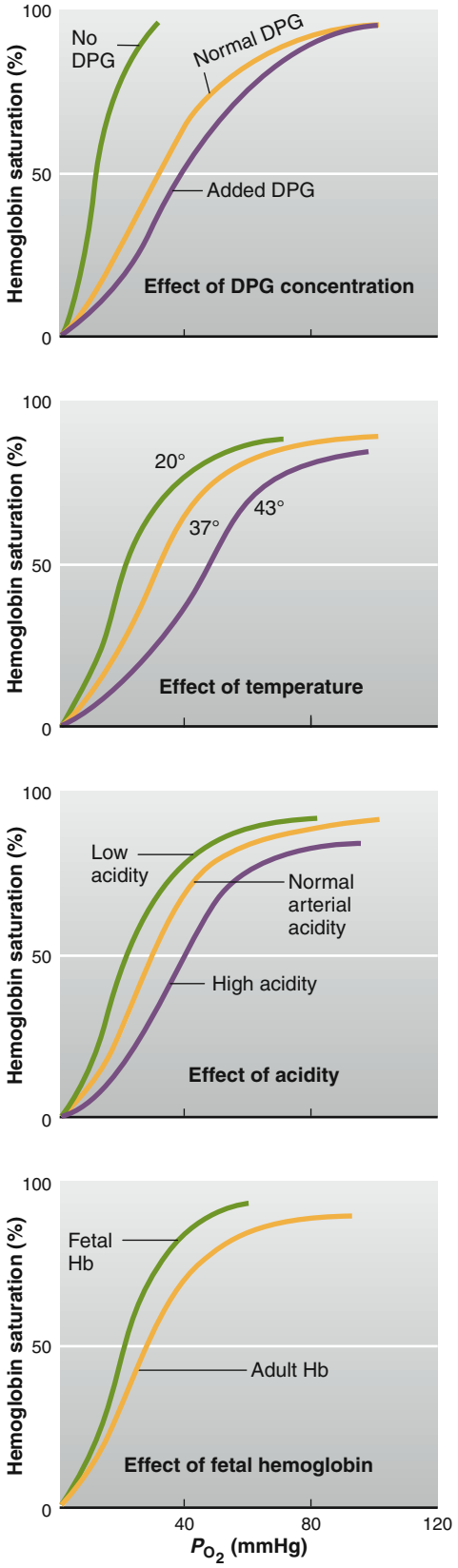


Figure 13.29 Effects of DPG concentration, temperature, acidity, and the presence of fetal hemoglobin on the relationship between P_{O_2} and hemoglobin saturation. The temperature of normal blood, of course, never diverges from 37°C as much as shown in the figure, but the principle is still the same when the changes are within the physiological range. High acidity and low acidity can be caused by high P_{CO_2} and low P_{CO_2}, respectively. Fetal hemoglobin has a higher affinity for oxygen than adult hemoglobin, allowing an adequate oxygen content from oxygen diffusion from the maternal to fetal blood in the placenta. Source: Adapted from Comroe, J. H., "Physiology of Respiration," Year Book, Chicago, 1965.

PHYSIOLOGICAL INQUIRY

- Researchers are developing blood substitutes to meet the demand for emergency transfusions. What would be the effect of artificial blood in which binding of O_2 is not altered by acidity?

Answer can be found at end of chapter.

DPG, which is produced during glycolysis, reversibly binds with hemoglobin, allosterically causing it to have a lower affinity for oxygen (see Figure 13.29). Erythrocytes have no mitochondria and, therefore, rely exclusively on glycolysis. Consequently, erythrocytes contain large quantities of DPG, which is present in only trace amounts in cells with mitochondria. The net result is that whenever DPG concentrations increase, 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. For example, the increase in DPG is important during exposure to high altitude when the P_{O_2} of the blood is decreased, because DPG increases the unloading of oxygen in the tissue capillaries.

Finally, the fetus has a unique form of hemoglobin called **fetal hemoglobin** (see Figure 13.29). Fetal hemoglobin contains subunits that are coded for by different genes than those that are expressed postnatally. These subunits alter the shape of the final protein and result in a hemoglobin molecule that has a higher affinity for oxygen than adult hemoglobin. That is, fetal hemoglobin binds considerably more oxygen than adult hemoglobin at any given P_{O_2}. This allows an increase in oxygen uptake across the placental diffusion barrier. Therefore, although fetal arterial P_{O_2} is much lower than that in the air-breathing newborn, fetal hemoglobin allows adequate oxygen uptake in the placenta to supply the developing fetus.

13.5 Transport of Carbon Dioxide in Blood

Carbon dioxide is a waste product that has toxicity in part because it generates H^+. Large changes in H^+ concentration, if not buffered, would lead to significant changes in pH, thus altering the tertiary structure of proteins, including enzymes. 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 13.30a**). Carbon dioxide is much more soluble in water than is oxygen, so blood carries more dissolved carbon dioxide than dissolved oxygen. Even so, only about 10% of the carbon dioxide entering the blood dissolves in the plasma and the cytosol of the erythrocytes. In order to transport all of the CO_2 produced in the tissues to the lung, much of the CO_2 in the blood must be carried in other forms.

Another 25% to 30% of the carbon dioxide molecules entering the blood react reversibly with the amino groups of hemoglobin to form **carbaminohemoglobin.** For simplicity, this reaction with hemoglobin is written as

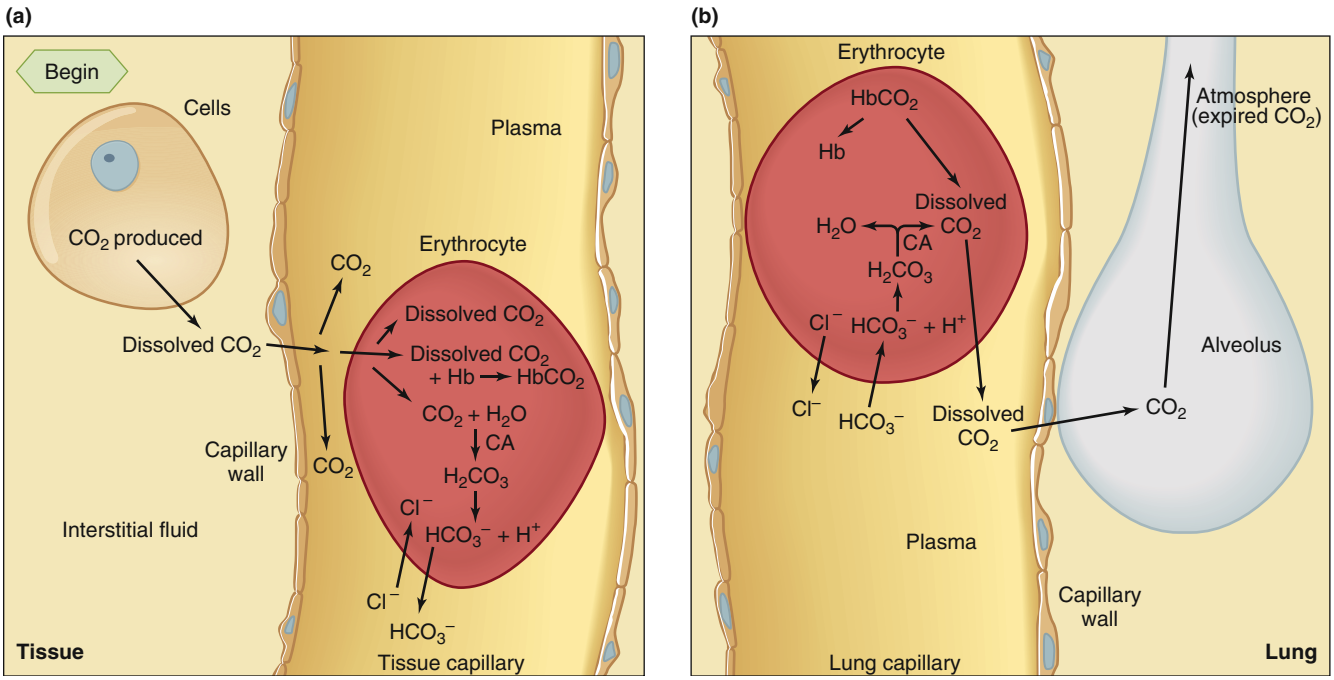
$$CO_2 + Hb \rightleftharpoons HbCO_2 \qquad \textbf{(13–10)}$$

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% to 65% of the carbon dioxide molecules entering the blood in the tissues is converted to HCO_3^-:

$$CO_2 + H_2O \underset{\text{carbonic anhydrase}}{\rightleftharpoons} \underset{\text{carbonic acid}}{H_2CO_3} \rightleftharpoons \underset{\text{bicarbonate}}{HCO_3^-} + H^+ \qquad \textbf{(13–11)}$$

The first reaction in equation 13–11 is rate limiting and is very slow unless catalyzed in both directions by the enzyme **carbonic anhydrase.** This enzyme is present in the erythrocytes but not in the plasma, so this reaction occurs mainly in the erythrocytes.



AP|R **Figure 13.30** Summary of CO_2 movement. Expiration of CO_2 is by bulk flow, whereas all movements of CO_2 across membranes are by diffusion. About two-thirds of the CO_2 entering the blood in the tissues ultimately is converted to HCO_3^- in the erythrocytes because carbonic anhydrase (CA) is located there, but most of the HCO_3^- then moves out of the erythrocytes into the plasma in exchange for Cl^- (the "chloride shift"). See Figure 13.31 for the fate of the H^+ generated in the erythrocytes.

In contrast, carbonic acid dissociates very rapidly into HCO_3^- and H^+ without any enzyme assistance. Once formed, most of the HCO_3^- moves out of the erythrocytes into the plasma via a transporter that exchanges one HCO_3^- for one chloride ion (this is called the "chloride shift," which maintains electroneutrality). HCO_3^- leaving the erythrocyte favors the balance of the reaction shown in equation 13–11 to the right.

The reactions shown in equation 13–11 also explain why, as mentioned earlier, the H^+ concentration in tissue capillary blood and systemic venous blood is higher than that in arterial blood and increases as metabolic activity increases. The fate of this H^+ 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, HCO_3^-, and carbon dioxide in carbaminohemoglobin to arrive at the **total-blood carbon dioxide,** which is measured as a component of routine blood chemistry testing.

The opposite events occur as systemic venous blood flows through the lung capillaries (**Figure 13.30b**). Because the blood P_{CO_2} is higher than alveolar P_{CO_2}, a net diffusion of CO_2 from blood into alveoli occurs. This loss of CO_2 from the blood decreases the blood P_{CO_2} and drives the reactions in equations 13–10 and 13–11 to the left. HCO_3^- and H^+ combine to produce H_2CO_3, which then dissociates to CO_2 and H_2O. Similarly, $HbCO_2$ generates Hb and free CO_2. Normally, as fast as CO_2 is generated from HCO_3^- and H^+ and from $HbCO_2$, it diffuses into the alveoli. In this manner, the CO_2 that was delivered into the blood in the tissues is now delivered into the alveoli, from where it is eliminated during expiration.

13.6 Transport of Hydrogen Ion Between Tissues and Lungs

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 HCO_3^- and H^+. What happens to this H^+?

