

A resin cast of the lung, with arteries in blue, veins in red, and the bronchial tree and alveoli in yellow

CHAPTER

22

The Respiratory System

CHAPTER OUTLINE

Anatomy of the Respiratory System 842

- The Nose 842
- The Pharynx 845
- The Larynx 845
- The Trachea and Bronchi 846
- The Lungs 847
- The Pleurae 849

Mechanics of Ventilation 850

- Pressure and Flow 851
- Inspiration 852
- Expiration 853
- Resistance to Airflow 854
- Alveolar Surface Tension 855
- Alveolar Ventilation 855
- Nonrespiratory Air Movements 855
- Measurements of Ventilation 855
- Patterns of Breathing 856

Neural Control of Ventilation 857

- Control Centers in the Brainstem 858
- Afferent Connections to the Brainstem 859
- Voluntary Control 859

Gas Exchange and Transport 859

- Composition of Air 859
- The Air-Water Interface 860

- Alveolar Gas Exchange 860
- Gas Transport 863
- Systemic Gas Exchange 864
- Alveolar Gas Exchange Revisited 866
- Adjustment to the Metabolic Needs of Individual Tissues 866

Blood Chemistry and the Respiratory Rhythm 867

- Hydrogen Ions 867
- Carbon Dioxide 868
- Oxygen 868

Respiratory Disorders 868

- Oxygen Imbalances 869
- Chronic Obstructive Pulmonary Diseases 869
- Smoking and Lung Cancer 869

Connective Issues 873

Chapter Review 874

INSIGHTS

22.1 Clinical Application: Tracheostomy 846

22.2 Clinical Application: Ondine's Curse 859

22.3 Clinical Application: Carbon Monoxide Poisoning 864

22.4 Clinical Application: Diving Physiology and Decompression Sickness 872

Brushing Up

To understand this chapter, it is important that you understand or brush up on the following concepts:

- Serous membranes (p. 182)
- Factors that affect simple diffusion (p. 107)
- The muscles of respiration (p. 345)
- The structure of hemoglobin (pp. 689–690)
- Principles of fluid pressure and flow (p. 733)
- Pulmonary blood circulation (p. 767)

842 Part Four Regulation and Maintenance

Most metabolic processes of the body depend on ATP, and most ATP production requires oxygen and generates carbon dioxide as a waste product. The respiratory and cardiovascular systems collaborate to provide this oxygen and remove the carbon dioxide. Not only do these two systems have a close spatial relationship in the thoracic cavity, they also have such a close functional relationship that they are often considered jointly under the heading *cardiopulmonary*. A disorder that affects the lungs has direct and pronounced effects on the heart, and vice versa.

Furthermore, as discussed in the next two chapters, the respiratory system works closely with the urinary system to regulate the body's acid-base balance. Changes in the blood pH, in turn, trigger autonomic adjustments of the heart rate and blood pressure. Thus, the cardiovascular, respiratory, and urinary systems have an especially close physiological relationship. It is important that we now address the roles of the respiratory and urinary systems in the homeostatic control of blood gases, pH, blood pressure, and other variables related to the body fluids. This chapter deals with the respiratory system and chapter 23 with the urinary system.

Anatomy of the Respiratory System

Objectives

When you have completed this section, you should be able to

- trace the flow of air from the nose to the pulmonary alveoli; and
- relate the function of any portion of the respiratory tract to its gross and microscopic anatomy.

The term **respiration** has three meanings: (1) ventilation of the lungs (breathing), (2) the exchange of gases between air and blood and between blood and tissue fluid, and (3) the use of oxygen in cellular metabolism. In this chapter, we are concerned with the first two processes. Cellular respiration was introduced in chapter 2 and is considered more fully in chapter 26.

The principal organs of the **respiratory system** are the nose, pharynx, larynx, trachea, bronchi, and lungs (fig. 22.1). These organs serve to receive fresh air, exchange gases with the blood, and expel the modified air. Within the lungs, air flows along a dead-end pathway consisting essentially of bronchi → bronchioles → alveoli (with some refinements to be introduced later). Incoming air stops in the alveoli (millions of thin-walled, microscopic air sacs in the lungs), exchanges gases with the bloodstream across the alveolar wall, and then flows back out.

The **conducting division** of the respiratory system consists of those passages that serve only for airflow, essentially from the nostrils through the bronchioles. The **respiratory division** consists of the alveoli and other distal gas-exchange regions. The airway from the nose through the larynx is often called the **upper respiratory tract** (that is, the respiratory organs in the head and neck),

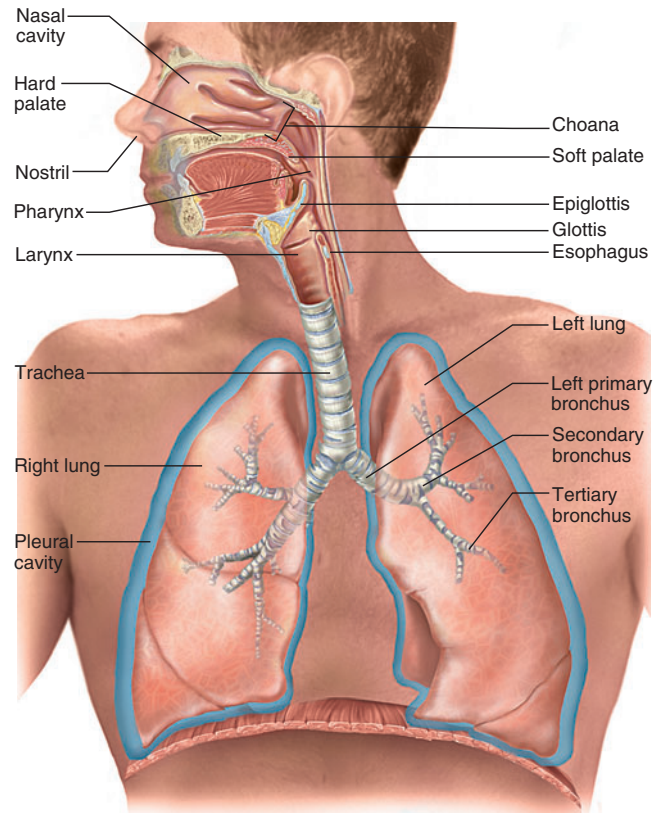


Figure 22.1 The Respiratory System.

and the regions from the trachea through the lungs compose the **lower respiratory tract** (the respiratory organs of the thorax).

The Nose

The **nose** has several functions: it warms, cleanses, and humidifies inhaled air; it detects odors in the airstream; and it serves as a resonating chamber that amplifies the voice. The external, protruding part of the nose is supported and shaped by a framework of bone and cartilage. Its superior half is supported by the nasal bones medially and the maxillae laterally. The inferior half is supported by the **lateral** and **alar cartilages** (fig. 22.2). Dense connective tissue shapes the flared portion called the **ala nasi**, which forms the lateral wall of each nostril.