Deoxyhemoglobin has a much greater affinity for H^+ than does oxyhemoglobin, so it binds (buffers) most of the H^+ (**Figure 13.31**). When deoxyhemoglobin binds H^+, it is abbreviated HbH.

$$HbO_2 + H^+ \rightleftharpoons HbH + O_2$$

In this manner, only a small amount of the H^+ generated in the blood remains free. This explains why venous blood (pH = 7.36) is only slightly more acidic than arterial blood (pH = 7.40).

As the venous blood passes through the lungs, this reaction is reversed. Deoxyhemoglobin becomes converted to oxyhemoglobin and, in the process, releases the H^+ it picked up in the tissues. The H^+ reacts with HCO_3^- to produce carbonic acid, which, under the influence of carbonic anhydrase, dissociates to form carbon dioxide and water. The carbon dioxide diffuses into the alveoli to be expired. Normally, all the H^+ that is generated in the tissue capillaries from the reaction of carbon dioxide and water recombines with HCO_3^- to form carbon dioxide and water in the pulmonary capillaries. Therefore, none of this H^+ appears in the *arterial* blood.

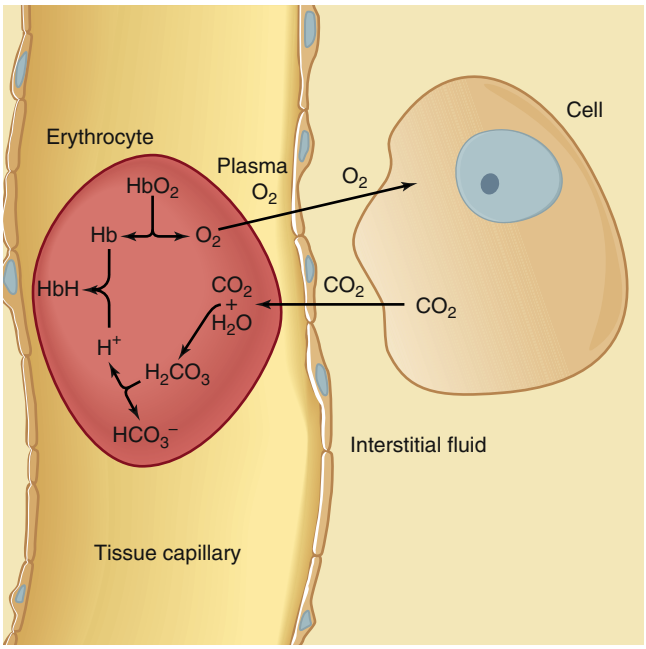


Figure 13.31 Binding of H^+ by hemoglobin as blood flows through tissue capillaries. This reaction is facilitated because deoxyhemoglobin, formed as oxygen dissociates from hemoglobin, has a greater affinity for H^+ than does oxyhemoglobin. For this reason, "Hb" and "HbH" are both abbreviations for deoxyhemoglobin. For simplicity, not shown is that H^+ binding to HbO_2 increases oxygen unloading.

What happens when a person is hypoventilating or has a lung disease that prevents normal elimination of carbon dioxide? Not only would arterial P_{CO_2} increase as a result, but so would arterial H^+ concentration. Increased arterial H^+ concentration due to carbon dioxide retention is termed ***respiratory acidosis.*** Conversely, hyperventilation would decrease arterial P_{CO_2} and H^+ concentration, producing ***respiratory alkalosis.***

The factors that influence the binding of CO_2 and O_2 by hemoglobin are summarized in **Table 13.8**.

13.7 Control of Respiration

The control of breathing at rest, altitude, and during and after exercise has intrigued physiologists for centuries. It is a wonderful example of several general principles of physiology, including how homeostasis is essential for health and survival, and how physiological functions are controlled by multiple regulatory systems, often working in opposition.

TABLE 13.8 Effects of Various Factors on Hemoglobin

The affinity of hemoglobin for oxygen is decreased by

- Increased H^+ concentration
- Increased P_{CO_2}
- Increased temperature
- Increased DPG concentration

The affinity of hemoglobin for both H^+ and CO_2 is decreased by increased P_{O_2}; that is, deoxyhemoglobin has a greater affinity for H^+ and CO_2 than does oxyhemoglobin.

Neural Generation of Rhythmic Breathing

The diaphragm and intercostal muscles are skeletal muscles and therefore do not contract unless motor neurons stimulate them to do so. Therefore, breathing depends entirely upon cyclical respiratory muscle excitation of the diaphragm and the intercostal muscles by their motor neurons. Destruction of these neurons or a disconnection between their origin in the brainstem and the respiratory muscles 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 spinal motor neurons to inspiratory muscles like the diaphragm. Then the action potentials cease, the inspiratory muscles relax, and expiration occurs as the elastic lungs recoil. In situations such as exercise when the contraction of expiratory muscles facilitates expiration, the neurons to these muscles, which were not active during inspiration, begin firing during expiration.

By what mechanism are impulses in the neurons innervating the respiratory muscles alternately increased and decreased? Control of this neural activity resides primarily in neurons in the medulla oblongata, the same area of the brain that contains the major cardiovascular control centers. (For the rest of this chapter, we will refer to the medulla oblongata simply as the medulla.) There are two main anatomical components of the **medullary respiratory center** (Figure 13.32). The neurons of the **dorsal**

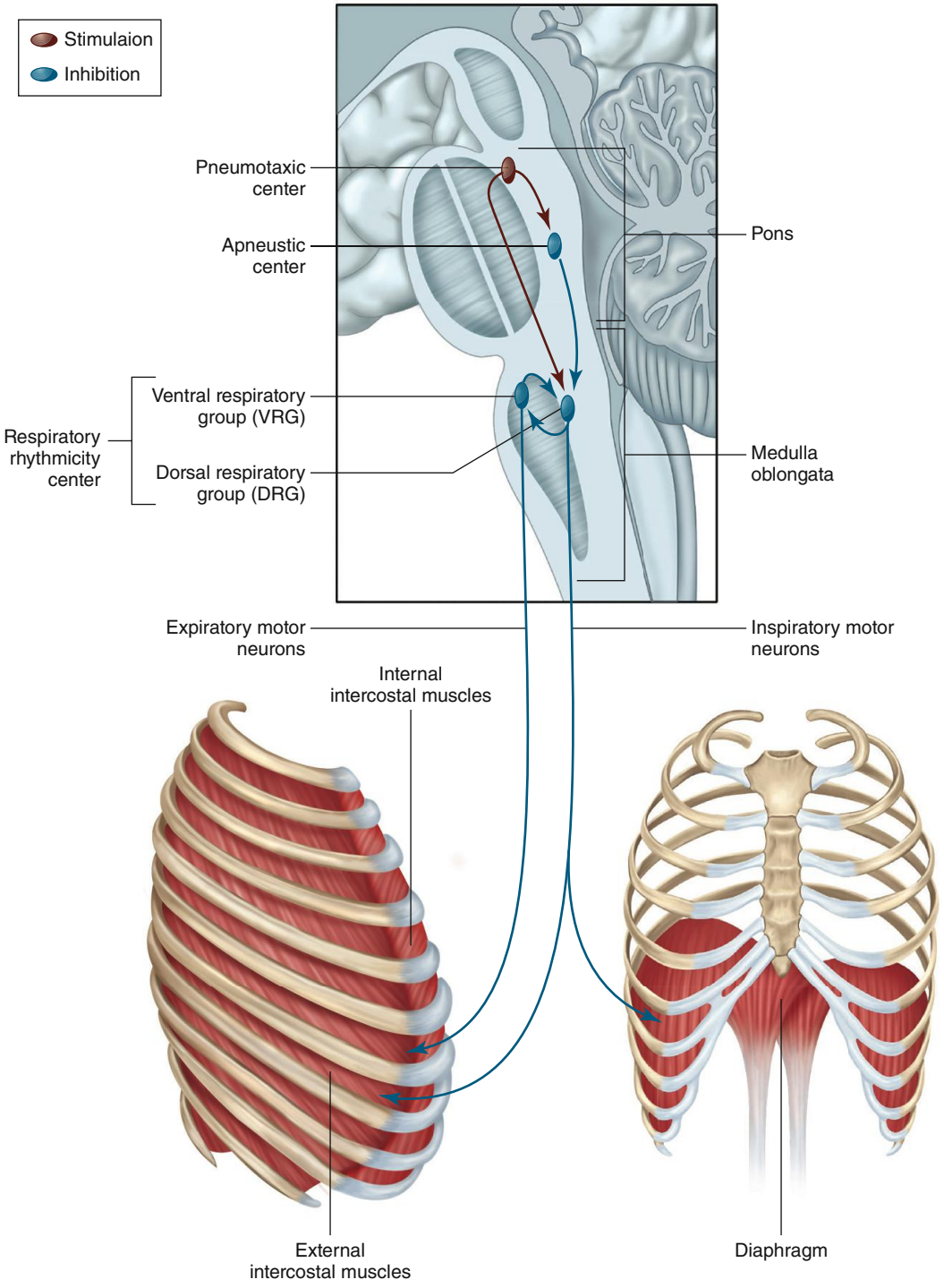


Figure 13.32 A simplified depiction of the brainstem centers that control respiratory rate and depth. Inspiratory motor neurons are driven primarily by the DRG while expiratory motor neurons (active mostly during forced expiration and strenuous exercise) are driven primarily by the VRG. Note that DRG and VRG innervate each other allowing phasic inspiration and expiration. The centers in the upper pons are primarily responsible for fine-tuning respiratory control.

respiratory group (**DRG**) primarily fire during inspiration and have input to the spinal motor neurons that activate respiratory muscles involved in inspiration—the diaphragm and inspiratory intercostal muscles. The primary inspiratory muscle at rest is the diaphragm, which is innervated by the phrenic nerves. The **ventral respiratory group** (**VRG**) is the other main complex of neurons in the medullary respiratory center. The **respiratory rhythm generator** is located in the **pre-Bötzinger complex** of neurons in the upper part of the VRG. This rhythm generator appears to be composed of pacemaker cells and a complex neural network that, acting together, set the basal respiratory rate.

The VRG contains expiratory neurons that appear to be most important when large increases in ventilation are required (for example, during strenuous physical activity). During active expiration, motor neurons activated by the expiratory output from the VRG cause the expiratory muscles to contract. This helps to rapidly move air out of the lungs rather than depending only on the passive expiration that occurs during quiet breathing.

During quiet breathing, the respiratory rhythm generator activates inspiratory neurons in the DRG that depolarize the inspiratory spinal motor neurons, causing the inspiratory muscles to contract. When the inspiratory motor neurons stop firing, the inspiratory muscles relax, allowing passive expiration. During increases in breathing, the inspiratory and expiratory motor neurons and muscles are not activated at the same time but, rather, alternate in function.

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 fine-tunes 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 (see Figure 13.32). The pneumotaxic center, also known as the **pontine respiratory group,** helps to smooth the transition between inspiration and expiration. The respiratory nerves in the medulla and pons also receive synaptic input from higher centers of the brain such that the pattern of respiration is controlled voluntarily during speaking, diving, and even with emotions and pain.

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 activity of the medullary inspiratory neurons. This is called the **Hering–Breuer reflex.** This allows feedback from the lungs to terminate inspiration by inhibiting inspiratory nerves in the DRG. However, this reflex is important in setting respiratory rhythm only under conditions of very large tidal volumes, as in strenuous exercise. The arterial chemoreceptors described next also have important input to the respiratory control centers such that the rate and depth of respiration can be increased when the levels of arterial oxygen decrease, or when arterial carbon dioxide or H^+ concentration increases.

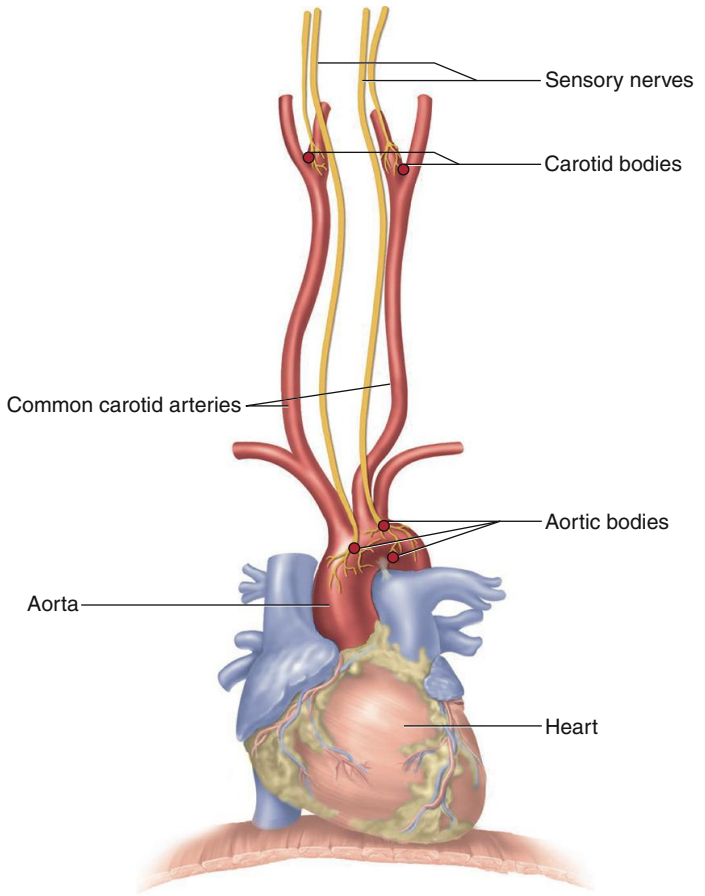
A final point about the medullary inspiratory neurons is that they are quite sensitive to inhibition by drugs such as barbiturates and morphine. Death from an overdose of these drugs is often due directly to a cessation of breathing.

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 will 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 come from peripheral (arterial) 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 13.33**) are called the **carotid bodies** and **aortic bodies,** respectively. In both locations, they are quite close to, but distinct from, the arterial baroreceptors



AP|R **Figure 13.33** Location of the carotid and aortic bodies. Note that each carotid body is quite close to a carotid sinus, the major arterial baroreceptor (see Figure 12.56). Both right and left common carotid bifurcations contain a carotid sinus and a carotid body.

PHYSIOLOGICAL INQUIRY

- Several decades ago, removal of the carotid bodies was tried as a treatment for asthma. It was thought that it would reduce shortness of breath and airway hyperreactivity. What would be the effect of bilateral carotid body removal on someone taking a trip to the top of a mountain (an altitude of 3000 meters)? (*Hint:* Look ahead to Table 13.10.)

Answer can be found at end of chapter.

TABLE 13.9 Major Stimuli for the Central and Peripheral Chemoreceptors

Peripheral chemoreceptors—carotid bodies and aortic bodies—respond to changes in the arterial blood. They are stimulated by

- Significantly decreased P_{O_2} (hypoxia)
- Increased H^+ concentration (metabolic acidosis)
- Increased P_{CO_2} (respiratory acidosis)

Central chemoreceptors—located in the medulla oblongata—respond to changes in the *brain extracellular fluid*. They are stimulated by increased P_{CO_2} via associated changes in H^+ concentration (see equation 13–11).

and are in intimate contact with the arterial blood. The carotid bodies, in particular, are strategically located to monitor oxygen supply to the brain. The peripheral chemoreceptors are composed of specialized receptor cells stimulated mainly by a decrease in the arterial P_{O_2} and an increase in the arterial H^+ concentration (**Table 13.9**). 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 carotid body input is the predominant peripheral chemoreceptor involved in the control of respiration.

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 will see later, such changes result mainly from changes in blood P_{CO_2}.

***Control by* P_{O_2}** **Figure 13.34** illustrates an experiment in which healthy subjects breathe low-P_{O_2} gas mixtures for several minutes. The experiment is performed 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 concentration of the inspired air is reduced enough to lower arterial P_{O_2} to 60 mmHg. Beyond this point, any further decrease in arterial P_{O_2} causes a marked reflex increase in ventilation.

This reflex is mediated by the peripheral chemoreceptors (**Figure 13.35**). The low arterial P_{O_2} increases the rate at which the receptors discharge, resulting in an increased number of action

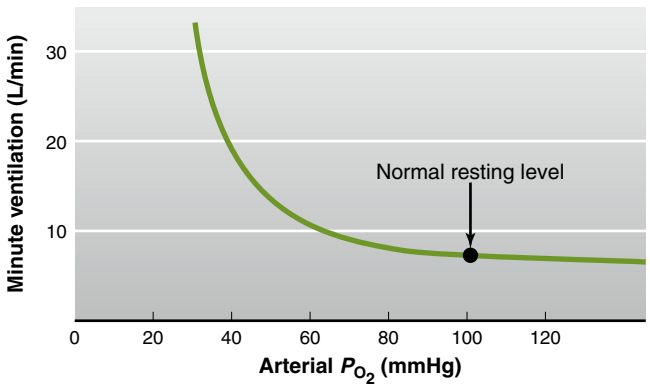


Figure 13.34 The effect on ventilation of breathing different oxygen mixtures. The arterial P_{CO_2} was maintained at 40 mmHg throughout the experiment.

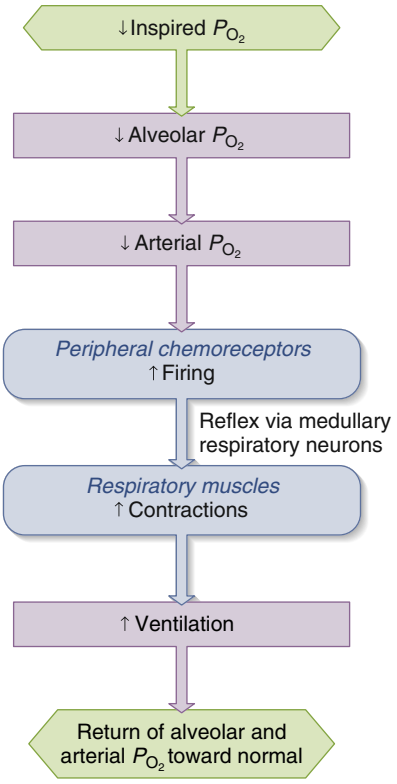


Figure 13.35 Sequence of events by which a low arterial P_{O_2} causes hyperventilation, which maintains alveolar (and, hence, arterial) P_{O_2} at a value higher than would exist if the ventilation had remained unchanged.

PHYSIOLOGICAL INQUIRY

- How does this figure illustrate the general principle of physiology described in Chapter 1 that homeostasis is essential for health and survival?

Answer can be found at end of chapter.

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 decrease in alveolar and arterial P_{O_2} produced by the low-P_{O_2} gas mixture.

It may seem surprising that we are insensitive to smaller reductions of arterial P_{O_2}, but look again at the oxygen–hemoglobin dissociation curve (see Figure 13.26). Total oxygen transport by the blood is not really decreased very much until the arterial P_{O_2} decreases below about 60 mmHg. Therefore, increased ventilation would not result in much more oxygen being added to the blood until that point is reached.

To reiterate, the peripheral chemoreceptors respond to decreases in arterial P_{O_2}, as occurs in lung disease or exposure to high altitude. However, the peripheral chemoreceptors are *not* stimulated in situations in which modest reductions take place in the oxygen *content* of the blood but no change occurs in arterial P_{O_2}. As stated earlier, anemia is a decrease in the amount of hemoglobin present in the blood without a decrease in arterial P_{O_2}, because the concentration of dissolved oxygen in the arterial blood is normal; that is, the P_{O_2} of arterial blood is determined

primarily by the oxygen-diffusion capacity of the lung, whereas the total amount of oxygen in the blood is also dependent on the amount of hemoglobin there to carry the oxygen. Therefore, mild to moderate anemia, in which arterial P_{O_2} is usually normal, does not activate peripheral chemoreceptors and does not stimulate increased ventilation.

This same analysis holds true when oxygen content is decreased moderately by the presence of carbon monoxide, which, as described earlier, reduces the amount of oxygen combined with hemoglobin by competing for these sites. Because carbon monoxide does not affect the amount of oxygen that can dissolve in blood and does not alter the oxygen-diffusion capacity of the lung, the arterial P_{O_2} is unaltered, and no increase in peripheral chemoreceptor output or ventilation occurs.

Control by P_{CO_2}

Figure 13.36 illustrates an experiment in which subjects breathe air with variable quantities of carbon dioxide added. The presence of carbon dioxide in the inspired air causes an increase in alveolar P_{CO_2}, and therefore the diffusion gradient for CO_2 is reversed from the normal situation. This results in a net uptake of CO_2 from the alveolar air and, therefore, an increase in arterial P_{CO_2}. Note that even a very small increase in arterial P_{CO_2} causes a marked reflex increase in ventilation. Experiments like this have documented that the reflex mechanisms controlling ventilation prevent small increases in arterial P_{CO_2} to a much greater degree than they prevent equivalent decreases in arterial P_{O_2}.

Of course, we do not usually breathe bags of gas containing carbon dioxide. Some pulmonary diseases, such as emphysema, can cause the body to retain carbon dioxide, resulting in an increase in arterial P_{CO_2} that stimulates ventilation. This promotes the elimination of the carbon dioxide. Conversely, if arterial P_{CO_2} decreases below normal levels for whatever reason, this removes some of the stimulus for ventilation. This decreases ventilation and allows metabolically produced carbon dioxide to accumulate, thereby returning the P_{CO_2} to normal. In this manner, the arterial P_{CO_2} is stabilized near the normal value of 40 mmHg.

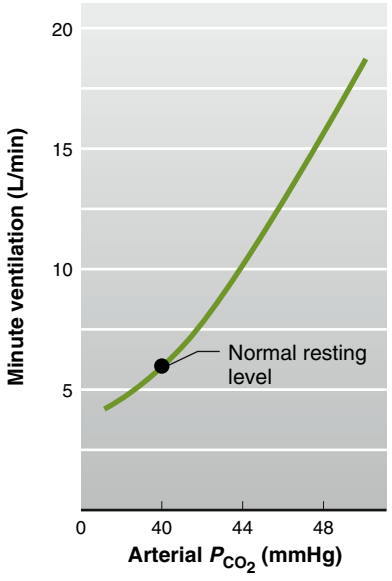


Figure 13.36 Effects on respiration of increasing arterial P_{CO_2} achieved by adding CO_2 to inspired air.