The **nasal cavity** (fig. 22.3) extends from the **anterior (external) nares** (NERR-eez) (singular, *naris*), or **nostrils**, to the **posterior (internal) nares**, or **choanae**¹ (co-AH-nee). The dilated chamber inside the ala nasi is called the **vestibule**. It is lined with stratified squamous epithelium

¹choana = funnel

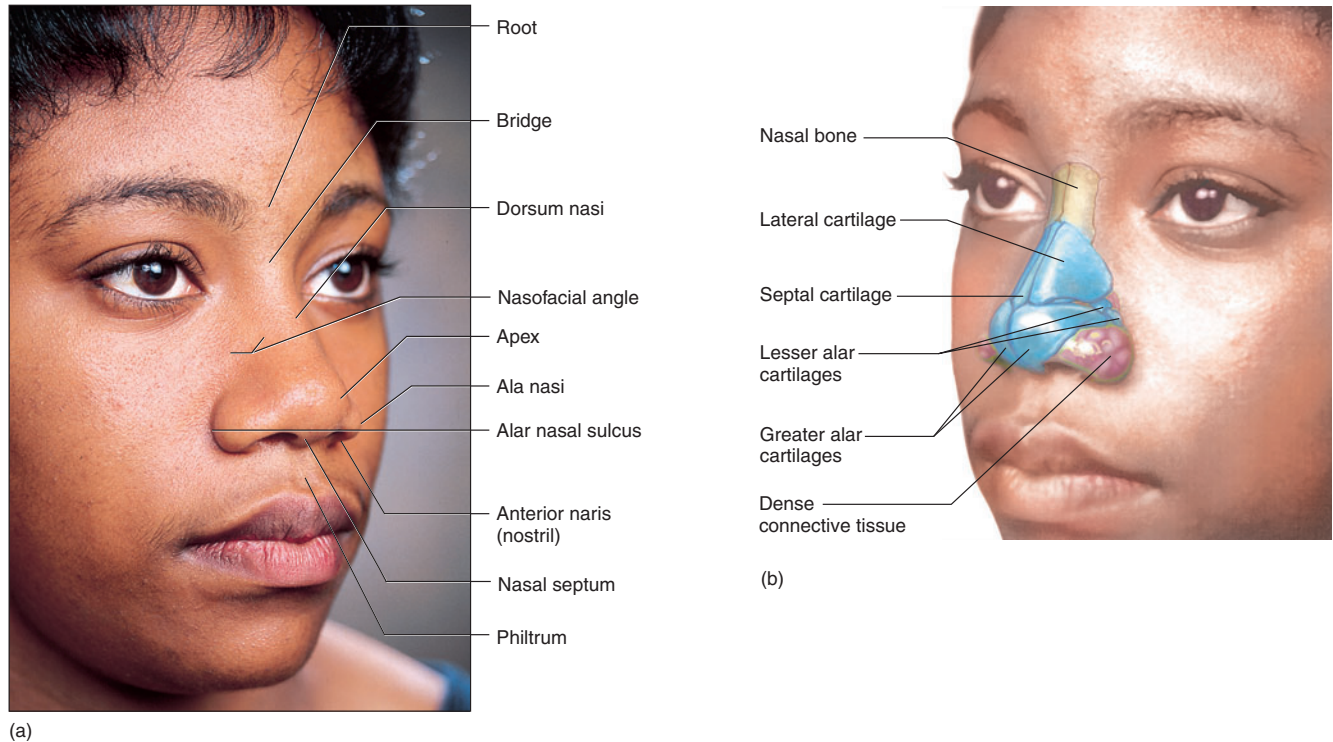


Figure 22.2 Anatomy of the Nasal Region. (a) External anatomy. (b) Connective tissues that shape the nose.

and has stiff **vibrissae** (vy-BRIS-ee), or **guard hairs**, that block the inhalation of large particles.

The **nasal septum** divides the nasal cavity into right and left chambers called **nasal fossae** (FOSS-ee). The vomer forms the inferior part of the septum, the perpendicular plate of the ethmoid bone forms its superior part, and the **septal cartilage** forms its anterior part. The ethmoid and sphenoid bones compose the roof of the nasal cavity and the palate forms its floor. The palate separates the nasal cavity from the oral cavity and allows you to breathe while there is food in your mouth. The paranasal sinuses (see chapter 8) and the nasolacrimal ducts of the orbits drain into the nasal cavity.

The lateral wall of the fossa gives rise to three folds of tissue—the **superior, middle, and inferior nasal conchae**² (CON-kee)—that project toward the septum and occupy most of the fossa. They consist of mucous membranes supported by thin scroll-like **turbinate bones**. Beneath each concha is a narrow air passage called a **meatus** (me-AY-tus). The narrowness of these passages and the turbulence caused by the conchae ensure that most air contacts the mucous membrane on its way through, enabling the nose to cleanse, warm, and humidify it.

²concha = seashell

The **olfactory mucosa**, concerned with the sense of smell, lines the roof of the nasal fossa and extends over part of the septum and superior concha. The rest of the cavity is lined by ciliated pseudostratified **respiratory mucosa**. The cilia continually beat toward the posterior nares and drive debris-laden mucus into the pharynx to be swallowed and digested. The nasal mucosa has an important defensive role. Goblet cells in the epithelium and glands in the lamina propria secrete a layer of mucus that traps inhaled particles. Bacteria are destroyed by lysozyme in the mucus. Additional protection against bacteria is contributed by lymphocytes, which populate the lamina propria in large numbers, and by antibodies (IgA) secreted by plasma cells.

The lamina propria contains large blood vessels that help to warm the air. The inferior concha has an especially extensive venous plexus called the **erectile tissue** (*swell body*). Every 30 to 60 minutes, the erectile tissue on one side becomes engorged with blood and restricts airflow through that fossa. Most air is then directed through the other naris and fossa, allowing the engorged side time to recover from drying. Thus the preponderant flow of air shifts between the right and left nares once or twice each hour. The inferior concha is the most common site of spontaneous **epistaxis** (nosebleed), which is sometimes a sign of hypertension.

844 Part Four Regulation and Maintenance

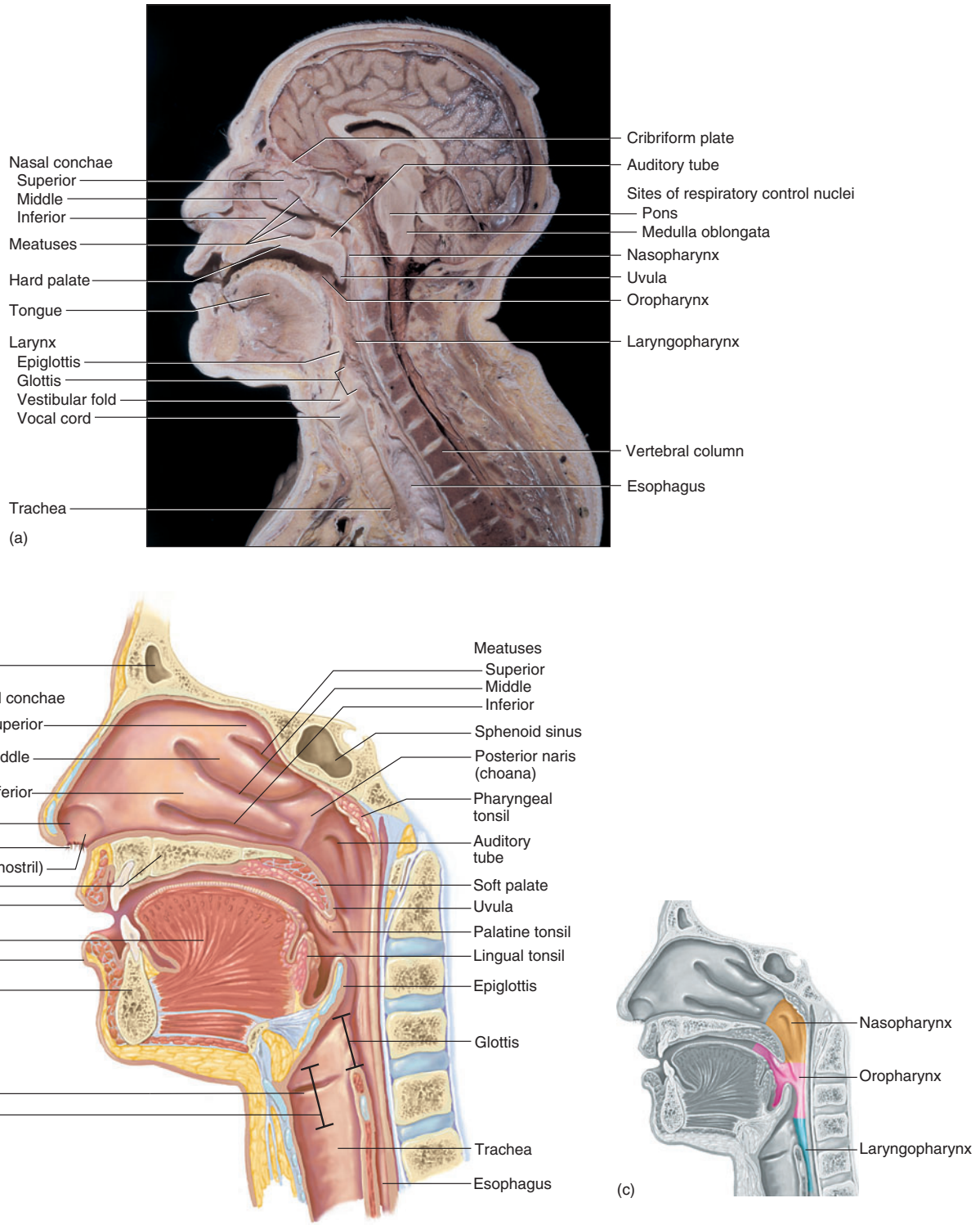


Figure 22.3 Anatomy of the Upper Respiratory Tract. (a) Median section of the head. (b) Internal anatomy. (c) Regions of the pharynx. Why do throat infections so easily spread to the middle ear?