The ability of changes in arterial P_{CO_2} to reflexively control ventilation is largely due to associated changes in H^+ concentration (see equation 13–11). As summarized in **Figure 13.37**, both the peripheral and central chemoreceptors initiate the pathways that mediate these reflexes. 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 interstitial fluid, the increase in arterial P_{CO_2} causes a rapid

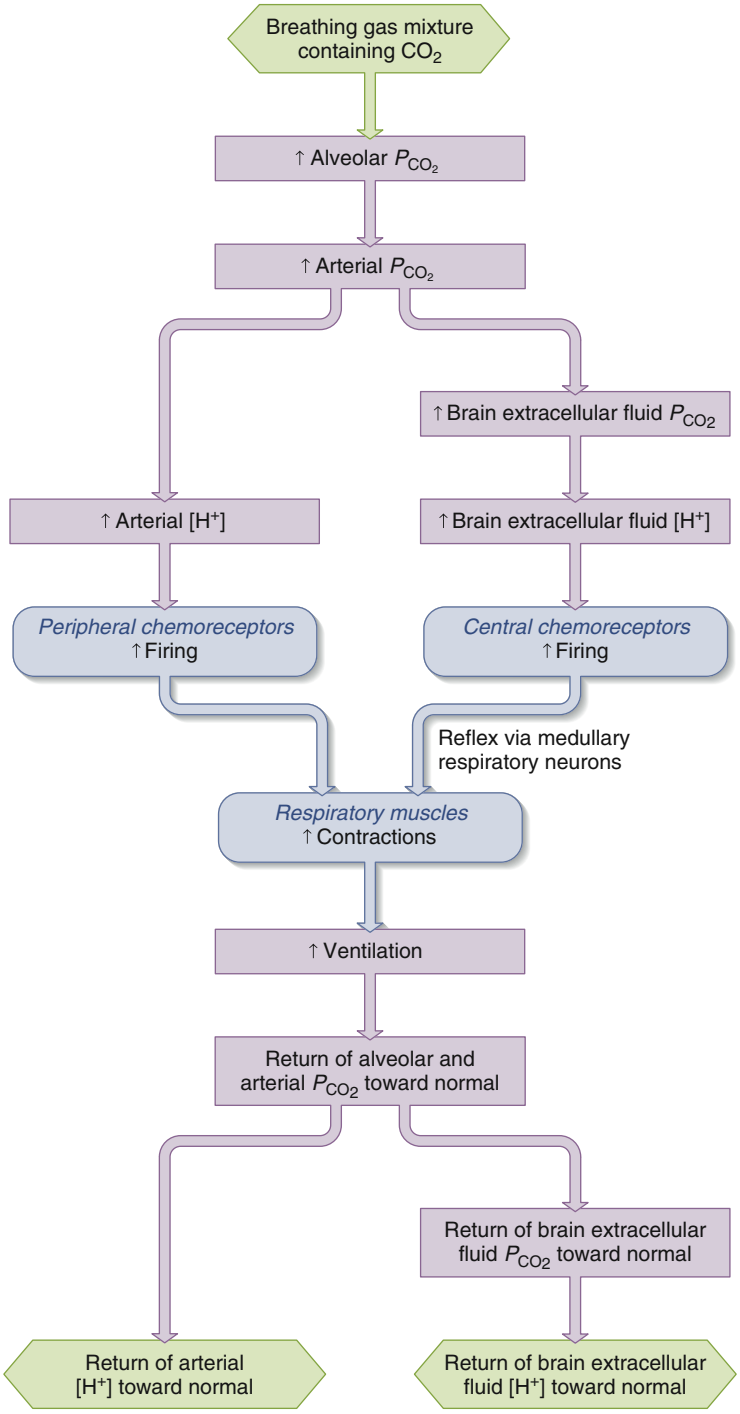


Figure 13.37 Pathways by which increased arterial P_{CO_2} stimulates ventilation. Note that the peripheral chemoreceptors are stimulated by an *increase* in H^+ concentration, whereas they are also stimulated by a *decrease* in P_{O_2} (see Figure 13.35).

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% 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 potentiate each other's effects. The 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 Changes in 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}. This is termed ***metabolic acidosis*** when H^+ concentration is increased and ***metabolic alkalosis*** when it is decreased. In such cases, the peripheral chemoreceptors provide the major afferent inputs to the brain in altering ventilation.

For example, the addition of lactic acid to the blood, as in strenuous exercise, causes hyperventilation almost entirely by stimulation of the peripheral chemoreceptors (**Figure 13.38** and **Figure 13.39**). 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 H^+ generated from the lactic acid. This is because H^+ penetrates the blood–brain barrier very slowly. In contrast, as described earlier, carbon dioxide penetrates the blood–brain barrier easily and changes brain H^+ concentration.

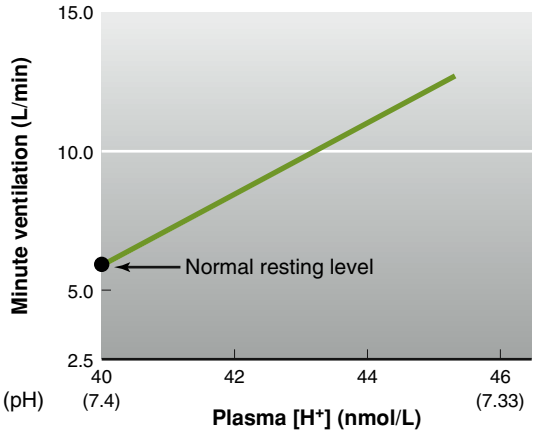


Figure 13.38 Changes in ventilation in response to an increase in plasma H^+ concentration produced by the administration of lactic acid. Source: Adapted from Lamberstein, C. J., in P. Bard (ed.), "*Medical Physiological Psychology*," 11th ed., Mosby, St. Louis, 1961.

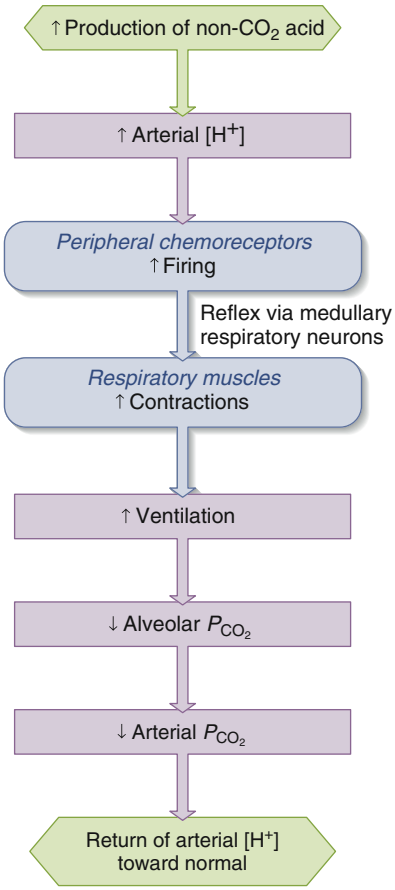


Figure 13.39 Reflexively induced hyperventilation minimizes the change in arterial H^+ concentration when acids are produced in excess in the body. Note that under such conditions, arterial P_{CO_2} is reflexively reduced below its normal value.

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

The adaptive value such reflexes have in regulating arterial H^+ concentration is shown in Figure 13.39. The increased ventilation induced by a metabolic acidosis reduces arterial P_{CO_2}, which decreases arterial H^+ concentration back toward normal. Similarly, hypoventilation induced by a metabolic alkalosis results in an increase in arterial P_{CO_2} and consequently a restoration of H^+ concentration toward normal.

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}. Maintenance of normal arterial H^+ is necessary because nearly all enzymes of the body function best at physiological pH.

Figure 13.40 summarizes the control of ventilation by P_{O_2}, P_{CO_2}, and H^+ concentration.

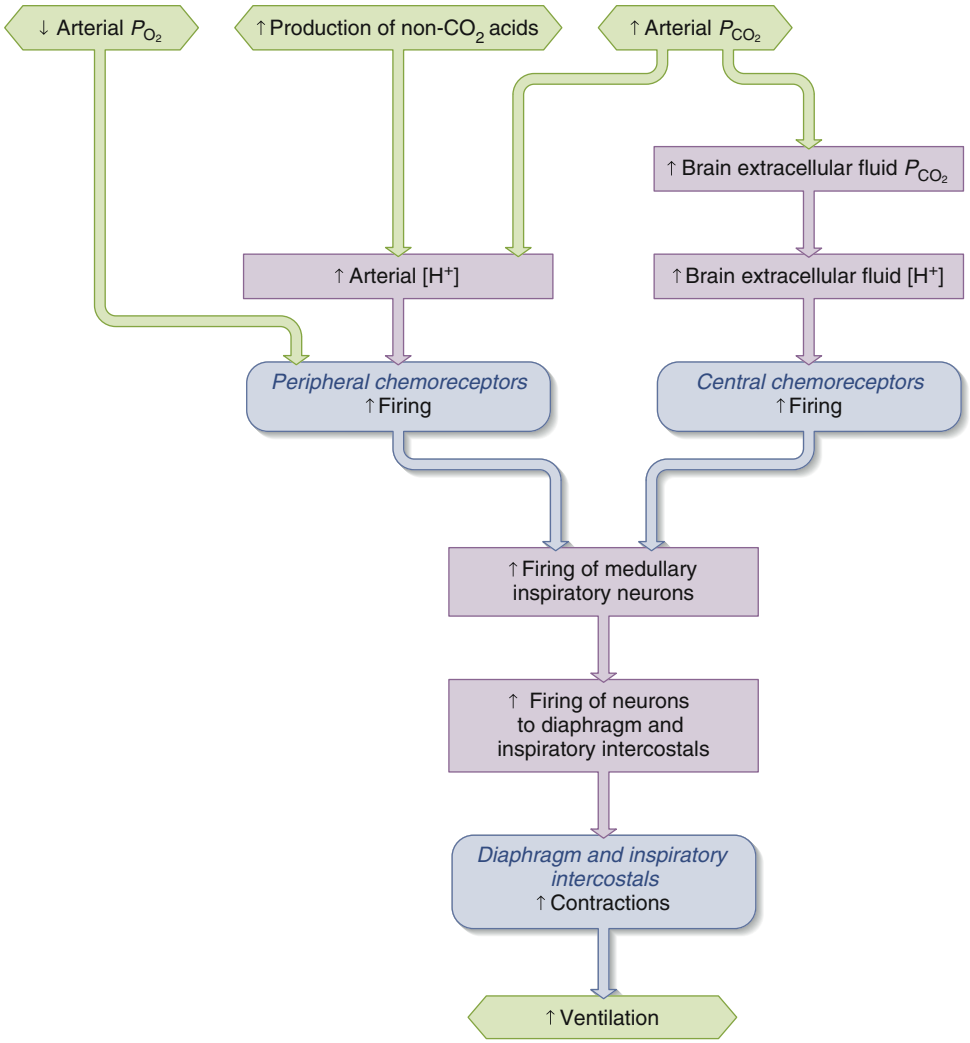


Figure 13.40 Summary of the major chemical inputs that stimulate ventilation. This is a combination of Figures 13.35, 13.37, and 13.39. When arterial P_{O_2} increases or when P_{CO_2} or H^+ concentration decreases, ventilation is reflexively decreased.