The Pharynx

The **pharynx** (FAIR-inks) is a muscular funnel extending about 13 cm (5 in.) from the choanae to the larynx. It has three regions: the *nasopharynx*, *oropharynx*, and *laryngopharynx* (fig. 22.3c).

The **nasopharynx**, which lies posterior to the choanae and dorsal to the soft palate, receives the auditory (eustachian) tubes from the middle ears and houses the pharyngeal tonsil. Inhaled air turns 90° downward as it passes through the nasopharynx. Dust particles larger than 10 μm generally cannot make the turn because of their inertia. They collide with the posterior wall of the nasopharynx and stick to the mucosa near the tonsil, which is well positioned to respond to airborne pathogens.

The **oropharynx** is a space between the soft palate and root of the tongue that extends inferiorly as far as the hyoid bone. It contains the palatine and lingual tonsils. Its anterior border is formed by the base of the tongue and the *fauces* (FAW-seez), the opening of the oral cavity into the pharynx.

The **laryngopharynx** (la-RING-go-FAIR-inks) begins with the union of the nasopharynx and oropharynx at the level of the hyoid bone. It passes inferiorly and dorsal to the larynx and ends at the level of the *cricoid cartilage* at the inferior end of the larynx (described next). The esophagus begins at that point. The nasopharynx passes only air and is lined by pseudostratified columnar epithelium, whereas the oropharynx and laryngopharynx pass air,

food, and drink and are lined by stratified squamous epithelium.

The Larynx

The **larynx** (LAIR-inks), or “voicebox” (figs. 22.4 and 22.5), is a cartilaginous chamber about 4 cm (1.5 in.) long. Its primary function is to keep food and drink out of the airway, but it has evolved the additional role of producing sound.

The superior opening of the larynx, the **glottis**,³ is guarded by a flap of tissue called the **epiglottis**.⁴ During swallowing, *extrinsic muscles* of the larynx pull the larynx upward toward the epiglottis, the tongue pushes the epiglottis downward to meet it, and the epiglottis directs food and drink into the esophagus dorsal to the airway. The *vestibular folds* of the larynx, discussed shortly, play a greater role in keeping food and drink out of the airway, however. People who have had their epiglottis removed because of cancer do not choke any more than when it was present.

In infants, the larynx is relatively high in the throat and the epiglottis touches the soft palate. This creates a more or less continuous airway from the nasal cavity to the larynx and allows an infant to breathe continually while swallowing. The epiglottis deflects milk away from

³glottis = back of the tongue

⁴epi = above, upon

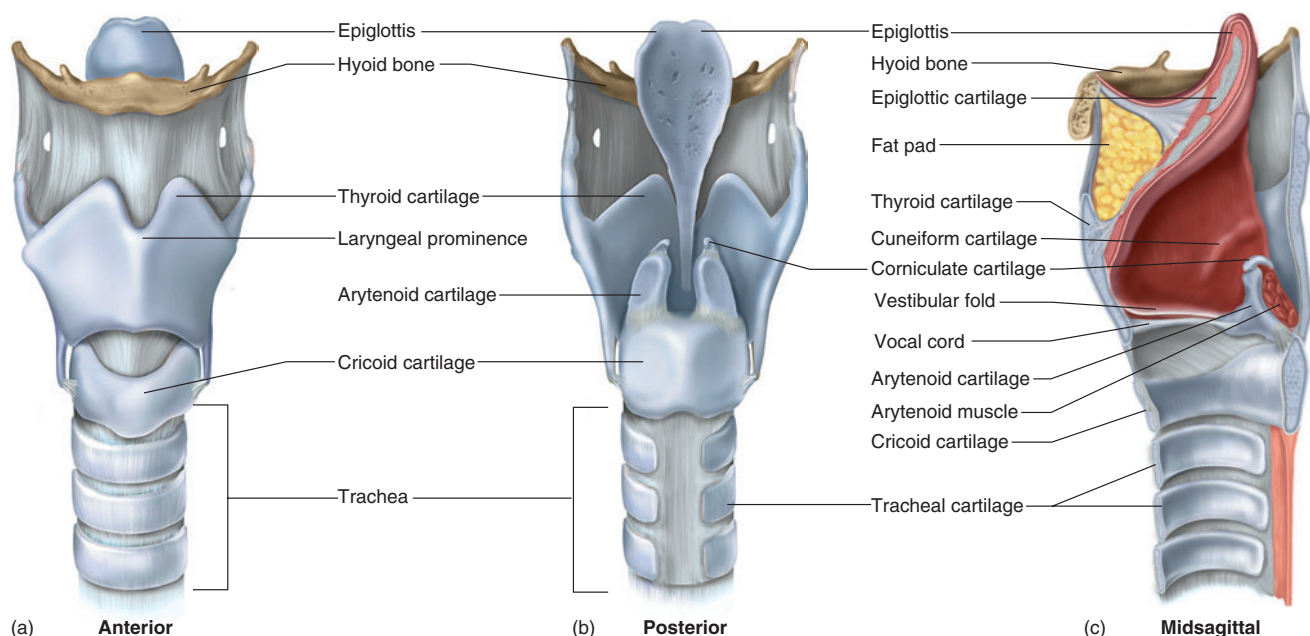


Figure 22.4 Anatomy of the Larynx. (a) Anterior aspect. (b) Posterior aspect. (c) Median section, anterior aspect facing left.

846 Part Four Regulation and Maintenance

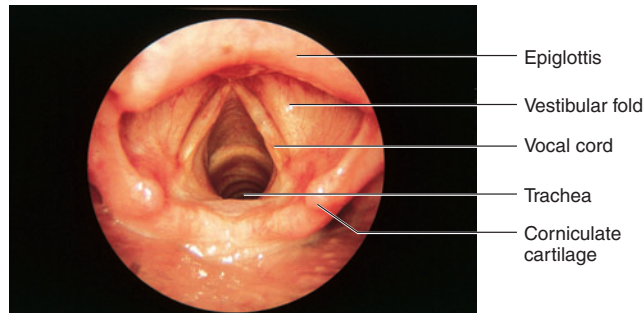


Figure 22.5 Superior View into the Larynx of a Living Person, as Seen with a Laryngoscope.

the airstream, like rain running off a tent while it remains dry inside. By age two, the root of the tongue becomes more muscular and forces the larynx to descend to a lower position.

The framework of the larynx consists of nine cartilages. The first three are relatively large and unpaired. The most superior one, the **epiglottic cartilage**, is a spoon-shaped supportive plate in the epiglottis. The largest, the **thyroid cartilage**, is named for its shieldlike shape. It has an anterior peak, the *laryngeal prominence*, commonly known as the Adam's apple. Testosterone stimulates the growth of this prominence, which is therefore significantly larger in males than in females. Inferior to the thyroid cartilage is a ringlike **cricoid**⁵ (CRY-coyd) **cartilage**, which connects the larynx to the trachea.