Control of Ventilation During Exercise

During exercise, the alveolar ventilation may increase as much as 20-fold. On the basis of our three variables—P_{O_2}, P_{CO_2}, and H^+ concentration—it may seem easy to explain the mechanism that induces this increased ventilation. This is not the case, however, and the major stimuli to ventilation during exercise, at least moderate exercise, 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 is it that arterial P_{CO_2} does not increase during exercise? Recall two facts from the section on alveolar gas pressures: (1) Arterial P_{CO_2} is determined by alveolar 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, so alveolar and therefore arterial P_{CO_2} do not change. In fact, in very strenuous exercise, the alveolar ventilation increases relatively more than carbon dioxide production. In other words, during strenuous exercise, a person may hyperventilate; thus, alveolar and systemic arterial P_{CO_2} may actually decrease (**Figure 13.41**)!

Decreased P_{O_2} as the Stimulus?

The story is similar for oxygen. Although systemic *venous* P_{O_2} decreases during exercise due to an increase in oxygen consumption in the tissues, alveolar P_{O_2} and, therefore, systemic *arterial* P_{O_2} usually remain unchanged (see Figure 13.41). This is because cellular oxygen consumption and alveolar ventilation increase in exact proportion to each other, at least during moderate exercise.

This is a good place to recall an important point made in Chapter 12. In healthy individuals, ventilation is not the limiting factor in strenuous exercise—cardiac output is. Ventilation can, as we have just seen, increase enough to maintain arterial P_{O_2}.

Increased H^+ Concentration as the Stimulus?

Because the arterial P_{CO_2} does not change during moderate exercise and decreases during strenuous 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 (see Figure 13.41) due to the generation and release of lactic acid into the blood. This change in H^+ concentration is responsible, in part, for stimulating the hyperventilation accompanying strenuous exercise.

Other Factors

A variety of other factors are involved 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 (central command), (4) an increase in the plasma epinephrine concentration, (5) an increase in the plasma K^+ concentration due to movement of K^+ out of the exercising muscles, and (6) a conditioned (learned) response mediated by neural input to the respiratory centers. Factors (1) and (3) are most likely to be significant (**Figure 13.42**). 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 by altered body temperature.

Figure 13.43 summarizes various factors that influence ventilation during exercise. Oscillations in arterial P_{O_2}, P_{CO_2}, or H^+ concentration—despite unchanged *average* levels of these variables—may provide additional input to the respiratory centers.

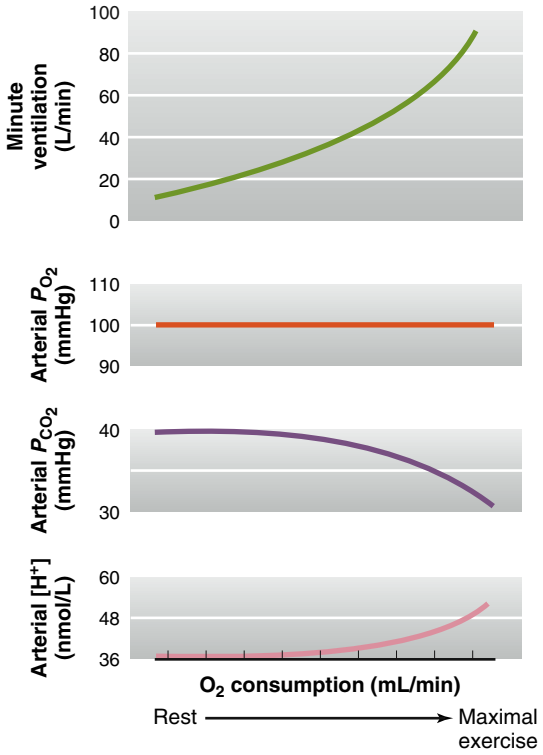


Figure 13.41 The effect of exercise on ventilation, arterial gas pressures, and H^+ concentration. All these variables remain constant during moderate exercise; any change occurs only during strenuous exercise, when the person is actually hyperventilating (decrease in P_{CO_2}). Source: Adapted from Comroe, J. H., "*Physiology of Respiration*," Year Book, Chicago, 1965.

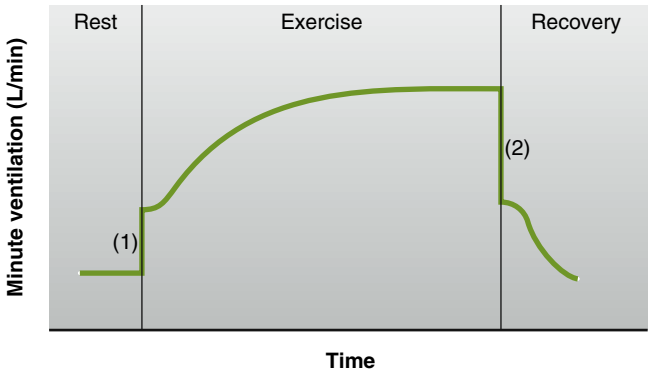


Figure 13.42 Ventilation changes during exercise. Note (1) the abrupt increase at the onset of exercise and (2) the equally abrupt but larger decrease at the end of exercise.

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 sensory receptors located between airway epithelial cells. The receptors for the sneeze reflex are in the nose or pharynx; those for cough are in the larynx, trachea, and bronchi. When the receptors initiating a cough are stimulated, the medullary respiratory neurons reflexively 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.

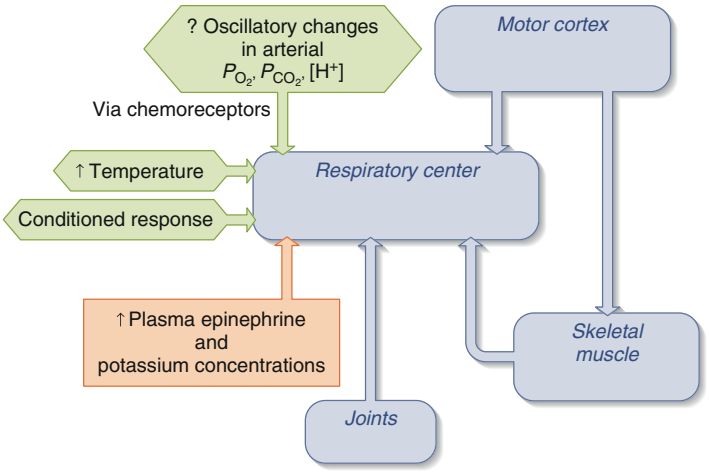


Figure 13.43 Summary of factors that stimulate ventilation during exercise. *Note:* "?" indicates a theoretical input.

PHYSIOLOGICAL INQUIRY

- The existence of chemoreceptors in the pulmonary artery has been suggested. Hypothesize a function for peripheral chemoreceptors located on and sensing the P_{O_2} and P_{CO_2} of the blood in the pulmonary artery.

Answer can be found at end of chapter.

Alcohol inhibits the cough reflex, which may partially explain the susceptibility of alcoholics to choking and pneumonia.

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

Voluntary Control of Breathing Although we have discussed in detail the involuntary nature of most respiratory reflexes, the voluntary control of respiratory movements is important. 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 increased P_{CO_2} or H^+ concentration, become intense. An example is the inability to hold your 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 decreasing 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, singing, and swallowing.

Reflexes from J Receptors In the lungs, either in the capillary walls or the interstitium, are a group of sensory 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 (called a ***pulmonary embolism***) or left ventricular heart failure (Chapter 12), as well as by strenuous 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.

13.8 Hypoxia

Hypoxia is defined as a deficiency of oxygen at the tissue level. There are many potential causes of hypoxia, but they can be classified into four general categories: (1) ***hypoxic hypoxia*** (also termed ***hypoxemia***), in which the arterial P_{O_2} is reduced; (2) ***anemic hypoxia*** or ***carbon monoxide hypoxia,*** in which the arterial P_{O_2} is normal but the total oxygen *content* of the blood is decreased 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.

Hypoxic hypoxia is a common cause of hypoxia. The primary causes of hypoxic hypoxia in disease are listed in **Table 13.10**. Exposure to the decreased P_{O_2} of high altitude also causes hypoxic hypoxia but is, of course, not a disease. The brief summaries in Table 13.10 provide a review of many of the key aspects of respiratory physiology and pathophysiology described in this chapter.

This table also emphasizes that some of the diseases that produce hypoxia also produce carbon dioxide retention and an increased arterial P_{CO_2} (***hypercapnia***). In such cases, treating only the oxygen deficit by administering oxygen may be inadequate because it does nothing about the hypercapnia. Indeed, such therapy may be dangerous. The primary respiratory drive in such patients is the hypoxia, because for several reasons the reflex ventilatory response to an increased P_{CO_2} may be lost in chronic situations. The administration of pure oxygen may cause such patients to stop breathing; consequently, such individuals are typically treated with a mixture of air and oxygen rather than 100% oxygen.

TABLE 13.10 Causes of a Decreased Arterial P_{O_2} (Hypoxic Hypoxia) in Disease

I. ***Hypoventilation*** may be caused by
- A. A defect anywhere along the respiratory control pathway, from the medulla through the respiratory muscles
- B. Severe thoracic cage abnormalities
- C. Major obstruction of the upper airway

The hypoxemia of hypoventilation is always accompanied by an increased arterial P_{CO_2}.

II. ***Diffusion impairment*** results from thickening of the alveolar membranes or a decrease in their surface area. In turn, it causes blood P_{O_2} and alveolar P_{O_2} to fail to equilibrate. Often, it is apparent only during exercise. Arterial P_{CO_2} can be normal because carbon dioxide diffuses more readily than oxygen, decreased if the hypoxemia reflexively stimulates alveolar ventilation, or increased if the impairment is severe enough to limit CO_2 diffusion.

III. A ***shunt*** is
- A. An anatomical abnormality of the cardiovascular system that causes mixed venous blood to bypass ventilated alveoli in passing from the right side of the heart to the left side
- B. An intrapulmonary defect in which mixed venous blood perfuses unventilated alveoli. Arterial P_{CO_2} usually does not increase because the effect of the shunt on arterial P_{CO_2} is counterbalanced by the increased ventilation reflexively stimulated by the hypoxemia.

IV. ***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 reflexively stimulated.

Why Do Ventilation–Perfusion Abnormalities Affect O_2 More Than CO_2?

As described in Table 13.10, ventilation–perfusion inequalities often cause hypoxemia without associated increases in P_{CO_2}. The explanation for this resides in the fundamental difference between the transport of O_2 and the transport of CO_2 in the blood. Recall that the shape of the oxygen–hemoglobin dissociation curve is sigmoidal (see Figure 13.26). An increase in P_{O_2} above 100 mmHg does not add much oxygen to hemoglobin that is already almost 100% saturated. If poorly ventilated, diseased alveoli are perfused with blood and they will contribute blood with low oxygen to the pulmonary vein and, thus, to the general circulation. If increases in ventilation ensue in order to compensate for this, the increase in P_{O_2} in the healthy part of the lung does not add much oxygen to the blood from that region because of the minimal increase in oxygen saturation. As blood from these different areas of the lung mix in the pulmonary vein, the net result is still deoxygenated blood (hypoxemia).

The situation for CO_2, however, is very different. The CO_2 content curve is relatively linear because CO_2 is transported in the blood mainly as highly soluble HCO_3^-, which does not saturate at physiological concentrations. Therefore, although poorly ventilated areas of the lungs do cause increases in the CO_2 content of the blood entering the pulmonary vein (because CO_2 accumulates in the alveoli in those areas), a compensatory increase in ventilation *lowers* CO_2 content below normal in the blood from the well-ventilated areas of the lung. The net result, as blood mixes in the pulmonary vein in this case, is essentially normal arterial CO_2 content and P_{CO_2}. Thus, clinically significant ventilation–perfusion mismatching can lead to low arterial P_{O_2} with normal P_{CO_2}.