The remaining cartilages are smaller and occur in three pairs. Posterior to the thyroid cartilage are the two **arytenoid**⁶ (AR-ih-TEE-noyd) **cartilages**, and attached to their upper ends are a pair of little horns, the **corniculate**⁷ (cor-NICK-you-late) **cartilages**. The arytenoid and corniculate cartilages function in speech, as explained shortly. A pair of **cuneiform**⁸ (cue-NEE-ih-form) **cartilages** support the soft tissues between the arytenoids and the epiglottis. The epiglottic cartilage is elastic cartilage; all the others are hyaline.

The walls of the larynx are also quite muscular. The deep **intrinsic muscles** operate the vocal cords, and the superficial **extrinsic muscles** connect the larynx to the hyoid bone and elevate the larynx during swallowing. The extrinsic muscles, also called the *infrahyoid group*, are named and described in chapter 10.

The interior wall of the larynx has two folds on each side that stretch from the thyroid cartilage in front to the arytenoid cartilages in back. The superior pair, called the

vestibular folds (fig. 22.5), play no role in speech but close the glottis during swallowing. The inferior pair, the **vocal cords** (vocal folds), produce sound when air passes between them. They are covered with stratified squamous epithelium, best suited to endure vibration and contact between the cords.

The intrinsic muscles control the vocal cords by pulling on the corniculate and arytenoid cartilages, causing the cartilages to pivot. Depending on their direction of rotation, the arytenoid cartilages abduct or adduct the vocal cords (fig. 22.6). Air forced between the adducted vocal cords vibrates them, producing a high-pitched sound when the cords are relatively taut and a lower-pitched sound when they are more relaxed. In adult males, the vocal cords are longer and thicker, vibrate more slowly, and produce lower-pitched sounds than in females. Loudness is determined by the force of the air passing between the vocal cords. The crude sounds of the vocal cords are formed into words by actions of the pharynx, oral cavity, tongue, and lips.

The Trachea and Bronchi

The **trachea** (TRAY-kee-uh), or “windpipe,” is a rigid tube about 12 cm (4.5 in.) long and 2.5 cm (1 in.) in diameter, lying anterior to the esophagus (fig. 22.7a). It is supported by 16 to 20 C-shaped rings of hyaline cartilage, some of which you can palpate between your larynx and sternum. Like the wire spiral in a vacuum cleaner hose, the cartilage rings reinforce the trachea and keep it from collapsing when you inhale. The open part of the C faces posteriorly, where it is spanned by a smooth muscle, the **trachealis** (fig. 22.7c). The gap in the C allows room for the esophagus to expand as swallowed food passes by. The trachealis muscles can contract or relax to adjust tracheal airflow. At its inferior end, the trachea branches into the right and left *primary bronchi*, which supply the lungs. They are further traced in the following discussion of the *bronchial tree* in the lungs.

The larynx, trachea, and bronchial tree are lined mostly by ciliated pseudostratified columnar epithelium (figs. 22.7b and 22.8), which functions as a **mucociliary escalator**. That is, the mucus traps inhaled debris and then the ciliary beating drives the mucus up to the pharynx, where it is swallowed.

Insight 22.1 Clinical Application

Tracheostomy

If the airway is obstructed with secretions or foreign matter, it may be necessary to make a temporary opening in the trachea inferior to the larynx and insert a tube to allow airflow—a procedure called *tracheostomy*. This prevents asphyxiation, but the inhaled air bypasses the nasal cavity and thus is not humidified. If the opening is left for long,

⁵crico = ring + oid = resembling

⁶aryten = ladle

⁷corni = horn + cul = little + ate = possessing

⁸cune = wedge + form = shape

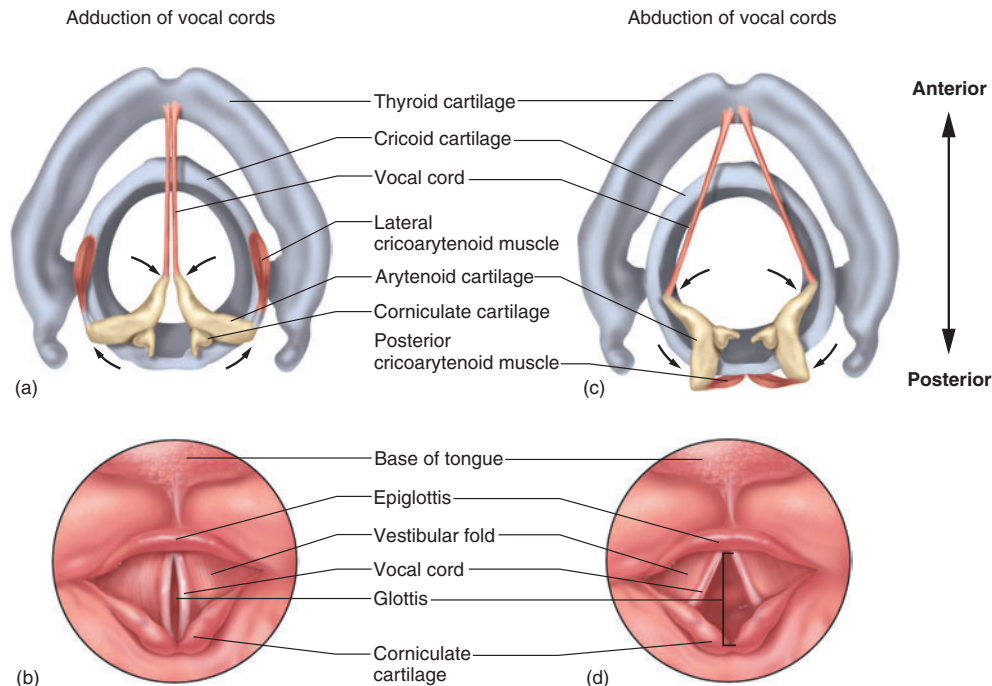


Figure 22.6 Action of Some of the Intrinsic Laryngeal Muscles on the Vocal Cords. (a) Adduction of the vocal cords by the lateral cricoarytenoid muscles. (b) Adducted vocal cords seen with the laryngoscope. (c) Abduction of the vocal cords by the posterior cricoarytenoid muscles. (d) Abducted vocal cords seen with the laryngoscope.

the mucous membranes of the respiratory tract can dry out and become encrusted, interfering with the clearance of mucus from the tract and leading to severe infection. We can understand the functional importance of the nasal cavity especially well when we see the consequences of bypassing it.

The Lungs

Each **lung** (fig. 22.9) is a somewhat conical organ with a broad, concave **base** resting on the diaphragm and a blunt peak called the **apex** projecting slightly superior to the clavicle. The broad **costal surface** is pressed against the rib cage, and the smaller concave **mediastinal surface** faces medially. The lungs do not fill the entire rib cage. Inferior to the lungs and diaphragm, much of the space within the rib cage is occupied by the liver, spleen, and stomach (see fig. A.14, p. 45).

The lung receives the bronchus, blood vessels, lymphatic vessels, and nerves through its **hilum**, a slit in the mediastinal surface (see fig. 22.26a, p. 870). These structures entering the hilum constitute the **root** of the lung. Because the heart tilts to the left, the left lung is a little smaller than the right and has an indentation called the **cardiac impression** to accommodate it. The left lung has a **superior lobe** and an **inferior lobe** with a deep fissure

between them; the right lung, by contrast, has three lobes—**superior**, **middle**, and **inferior**—separated by two fissures.

The Bronchial Tree

The lung has a spongy parenchyma containing the **bronchial tree** (fig 22.10), a highly branched system of air tubes extending from the primary bronchus to about 65,000 *terminal bronchioles*. Two **primary bronchi** (BRONK-eye) arise from the trachea at the level of the angle of the sternum. Each continues for 2 to 3 cm and enters the hilum of its respective lung. The right bronchus is slightly wider and more vertical than the left; consequently, *aspirated* (inhaled) foreign objects lodge in the right bronchus more often than in the left. Like the trachea, the primary bronchi are supported by C-shaped hyaline cartilages. All divisions of the bronchial tree also have a substantial amount of elastic connective tissue, which is important in expelling air from the lungs.