Emphysema

The pathophysiology of emphysema, a major cause of hypoxia, offers an instructive review of many basic principles of respiratory physiology. ***Emphysema*** is characterized by a loss of elastic tissue and the destruction of the alveolar walls leading to an increase in compliance. Furthermore, atrophy and collapse of the lower airways—those from the terminal bronchioles on down—can occur. The lungs actually self-destruct, attacked by proteolytic enzymes secreted by leukocytes in response to a variety of factors. Smoking tobacco products is by far the most important of these factors; it stimulates the release of the proteolytic enzymes and destroys other protective 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 balloonlike structures, reduces the *total* surface area available for diffusion, and this impairs gas exchange. Moreover, because the destructive changes are not uniform throughout the lungs, some areas may receive large amounts of air and little blood, whereas others show just the opposite pattern. The result is marked ventilation–perfusion inequality.

In addition to problems in gas exchange, emphysema is associated with a large 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 caused by the collapse of the lower airways, particularly during expiration. 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, so the airways collapse.

In summary, patients with emphysema suffer from decreased elastic recoil of the lungs, 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. As already explained, an increase in arterial P_{CO_2} usually does not occur until the disease becomes extensive and prevents increases in alveolar ventilation.

Acclimatization to High Altitude

Atmospheric pressure progressively decreases as altitude increases. Thus, at the top of Mt. Everest (approximately 29,029 ft or 8848 m), the atmospheric pressure is 253 mmHg, compared to 760 mmHg at sea level. The air is still 21% oxygen, which means that the inspired P_{O_2} is 53 mmHg (0.21 × 253 mmHg). Therefore, the alveolar and arterial P_{O_2} must decrease as persons ascend unless they breathe pure oxygen. The highest villages permanently inhabited by people are in the Andes at approximately 18,000 ft (5486 m).

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*** (***altitude 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, which is the leakage of fluid from the pulmonary capillaries into the alveolar walls and eventually the airspaces themselves. This occurs because of the development of pulmonary hypertension, as pulmonary arterioles reflexively constrict in the presence of low oxygen, as described earlier. Brain edema can also occur. Supplemental oxygen and diuretic therapy are used to treat mountain sickness; diuretics help reduce blood pressure, including in the pulmonary circulation, by promoting water loss in the urine. This reduces the amount of fluid leaving the capillaries in the lungs and brain.

Over the course of several days, the symptoms of mountain sickness usually disappear, although maximal physical capacity remains reduced. Acclimatization to high altitude is achieved by the compensatory mechanisms listed in **Table 13.11**.

Finally, note 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.

TABLE 13.11 Acclimatization to the Hypoxia of High Altitude

The peripheral chemoreceptors stimulate ventilation.
Erythropoietin, a hormone secreted primarily by the kidneys, stimulates erythrocyte synthesis—resulting in increased erythrocyte and hemoglobin concentration in blood—and the oxygen-carrying capacity of blood.
DPG increases and shifts the oxygen–hemoglobin dissociation curve to the right, facilitating oxygen unloading in the tissues. However, this DPG change is not always adaptive and may be maladaptive. For example, at very high altitudes, a right shift in the curve impairs oxygen *loading* in the lungs, an effect that may outweigh the benefit from facilitation of *unloading* in the tissues.
Increases in skeletal muscle capillary density (due to hypoxia-induced expression of the genes that code for angiogenic factors), number of mitochondria, and muscle myoglobin occur, all of which increase oxygen transfer.
Plasma volume can be decreased, resulting in an increased concentration of the erythrocytes and hemoglobin in the blood.

13.9 Nonrespiratory Functions of the Lungs

The lungs perform 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 new substances and add them to the blood. Some of these substances have local regulatory functions 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 (see Chapter 18) in the lung may lead, via excessive release of potent chemicals such as histamine, to alterations of systemic blood pressure or flow. In at least one case, the lungs contribute to the production of a hormone, angiotensin II, which is produced by the action of an enzyme located on endothelial cells throughout much of the body (see Chapter 14).

Finally, the lungs also act as a sieve that traps 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.

Table 13.12 summarizes the functions of the respiratory system. ■

TABLE 13.12 Functions of the Respiratory System
Provides oxygen
Eliminates carbon dioxide
Regulates the blood's hydrogen ion concentration (pH) in coordination with the kidneys
Forms speech sounds (phonation)
Defends against microbes
Influences arterial concentrations of chemical messengers by removing some from pulmonary capillary blood and producing and adding others to this blood
Traps and dissolves blood clots arising from systemic veins such as those in the legs

SUMMARY

Organization of the Respiratory System

I. The respiratory system comprises the lungs, the airways leading to them, and the chest structures responsible for moving 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.

III. The steps involved in respiration are summarized in Figure 13.6. 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.

Ventilation and Lung Mechanics

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

II. Between breaths at the end of an unforced expiration, $P_{atm} = P_{alv}$, 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 they do between breaths.
   b. This expansion initially makes alveolar pressure subatmospheric, which creates the pressure difference between the atmosphere and alveoli to drive airflow into the lungs.

IV. During expiration, the inspiratory muscles cease contracting, allowing the elastic recoil of the lungs to return them to their original between-breaths 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. Surfactant also stabilizes alveoli by decreasing surface tension in smaller alveoli.

VI. Airway resistance determines how much air flows into the lungs at any given pressure difference between atmosphere and alveoli. The major determinants of airway resistance are 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 measurement is the FEV_1 and normally averages 80% of forced vital capacity.

VIII. Minute ventilation is the product of tidal volume and respiratory rate. Alveolar ventilation = (Tidal volume − Anatomical dead space) × Respiratory rate.

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. At rest and at a respiratory quotient (RQ) of 0.8, oxygen consumption is approximately 250 mL per minute, whereas carbon dioxide production is approximately 200 mL per minute.

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 alveolar-capillary 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, 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 Blood

I. Each liter of systemic arterial blood normally contains 200 mL of oxygen, more than 98% 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% saturated at the normal systemic arterial P_{O_2} of 100 mmHg. The fact that saturation is already more than 90% 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% saturated at the normal systemic mixed venous P_{O_2} of 40 mmHg. Thus, only 25% of the oxygen has dissociated from hemoglobin and diffused into the tissues.

III. The affinity of hemoglobin for oxygen is decreased by an increase in P_{CO_2}, H^+ concentration, and temperature. All these conditions exist in the tissues and facilitate the dissociation of oxygen from hemoglobin. Fetal hemoglobin has a higher affinity for oxygen allowing adequate uptake of oxygen in the placenta and delivery to the tissues.

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% remain dissolved in plasma and erythrocytes, 25% to 30% combine in the erythrocytes with deoxyhemoglobin to form carbamino compounds, and 60% to 65% combine in the erythrocytes with water to form carbonic acid, which then dissociates to yield HCO_3^- and H^+. Most of the HCO_3^- 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 the diffusion of carbon dioxide out of the blood into the alveoli, and the reactions are reversed.

Transport of Hydrogen Ion Between Tissues and Lungs

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

II. As the blood flows through the lung capillaries, H^+ bound to deoxyhemoglobin is released and combines with HCO_3^- 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 medullary respiratory center is composed of the dorsal respiratory group, which contains inspiratory neurons, and the ventral respiratory group, where the respiratory rhythm generator is located.

III. 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.

IV. Ventilation is reflexively stimulated via the peripheral chemoreceptors by a decrease in arterial P_{O_2} but only when the decrease is large.

V. Ventilation is reflexively stimulated via both the peripheral and central chemoreceptors when the arterial P_{CO_2} increases even a small amount. The stimulus for this reflex is not the increased P_{CO_2} itself but the concomitant increased H^+ concentration in arterial blood and brain extracellular fluid.

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

VII. Ventilation is reflexively inhibited by an increase in arterial P_{O_2} and by a decrease in arterial P_{CO_2} or H^+ concentration.

VIII. During moderate exercise, ventilation increases in exact proportion to metabolism, but the signals causing this are not certain. 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 H^+ concentration to remain unchanged.
   b. Arterial H^+ concentration increases during very strenuous exercise because of increased lactic acid production. This accounts for some of the hyperventilation that occurs.

IX. 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 13.10.

II. During exposure to hypoxia, as at high altitude, oxygen supply to the tissues is maintained by the five responses listed in Table 13.11.

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 trap and dissolve small clots formed in the systemic tissues.

REVIEW QUESTIONS

1. List the functions of the respiratory system.
2. At rest, how many liters of air flow in and out of the lungs and how many liters of 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 do the lungs and chest wall tend 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 airflow into or out of the lungs to alveolar pressure, atmospheric 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? How does surfactant stabilize alveoli by preventing small alveoli from emptying into large alveoli?
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 equation relating minute ventilation, tidal volume, and respiratory rate. Give representative values for each in a normal person at rest.
17. State the equation 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 healthy 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 healthy 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 has little effect on carbon dioxide exchange?
23. What is the major result of ventilation–perfusion inequalities throughout the lungs? Describe homeostatic responses that minimize 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? Of the steep portion?
28. Would breathing pure oxygen cause a large increase in oxygen transport by the blood in a healthy person? In a person with a low alveolar P_{O_2}?
29. Describe the effects of increased P_{CO_2}, 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. What is the adaptive importance of the effect of DPG on the curve?
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, HCO_3^-, and carbaminohemoglobin?
32. What happens to most of the H^+ 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_{O_2} on carbaminohemoglobin formation and H^+ binding by hemoglobin?
34. Describe the area of the brain in which automatic control of rhythmic respirations resides.
35. Describe the function of the pulmonary stretch receptors.
36. What changes stimulate the peripheral chemoreceptors? The central chemoreceptors?
37. Why is it that moderate anemia or carbon monoxide exposure does 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 H^+ concentration independent of altered carbon dioxide influences ventilation. What is the adaptive value of this reflex?
41. What happens to arterial P_{O_2}, P_{CO_2}, and H^+ concentration during moderate and strenuous exercise? List other factors that may stimulate ventilation during exercise.
42. List four general causes of hypoxic hypoxia.
43. Explain how ventilation–perfusion mismatch due to regional lung disease can cause hypoxic hypoxia but not hypercapnia.
44. Describe two general ways in which the lungs can alter the concentrations of substances other than oxygen, carbon dioxide, and H^+ in the arterial blood.
45. List two types of sleep apnea. Why does nasal CPAP prevent obstructive sleep apnea?

KEY TERMS

pulmonary respiration
respiratory system

13.1 Organization of the Respiratory System

airways
alveolar sacs
alveoli (alveolus)
alveolus
bronchi (bronchus)
bronchioles
CF transmembrane conductance regulator (CFTR)
conducting zone
diaphragm
expiration
inspiration
intercostal muscles
intrapleural fluid
intrapleural pressure (P_{ip})
larynx
parietal pleura
pharynx
pleura
pleural sac
respiratory bronchioles
respiratory cycle
respiratory zone
thorax
trachea
type I alveolar cells
type II alveolar cells
upper airways
visceral pleura
vocal cords

13.2 Ventilation and Lung Mechanics

alveolar dead space
alveolar pressure (P_{alv})
alveolar ventilation ($\dot{V}_A$)
anatomical dead space (V_D)
atmospheric pressure (P_{atm})
Boyle's law
elastic recoil
expiratory reserve volume (ERV)
functional residual capacity (FRC)
inspiratory reserve volume (IRV)
lateral traction
Law of Laplace
lung compliance (C_L)
minute ventilation ($\dot{V}_E$)
phrenic nerves
physiological dead space
residual volume (RV)
surface tension
surfactant
tidal volume (V_t)
transmural pressure
transpulmonary pressure (P_{tp})
ventilation
vital capacity (VC)

13.3 Exchange of Gases in Alveoli and Tissues

Dalton's law
Henry's law
partial pressures
respiratory quotient (RQ)

13.4 Transport of Oxygen in Blood

deoxyhemoglobin (Hb)
2,3-diphosphoglycerate (DPG)
fetal hemoglobin
globin
heme
hemoglobin
oxygen-carrying capacity
oxygen–hemoglobin dissociation curve
oxyhemoglobin (HbO_2)
percent hemoglobin saturation

13.5 Transport of Carbon Dioxide in Blood

carbaminohemoglobin
carbonic anhydrase
total-blood carbon dioxide

13.7 Control of Respiration

aortic bodies
apneustic center
carotid bodies
central chemoreceptors
dorsal respiratory group (DRG)
Hering–Breuer reflex
J receptors
medullary respiratory center
peripheral chemoreceptors
pneumotaxic center
pontine respiratory group
pre-Bötzinger complex
pulmonary stretch receptors
respiratory rhythm generator
ventral respiratory group (DRG)

CLINICAL TERMS

13.1 Organization of the Respiratory System

cystic fibrosis (CF)

13.2 Ventilation and Lung Mechanics

anti-inflammatory drugs
asthma
bronchodilator drugs
chronic bronchitis
chronic obstructive pulmonary disease (COPD)
forced expiratory volume in 1 sec (FEV_1)
obstructive lung diseases
pneumothorax
pulmonary function tests
respiratory distress syndrome of the newborn
restrictive lung diseases

13.3 Exchange of Gases in Alveoli and Tissues

diffuse interstitial fibrosis
hyperventilation
hypoventilation
pulmonary edema
shunt
ventilation–perfusion inequality

13.4 Transport of Oxygen in Blood

anemia
carbon monoxide

13.6 Transport of Hydrogen Ion Between Tissues and Lungs

respiratory acidosis
respiratory alkalosis

13.7 Control of Respiration

dyspnea
metabolic acidosis
metabolic alkalosis
pulmonary embolism

13.8 Hypoxia

anemic hypoxia
carbon monoxide hypoxia
diffusion impairment
emphysema
histotoxic hypoxia
hypercapnia
hypoventilation
hypoxemia
hypoxia
hypoxic hypoxia
ischemic hypoxia
mountain sickness (altitude sickness)
shunt
ventilation–perfusion inequality

CHAPTER 13

Clinical Case Study: High Blood Pressure and Chronic Sleepiness in an Obese Man

An obese man is discovered to have high blood pressure (hypertension) and is sleepy all of the time. His wife reports that he snores very loudly and often sounds like he stops breathing in his sleep. The doctor orders a sleep study, and the diagnosis of obstructive sleep apnea is made.

Sleep apnea is characterized by periodic cessation of breathing during sleep. This results in the combination of hypoxemia and hypercapnia (termed ***asphyxia***). In severe cases, this may occur more than 20 times an hour. During a sleep study, these frequent blood oxygen desaturations are documented. Sleep apnea has two general types. ***Central sleep apnea*** is primarily due to a decrease in neural output from the respiratory center in the medulla to the phrenic motor nerve to the diaphragm. ***Obstructive sleep apnea*** is caused by increased airway resistance because of narrowing or collapse of the upper airways (primarily the pharynx) during inspiration (**Figure 13.44**).

Reflect and Review #1

- Describe the relationship between air flow, alveolar pressure, and airway resistance. (*Hint:* Look at equation 13-2.)

Obstructive sleep apnea may occur in as much as 4% of the adult population with a greater frequency in elderly persons and in men. Significant snoring may be an early sign of the eventual development of obstructive sleep apnea. Obesity is clearly a contributing factor because the excess fat in the neck compresses the upper airways. A decrease in the activity of the upper airway dilating muscles, particularly during REM sleep, also contributes to airway collapse. Finally, anatomical narrowing of the upper airways contributes to periodic inspiratory obstruction during sleep.

Untreated sleep apnea can have many serious consequences, including hypertension of the pulmonary arteries

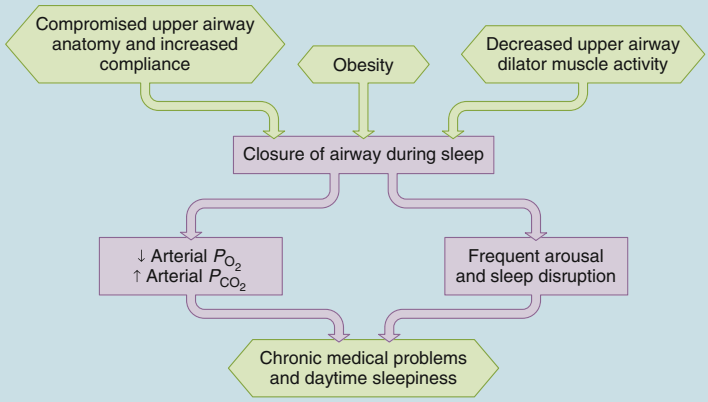


Figure 13.44 Pathogenesis of obstructive sleep apnea.

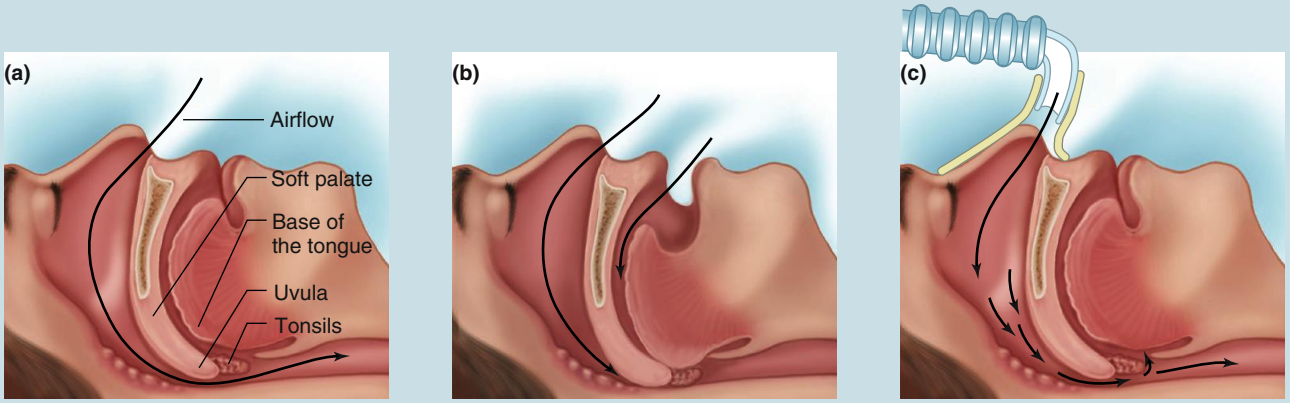
(***pulmonary hypertension***) and added strain on the right ventricle of the heart.

Reflect and Review #2

- What might be the cause of pulmonary hypertension in sleep apnea? (*Hint:* See Figure 13.24.)

This can lead to heart failure and abnormal heart rhythm, either of which can be fatal. The periodic arousal that occurs during these apneic episodes results in serious disruption of normal sleep patterns and can lead to sleepiness during the day (***daytime somnolence***). These arousals can activate the sympathetic nervous system thereby increasing catecholamine release from the adrenal medulla (see Figure 11.12). The increased adrenergic activity can increase total peripheral resistance (see Table 12.2) and contribute to the development of arterial hypertension (see Chapter 12, Section 12.19).

A variety of treatments exist for obstructive sleep apnea. Surgery such as laser-assisted widening of the soft palate and uvula can sometimes be of benefit. Weight loss is often quite helpful. However, the mainstay of therapy is ***continuous positive airway pressure***



During normal sleep, air flows freely past the structures in the throat.

During sleep apnea, airflow is completely blocked.

With CPAP, a mask over the nose gently directs air into the throat to keep the air passage open.

Figure 13.45 The pathophysiology and a standard treatment of obstructive sleep apnea. (a) Normal sleep with air flowing freely past the structures of the throat during an inspiration. (b) In obstructive sleep apnea (particularly with the patient sleeping in the supine position), the soft palate, uvula, and tongue occlude the airway, greatly increasing the resistance to airflow. (c) Continuous positive airway pressure (CPAP) is applied with a nasal mask, preventing airway collapse.

(***CPAP***) (**Figure 13.45**). The patient wears a small mask over the nose during sleep, which is attached to a positive-pressure-generating device. By increasing airway pressure greater than P_{atm}, the collapse of the upper airways during inspiration is prevented. Although the CPAP nasal mask may seem obtrusive, many patients sleep much better with it, and many of the symptoms resolve with this treatment. Our patient was treated with CPAP during the night and also was able to lose a considerable amount of body weight. As a result, his daytime somnolence and hypertension improved over the next year.

Clinical terms: asphyxia, central sleep apnea, continuous positive airway pressure (CPAP), daytime somnolence, obstructive sleep apnea, pulmonary hypertension, sleep apnea

See Chapter 19 for complete, integrative case studies.

CHAPTER 13 TEST QUESTIONS *Recall and Comprehend*

Answers appear in Appendix A.

These questions test your recall of important details covered in this chapter. They also help prepare you for the type of questions encountered in standardized exams. Many additional questions of this type are available on Connect and LearnSmart.

1. If $P_{atm} = 0$ mmHg and $P_{alv} = -2$ mmHg, then
   a. transpulmonary pressure (P_{tp}) is 2 mmHg.
   b. it is at the end of the normal inspiration and there is no airflow.
   c. it is at the end of the normal expiration and there is no airflow.
   d. transpulmonary pressure (P_{tp}) is −2 mmHg.
   e. air is flowing into the lung.
2. Transpulmonary pressure (P_{tp}) increases by 3 mmHg during a normal inspiration. In subject A, 500 mL of air is inspired. In subject B, 250 mL of air is inspired for the same change in P_{tp}. Which is *true*?
   a. The compliance of the lung of subject B is less than that of subject A.
   b. The airway resistance of subject A is greater than that of subject B.
   c. The surface tension in the lung of subject B is less than that in subject A.
   d. The lung of subject A is deficient in surfactant.
   e. The compliance cannot be estimated from the data provided.
3. If alveolar ventilation is 4200 mL/min, respiratory frequency is 12 breaths per minute, and tidal volume is 500 mL, what is the anatomical-dead-space ventilation?
   a. 1800 mL/min
   b. 6000 mL/min
   c. 350 mL/min
   d. 1200 mL/min
   e. It cannot be determined from the data provided.
4. Which of the following will increase alveolar P_{O_2}?
   a. increase in metabolism and no change in alveolar ventilation
   b. breathing air with 15% oxygen at sea level
   c. increase in alveolar ventilation matched by an increase in metabolism
   d. increased alveolar ventilation with no change in metabolism
   e. carbon monoxide poisoning
5. Which of the following will cause the largest increase in systemic arterial oxygen saturation in the blood?
   a. an increase in red cell concentration (hematocrit) of 20%
   b. breathing 100% O_2 in a healthy subject at sea level
   c. an increase in arterial P_{O_2} from 40 to 60 mmHg
   d. hyperventilation in a healthy subject at sea level
   e. breathing a gas with 5% CO_2, 21% O_2, and 74% N_2 at sea level
6. In arterial blood with a P_{O_2} of 60 mmHg, which of the following situations will result in the lowest blood oxygen saturation?
   a. decreased DPG with normal body temperature and blood pH
   b. increased body temperature, acidosis, and increased DPG
   c. decreased body temperature, alkalosis, and increased DPG
   d. normal body temperature with alkalosis
   e. increased body temperature with alkalosis
7. Which of the following is *not* true about asthma?
   a. The basic defect is chronic airway inflammation.
   b. It is always caused by an allergy.
   c. The airway smooth muscle is hyperresponsive.
   d. It can be treated with inhaled steroid therapy.
   e. It can be treated with bronchodilator therapy.