After entering the hilum, the primary bronchus branches into one **secondary (lobar) bronchus** for each pulmonary lobe. Thus, there are two secondary bronchi in the left lung and three in the right.

Each secondary bronchus divides into **tertiary (segmental) bronchi**—10 in the right lung and 8 in the left.

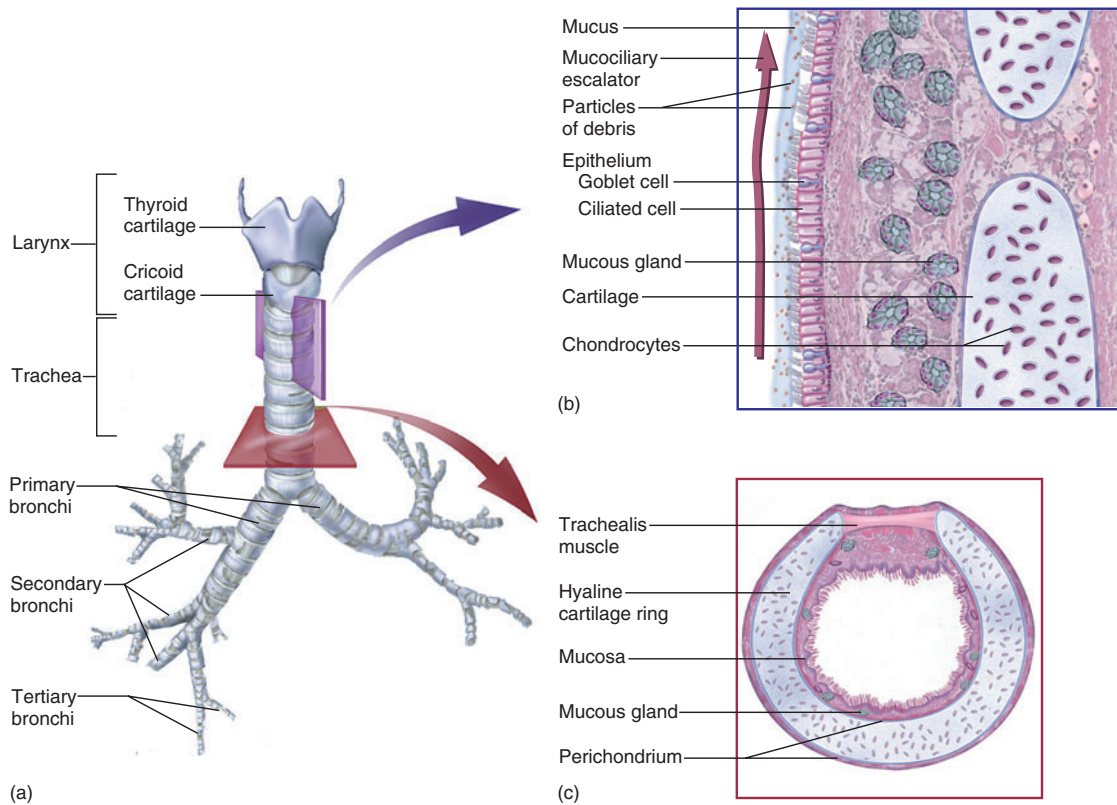


Figure 22.7 Anatomy of the Lower Respiratory Tract. (a) Anterior view. (b) Longitudinal section of the trachea showing the action of the mucociliary escalator. (c) Cross section of the trachea showing the C-shaped tracheal cartilage.

Why do inhaled objects more often go into the right primary bronchus than into the left?

The portion of the lung supplied by each tertiary bronchus is called a **bronchopulmonary segment**. Secondary and tertiary bronchi are supported by overlapping plates of cartilage, not rings. Branches of the *pulmonary artery* closely follow the bronchial tree on their way to the alveoli. The bronchial tree itself is nourished by the *bronchial artery*, which arises from the aorta and carries systemic blood.

Bronchioles are continuations of the airway that are 1 mm or less in diameter and lack cartilage. A well-developed layer of smooth muscle in their walls enables them to dilate or constrict, as discussed later. Spasmodic contractions of this muscle at death cause the bronchioles to exhibit a wavy lumen in most histological sections. The portion of the lung ventilated by one bronchiole is called a **pulmonary lobule**.

Each bronchiole divides into 50 to 80 **terminal bronchioles**, the final branches of the conducting division. They measure 0.5 mm or less in diameter and have no mucous glands or goblet cells. They do have cilia, however, so that mucus draining into them from the higher passages can be driven back by the mucociliary escalator, thus preventing congestion of the terminal bronchioles and alveoli.

Each terminal bronchiole gives off two or more smaller **respiratory bronchioles**, which mark the beginning of the respiratory division. All branches of the respiratory division are defined by the presence of alveoli. The respiratory bronchioles have scanty smooth muscle, and the smallest of them are nonciliated. Each divides into 2 to 10 elongated, thin-walled passages called **alveolar ducts** that end in **alveolar sacs**, which are grapelike clusters of alveoli (fig. 22.11). Alveoli also bud from the walls of the respiratory bronchioles and alveolar ducts.

The epithelium of the bronchial tree is pseudostratified columnar in the bronchi, simple cuboidal in the bronchioles, and simple squamous in the alveolar ducts, sacs, and alveoli. It is ciliated except in the distal reaches of the respiratory bronchioles and beyond.

Alveoli

The functional importance of human lung structure is best appreciated by comparison to the lungs of a few other animals. In frogs and other amphibians, the lung is a simple sac lined with blood vessels. This is sufficient to meet the oxygen needs of animals with relatively low metabolic

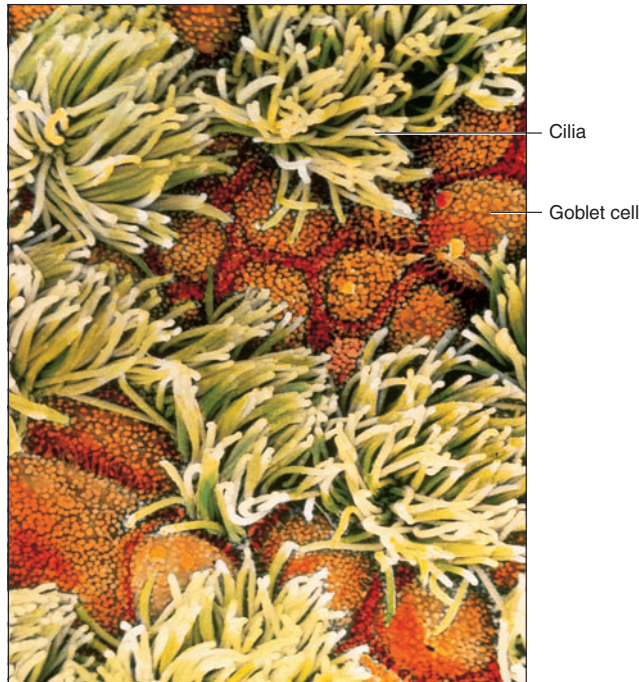


Figure 22.8 The Tracheal Epithelium Showing Ciliated Cells and Nonciliated Goblet Cells. The small bumps on the goblet cells are microvilli. (Colorized SEM micrograph)

rates. Mammals, with their high metabolic rates, could never have evolved with such a simple lung. Rather than consisting of one large sac, each human lung is a spongy mass composed of 150 million little sacs, the alveoli, which provide about 70 m² of surface for gas exchange.

An **alveolus** (AL-vee-OH-lus) (fig. 22.12) is a pouch about 0.2 to 0.5 mm in diameter. Its wall consists predominantly of **squamous (type I) alveolar cells**—thin cells that allow for rapid gas diffusion between the alveolus and bloodstream. About 5% of the alveolar cells are round to cuboidal **great (type II) alveolar cells**. They secrete a detergent-like lipoprotein called **pulmonary surfactant**, which forms a thin film on the insides of the alveoli and bronchioles. Its function is discussed later.

Alveolar macrophages (dust cells) wander the lumens of the alveoli and the connective tissue between them. They are the last line of defense against inhaled matter. Particles over 10 µm in diameter are usually strained out by the nasal vibrissae or trapped in the mucus of the upper respiratory tract. Most particles 2 to 10 µm in diameter are trapped in the mucus of the bronchi and bronchioles, where the airflow is relatively slow, and then removed by the mucociliary escalator. Many particles smaller than 2 µm, however, make their way into the alveoli, where they are phagocytized by the macrophages. In lungs that are infected or bleeding, the macrophages also phagocytize bacteria and loose blood cells. Alveolar

macrophages greatly outnumber all other cell types in the lung; as many as 50 million perish each day as they ride up the mucociliary escalator to be swallowed.

Each alveolus is surrounded by a basket of blood capillaries supplied by the pulmonary artery. The barrier between the alveolar air and blood, called the **respiratory membrane**, consists only of the squamous type I alveolar cell, the squamous endothelial cell of the capillary, and their fused basement membranes. These have a total thickness of only 0.5 µm.

The pulmonary circulation has very low blood pressure. In alveolar capillaries, the mean blood pressure is 10 mmHg and the oncotic pressure is 25 mmHg. The osmotic uptake of water thus overrides filtration and keeps the alveoli free of fluid. The lungs also have a more extensive lymphatic drainage than any other organ in the body. The low capillary blood pressure also prevents the rupture of the delicate respiratory membrane.

The Pleurae

The surface of the lung is covered by a serous membrane, the **visceral pleura** (PLOOR-uh), which extends into the fissures. At the hilum, the visceral pleura turns back on itself and forms the **parietal pleura**, which adheres to the mediastinum, superior surface of the diaphragm, and inner surface of the rib cage (see fig. 22.9b). An extension of the parietal pleura, the **pulmonary ligament**, extends from the base of each lung to the diaphragm. The space between the parietal and visceral pleurae is called the **pleural cavity**. The two membranes are normally separated only by a film of slippery **pleural fluid**; thus, the pleural cavity is only a *potential space*, meaning there is normally no room between the membranes, but under pathological conditions this space can fill with air or liquid.

The pleurae and pleural fluid have three functions:

1. **Reduction of friction.** Pleural fluid acts as a lubricant that enables the lungs to expand and contract with minimal friction. In some forms of *pleurisy*, the pleurae are dry and inflamed and each breath gives painful testimony to the function that the fluid should be serving.
2. **Creation of pressure gradient.** Pressure in the pleural cavity is lower than atmospheric pressure; as explained later, this assists in inflation of the lungs.
3. **Compartmentalization.** The pleurae, mediastinum, and pericardium compartmentalize the thoracic organs and prevent infections of one organ from spreading easily to neighboring organs.

Think About It

In what ways do the structure and function of the pleurae resemble the structure and function of the pericardium?

850 Part Four Regulation and Maintenance

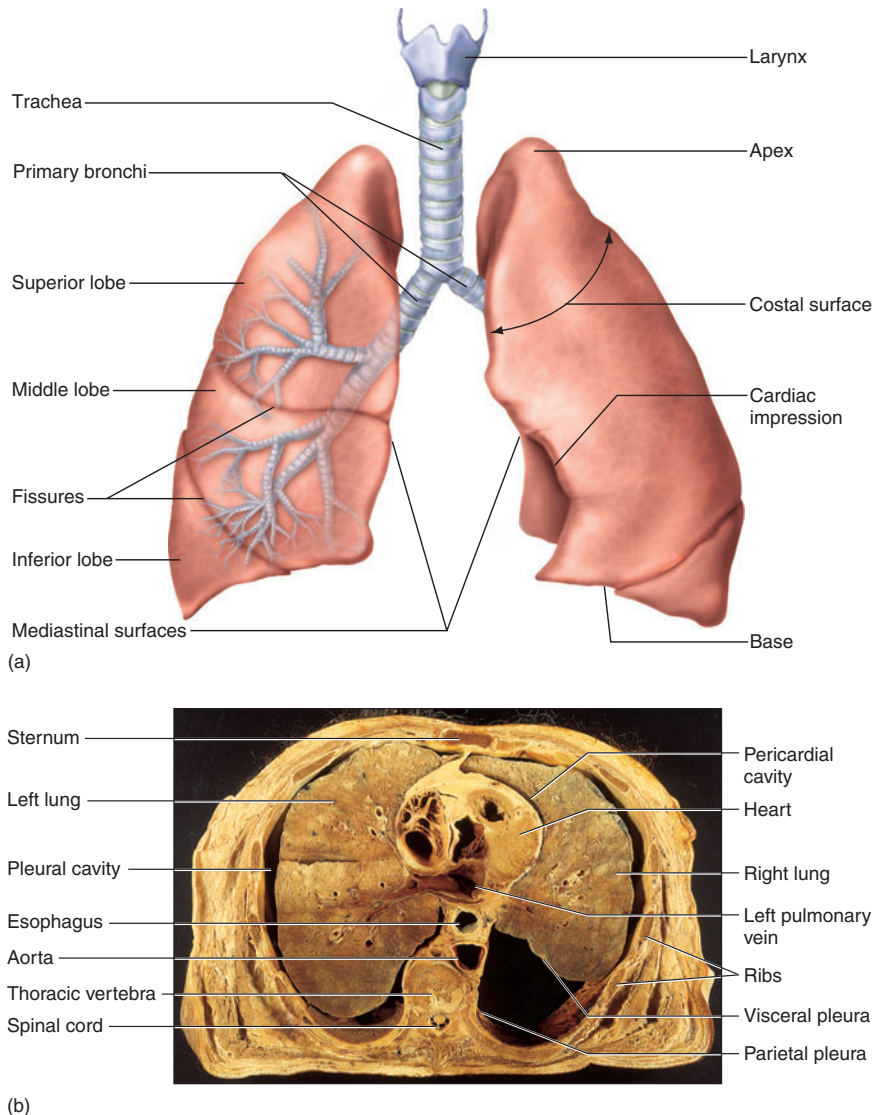


Figure 22.9 Gross Anatomy of the Lungs. (a) Anterior view. (b) Cross section through the thorax of a cadaver showing the heart, lungs, and pleurae.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

1. A dust particle is inhaled and gets into an alveolus without being trapped along the way. Describe the path it takes, naming all air passages from external naris to alveolus. What would happen to it after arrival in the alveolus?
2. Describe the histology of the epithelium and lamina propria of the nasal cavity and the functions of the cell types present.
3. Describe the roles of the intrinsic muscles, corniculate cartilages, and arytenoid cartilages in speech.
4. Contrast the epithelium of the bronchioles with that of the alveoli and explain how the structural difference is related to their functional differences.

Mechanics of Ventilation

Objectives

When you have completed this section, you should be able to

- explain how pressure gradients cause air to flow into and out of the lungs;
- explain how the respiratory muscles produce these pressure gradients;
- explain the relevance of pulmonary compliance and elasticity to ventilation;
- explain why the alveoli do not collapse when one exhales; and
- define various measurements of pulmonary function.



Figure 22.10 The Bronchial Trees. Each color identifies a bronchopulmonary segment supplied by a tertiary bronchus.

Understanding the ventilation of the lungs, the transport of gases in the blood, and the exchange of gases with the tissues is largely a matter of understanding gas behavior. Several of the gas laws of physics are highly relevant to understanding respiratory function, but since they are named after their discoverers, they are not intuitively easy to remember by name. Table 22.1 lists the gas laws used in this chapter and may be a helpful reference as you progress through respiratory physiology.

A resting adult breathes 10 to 15 times per minute, inhaling about 500 mL of air during **inspiration** and exhaling it again during **expiration**. In this section, we examine the muscular actions and pressure gradients that produce this airflow.