8. Which of the following is *true*?
   a. Peripheral chemoreceptors increase firing with low arterial P_{O_2} but are not sensitive to an increase in arterial P_{CO_2}.
   b. The primary stimulus to the central chemoreceptors is low arterial P_{O_2}.
   c. Peripheral chemoreceptors increase firing during a metabolic alkalosis.
   d. The increase in ventilation during exercise is due to a decrease in arterial P_{O_2}.
   e. Peripheral and central chemoreceptors both increase firing when arterial P_{CO_2} increases.
9. Ventilation–perfusion inequalities lead to hypoxemia because
   a. the relationship between P_{CO_2} and the content of CO_2 in blood is sigmoidal.
   b. a decrease in ventilation–perfusion matching in a lung region causes pulmonary arteriolar vasodilation in that region.
   c. increases in ventilation cannot fully restore O_2 content in areas with low ventilation–perfusion matching.
   d. increases in ventilation cannot normalize P_{CO_2}.
   e. pulmonary blood vessels are not sensitive to changes in P_{O_2}.
10. After the expiration of a normal tidal volume, a subject breathes in as much air as possible. The volume of air inspired is the
    a. inspiratory reserve volume.
    b. vital capacity.
    c. inspiratory capacity.
    d. total lung capacity.
    e. functional residual capacity.

CHAPTER 13 TEST QUESTIONS *Apply, Analyze, and Evaluate*

Answers appear in Appendix A.

These questions, which are designed to be challenging, require you to integrate concepts covered in the chapter to draw your own conclusions. See if you can first answer the questions without using the hints that are provided; then, if you are having difficulty, refer back to the figures or sections indicated in the hints.

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 of air. At the end of inspiration, the alveolar pressure is 0 mmHg and the intrapleural pressure is −8 mmHg. Calculate this person's lung compliance. *Hint:* See Figure 13.16 and equation 13-4 and recall the equation for compliance.
2. A patient is unable to produce surfactant. To inhale a normal tidal volume, will her intrapleural pressure have to be more or less subatmospheric during inspiration, relative to a healthy person? *Hint:* See Figures 13.13 and 13.16 and remember the effect of surfactant on surface tension.
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 anatomical dead space of 150 mL, is this patient receiving an adequate alveolar ventilation? *Hint:* See Table 13.4.
4. Why must a person floating on the surface of the water face down and breathing through a snorkel increase his tidal volume and/or breathing frequency if alveolar ventilation is to remain normal? *Hint:* See Figure 13.19 and remember the definition of *dead space*.
5. A healthy person breathing room air voluntarily increases alveolar ventilation twofold and continues to do so until reaching new steady-state alveolar gas pressures for oxygen and carbon dioxide. Are the new values higher or lower than normal? *Hint:* See Figure 13.22.
6. A person breathing room air has an alveolar P_{O_2} of 105 mmHg and an arterial P_{O_2} of 80 mmHg. Could hypoventilation due to, say, respiratory muscle weakness produce these values? *Hint:* See Figures 13.22 and 13.23 and remember the effect of hypoventilation on alveolar ventilation.
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_{O_2} at rest? During exercise? *Hint:* See Figure 13.23 and remember the effect of the thickness of a membrane on its permeability to a gas.
8. A person is breathing 100% 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? *Hint:* See Figure 13.26.
9. Which of the following have higher values in systemic venous blood than in systemic arterial blood: plasma P_{CO_2}, erythrocyte P_{CO_2}, plasma bicarbonate concentration, erythrocyte bicarbonate concentration, plasma hydrogen ion concentration, erythrocyte hydrogen ion concentration, erythrocyte carbamino concentration? *Hint:* See Figures 13.30 and 13.31.
10. If the spinal cord were severed where it joins the brainstem, what would happen to respiration? *Hint:* See Figure 13.32 and recall the innervation of the muscles of respiration.
11. Which inspired gas mixture leads to the largest increase in minute ventilation? *Hint:* See Table 13.9 and Figure 13.40 and remember the effects of hypoxia, hypercapnia, and carbon monoxide on chemoreceptor activity.
    a. 10% O_2/5% CO_2
    b. 100% O_2/5% CO_2
    c. 21% O_2/5% CO_2
    d. 10% O_2/0% CO_2
    e. 0.1% CO/5% CO_2
12. Patients with severe uncontrolled type 1 diabetes mellitus produce large quantities of certain organic acids. Can you predict the ventilation pattern in these patients and whether their arterial P_{O_2} and P_{CO_2} would increase or decrease? *Hint:* See Figure 13.39 and recall the definition of *metabolic acidosis*.
13. Why does an inspired O_2 of 100% increase arterial P_{O_2} much more in a patient with ventilation–perfusion mismatch than in a patient with pure anatomical shunt? *Hint:* See Section 13.8 and remember the difference in terms of absolute blood flow to an area of low perfusion compared to an area with no perfusion.

CHAPTER 13 TEST QUESTIONS *General Principles Assessment*

Answers appear in Appendix A.

These questions reinforce the key theme first introduced in Chapter 1, that general principles of physiology can be applied across all levels of organization and across all organ systems.

1. A general principle of physiology highlighted throughout this chapter is that *physiological processes are dictated by the laws of chemistry and physics*. What are some examples of how this applies to lung mechanics and the transport of oxygen and carbon dioxide in blood?
2. How is the anatomy of the alveoli and pulmonary capillaries an example of the general principle of physiology that *structure is a determinant of—and has coevolved with—function*?
3. A general principle of physiology is that *most physiological functions are controlled by multiple regulatory systems, often working in opposition*. What are some examples of factors that have opposing regulatory effects on alveolar ventilation in humans?

CHAPTER 13 ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS

Figure 13.4 The rate of diffusion of gases between the air and the capillaries may be decreased due to the increased resistance to diffusion (see Figures 4.1-4.4 for discussion of factors affecting diffusion).

Figure 13.11 A tube is placed through the chest wall into the now enlarged pleural space. (The original hole causing the pneumothorax would need to be repaired first.) Suction is then applied to the chest tube. The negative pressure decreases P_{ip} below P_{atm} and thereby increases P_{tp}, which results in re-expansion of the lung.

Figure 13.13

	P_{alv}	P_{ip}	P_{tp} ($P_{alv} - P_{ip}$)	Change in Lung Volume
1	0	–4	4	P_{tp} is increasing → lung volume ↑
2	–1	–6	5	P_{tp} is increasing → lung volume ↑
3	0	–7	7	P_{tp} is decreasing → lung volume ↓
4	1	–5	6	P_{tp} is decreasing → lung volume ↓
1	0	–4	4	

Note: The actual volume increase or decrease in mL is determined by the compliance of the lung (see Figure 13.16).

Figure 13.16 Anything that increases P_{tp} during inspiration will, theoretically, increase lung volume. This can be done with positive airway pressure generated by mechanical ventilation, which will increase P_{alv}. This approach can work but also increases the risk of pneumothorax by inducing air leaks from the lung into the intrapleural space.

Figure 13.19 The anatomical dead space would be increased by about 251 mL (or 251 cm^3). (The volume of the tube can be approximated as that of a perfect cylinder [$\pi\ r^2\ h = 3.1416 \times 2^2 \times 20$].) This large increase in anatomical dead space would decrease alveolar ventilation (see Table 13.5), and tidal volume would have to be increased in compensation. (There would also be an increase in airway resistance, which is discussed later in the chapter.)

Figure 13.20 The cells require oxygen for cellular respiration and, in turn, produce carbon dioxide as a toxic metabolic waste product. To support the net uptake of oxygen and net removal of carbon dioxide, oxygen must be transferred from the atmosphere to all of the cells and organs of the body while carbon dioxide must be transferred from the cells to the atmosphere. This requires a highly efficient transport process that involves diffusion of oxygen and carbon dioxide in opposite directions in the lungs and the cells, and bulk flow of blood carrying oxygen and carbon dioxide around the circulatory system from the lungs to the cells and then back to the lungs. These processes result in a net gain of oxygen (250 mL/per min at rest) from the atmosphere for consumption in the cells, and the net loss of carbon dioxide (200 mL/min at rest) from the cells to the atmosphere.

Figure 13.23 The increase in cardiac output with exercise greatly increases pulmonary blood flow and decreases the amount of time erythrocytes are exposed to increased oxygen from the alveoli. In a normal region of the lung, there is a large safety factor such that a large increase in blood flow still allows normal oxygen uptake. However, even small increases in the rate of capillary blood flow in a diseased portion of the lung will decrease oxygen uptake due to a loss of this safety factor.

Figure 13.29 Less O_2 will be unloaded in peripheral tissue as the blood is exposed to increased P_{CO_2} and decreased pH because the oxygen–hemoglobin dissociation curve will not shift to the right as it does in real blood. Also, less O_2 will be loaded in the lungs as P_{CO_2} diffuses from blood into the alveoli because the oxygen–hemoglobin dissociation curve will not shift to the left as it normally would with removal of CO_2 and decreased acidity.

Figure 13.33 The ventilatory response to the hypoxia of altitude would be greatly diminished, and it is likely that the person would be extremely hypoxemic as a result. Carotid body removal did not help in the treatment of asthma, and this approach was abandoned.

Figure 13.35 An adequate supply of oxygen to all cells is required for normal organ function, and maintenance of oxygen delivery in the face of decreased oxygen uptake in the lung is an important homeostatic reflex. The most common cause of a decrease in the inspired P_{O_2} is temporary or permanent habitation at altitude, where the atmospheric pressure and therefore the P_{O_2} of the air is lower than at sea level. Without compensation for the lower inspired P_{O_2}, arterial blood P_{O_2} could decrease to life-threatening levels. All homeostatic processes in the body depend on a continual input of energy derived from heat or ATP; synthesis of ATP requires oxygen. The arterial chemoreceptors (see Figure 13.33) can detect a decrease in arterial P_{O_2} that results from ascent to high altitude and reflexively increase alveolar ventilation to enhance oxygen uptake from the air into the pulmonary capillaries for delivery to the rest of the body. The inability to adequately increase alveolar ventilation at altitude can result in harmful consequences leading to organ damage and even death.

Figure 13.43 These receptors may facilitate the increase in alveolar ventilation that occurs during exercise because pulmonary artery P_{O_2} will decrease and pulmonary artery P_{CO_2} will increase.

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