Pressure and Flow

Airflow is governed by the same principles of flow, pressure, and resistance as blood flow (see chapter 20). The pressure that drives respiration is **atmospheric (barometric) pressure**—the weight of the air above us. At sea level, a column of air as thick as the atmosphere (60 mi) and 1 in. square weighs 14.7 lb; it is thus said to exert a force of 14.7 pounds per square inch (psi). In standard international (SI) units, this is a column of air 100 km high exerting a force of 1.013×10^6 dynes/cm². This pressure, called *1 atmosphere* (1 atm), is enough to force a column of mer-

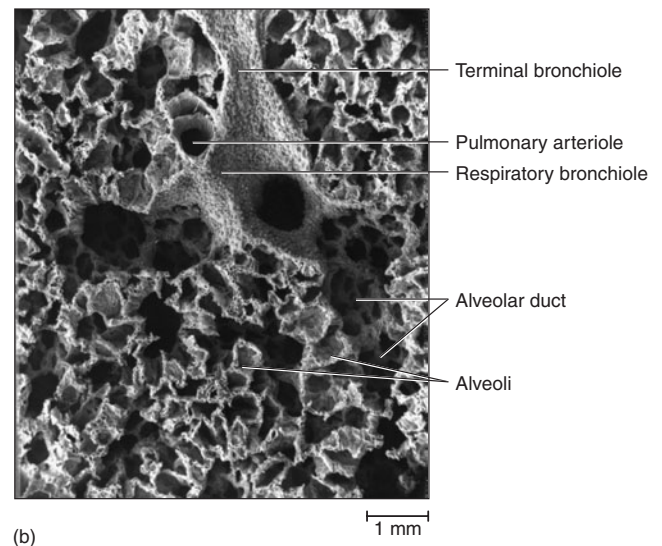
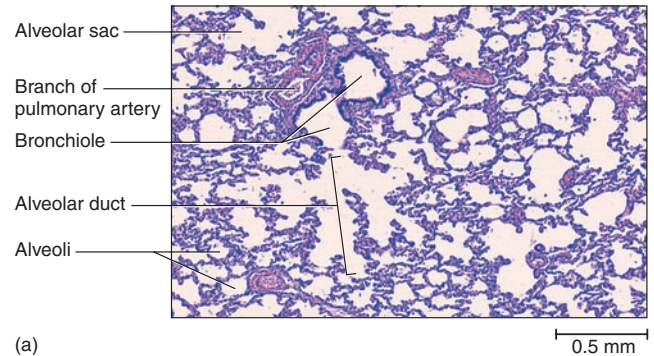


Figure 22.11 Tissue of the Lung. (a) Light micrograph; (b) SEM micrograph. Note the spongy texture of the lung.

cury 760 mm up an evacuated tube; therefore, 1 atm = 760 mmHg. This is the average atmospheric pressure at sea level; it fluctuates from day to day and is lower at higher altitudes.

One way to change the pressure of a gas, and thus to make it flow, is to change the volume of its container. **Boyle's law** states that *the pressure of a given quantity of gas is inversely proportional to its volume* (assuming a constant temperature). If the lungs contain a quantity of gas and lung volume increases, their **intrapulmonary pressure**—the pressure within the alveoli—falls. If lung volume decreases, intrapulmonary pressure rises. (Compare this to the syringe analogy on p. 734.) To make air flow into the lungs, it is necessary only to lower the intrapulmonary pressure below the atmospheric pressure. Raising the intrapulmonary pressure above the atmospheric pressure makes air flow out again. These changes are created as skeletal muscles of the thoracic and abdominal walls change the volume of the thoracic cavity.

852 Part Four Regulation and Maintenance

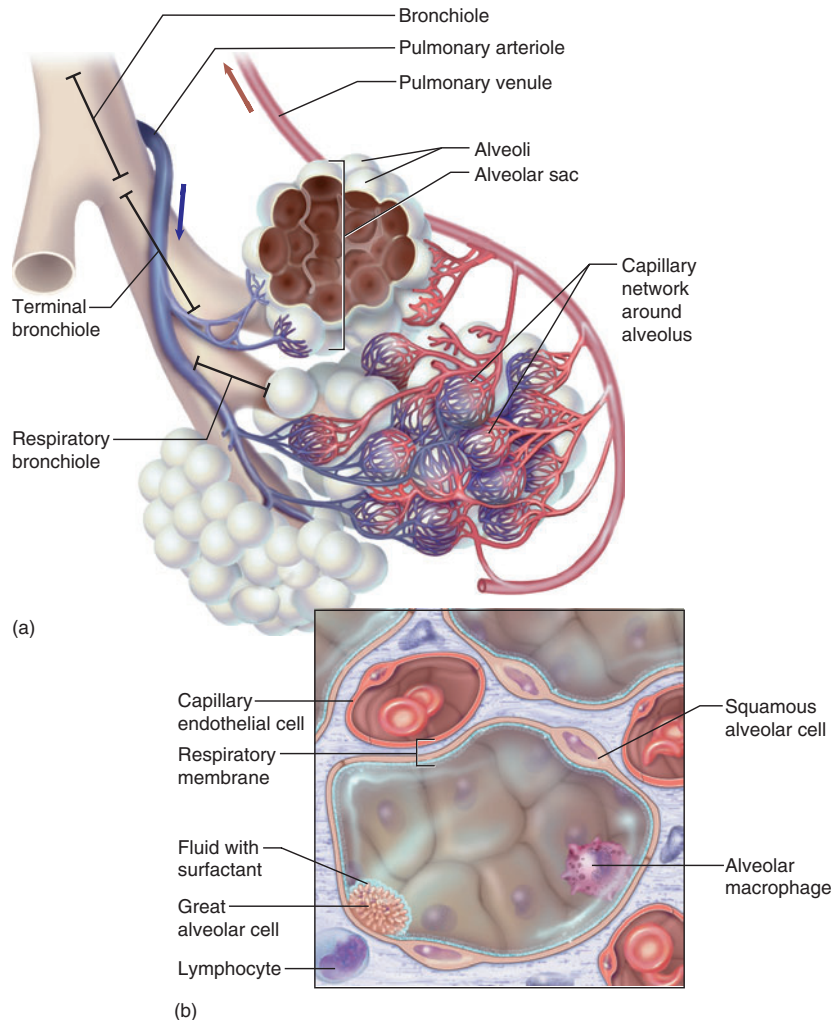


Figure 22.12 Pulmonary Alveoli. (a) Clusters of alveoli and their blood supply. (b) Structure of an alveolus.

What matters to flow is the *difference* between atmospheric pressure and intrapulmonary pressure. Since atmospheric pressures vary from one place and time to another, it is more useful for our discussion to refer to relative pressures. A relative pressure of -3 mmHg, for example, means 3 mmHg below atmospheric pressure; a relative pressure of $+3$ mmHg is 3 mmHg above atmospheric pressure. At an atmospheric pressure of 760 mmHg, these would represent absolute pressures of 757 and 763 mmHg, respectively.

Inspiration

Pulmonary ventilation is achieved by rhythmically changing the pressure in the thoracic cavity. Air flows into the

lungs when thoracic pressure falls below atmospheric pressure, then it's forced out when thoracic pressure rises above atmospheric pressure. The diaphragm does most of the work. It is dome-shaped at rest, but when stimulated by the phrenic nerves, it tenses and flattens somewhat, dropping about 1.5 cm in quiet respiration and as much as 7 cm in deep breathing. This enlarges the thoracic cavity and thus reduces its internal pressure. Other muscles help. The scalenes fix (immobilize) the first pair of ribs while the external intercostal muscles lift the remaining ribs like bucket handles, making them swing up and out. Deep inspiration is aided by the pectoralis minor, sternocleidomastoid, and erector spinae muscles.

As the rib cage expands, the parietal pleura clings to it. In the space between the parietal and visceral pleurae,

Table 22.1 The Gas Laws of Respiratory Physiology

<i>Boyle's Law</i> ⁹	The pressure of a given quantity of gas is inversely proportional to its volume (assuming a constant temperature).
<i>Charles' Law</i> ¹⁰	The volume of a given quantity of gas is directly proportional to its absolute temperature (assuming a constant pressure).
<i>Dalton's Law</i> ¹¹	The total pressure of a gas mixture is equal to the sum of the partial pressures of its individual gases.
<i>Henry's Law</i> ¹²	At the air-water interface, the amount of gas that dissolves in water is determined by its solubility in water and its partial pressure in the air (assuming a constant temperature).

⁹Robert Boyle (1627–91), English physicist

¹⁰Jacques A. C. Charles (1746–1823), French physicist

¹¹John Dalton (1766–1844), British chemist

¹²William Henry (1774–1836), British chemist

the **intrapleural pressure** drops from a value of about –4 mmHg at rest to –6 mmHg during inspiration (fig. 22.13). The visceral pleura clings to the parietal pleura like a sheet of wet paper, so it too is pulled outward. Since the visceral pleura forms the lung surface, the lung expands as well. Not all the pressure change in the pleural cavity is transferred to the interior of the lungs, but the intrapulmonary pressure drops to about –3 mmHg. At an atmospheric pressure of 760 mmHg (1 atm), the intrapleural pressure would be 754 mmHg and the intrapulmonary pressure 757 mmHg. The difference between these, 3 mmHg, is the **transpulmonary pressure**. The transpulmonary gradient of 757 → 754 mmHg helps the lungs expand in the thoracic cavity, and the gradient of 760 → 757 mmHg from atmospheric to intrapulmonary pressure makes air flow into the lungs. (All these values assume a barometric pressure of 1 atm.)

Another force that expands the lungs is warming of the inhaled air. **Charles' law** states that *the volume of a given quantity of gas is directly proportional to its absolute temperature*. On a day when the ambient temperature is 21°C (70°F), inhaled air is heated to 37°C (16°C warmer) by the time it reaches the alveoli. As the inhaled air expands, it helps to inflate the lungs.

When the respiratory muscles stop contracting, the inflowing air quickly achieves an intrapulmonary pressure equal to atmospheric pressure, and flow stops. The dimensions of the thoracic cage increase by only a few millimeters in each direction, but this is enough to increase its total volume by 500 mL. Thus, 500 mL of air flows into the respiratory tract during quiet breathing.

Think About It

When you inhale, does your chest expand because your lungs inflate, or do your lungs inflate because your chest expands? Explain.

Expiration

Inspiration requires a muscular effort and therefore an expenditure of ATP and calories. By contrast, normal expiration during quiet breathing is an energy-saving passive process that requires little muscular contraction other than a braking action explained shortly. Expiration is achieved by the elasticity of the lungs and thoracic cage—the tendency to return to their original dimensions when released from tension. The bronchial tree has a substantial amount of elastic connective tissue in its walls. The attachments of the ribs to the spine and sternum, and the tendons of the diaphragm and other respiratory muscles, also have a degree of elasticity that causes them to spring back when muscular contraction ceases. As these structures recoil, the thoracic cage diminishes in size. In accordance with Boyle's law, this raises the intrapulmonary pressure; it peaks at about +3 mmHg and expels air from the lungs (fig. 22.13). Diseases that reduce pulmonary elasticity interfere with expiration, as we will see in the discussion of emphysema.

When inspiration ceases, the phrenic nerves continue to stimulate the diaphragm for a little while longer. This produces a slight braking action that prevents the lungs from recoiling too abruptly, so it makes the transition from inspiration to expiration smoother. In relaxed breathing, inspiration usually lasts about 2 seconds and expiration about 3 seconds.

To exhale more completely than usual—say, in blowing out the candles on your birthday cake—you contract your internal intercostal muscles, which depress the ribs. You also contract the abdominal muscles (internal and external abdominal obliques, transversus abdominis, and rectus abdominis), which raise the intra-abdominal pressure and force the viscera and diaphragm upward, putting pressure on the thoracic cavity. Intrapulmonary pressure rises as high as 20 to 30 mmHg above atmospheric pressure, causing faster and deeper evacuation of the lungs. Abdominal control of expiration is important in singing and public speaking.

The effect of pulmonary elasticity is evident in a pathological state of pneumothorax and atelectasis. **Pneumothorax** is the presence of air in the pleural cavity. If the thoracic wall is punctured, for example, air is sucked through the wound into the pleural cavity during inspiration and separates the visceral and parietal pleurae. Without the negative intrapleural pressure to keep the lungs inflated, the lungs recoil and collapse. The collapse of a lung or part of a lung is called **atelectasis**¹³ (AT-eh-LEC-ta-sis).

¹³*atel* = imperfect, incomplete + *ectasis* = extension

854 Part Four Regulation and Maintenance

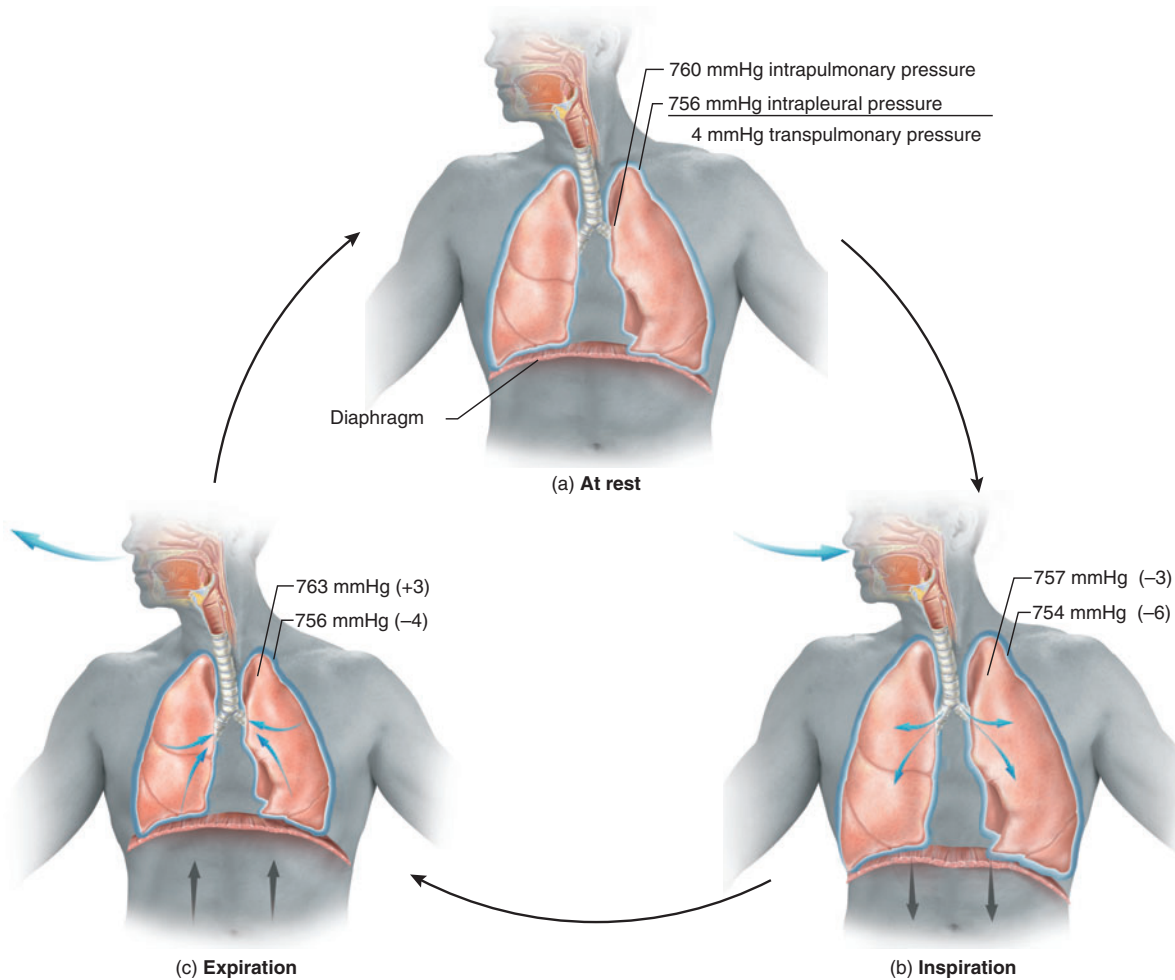


Figure 22.13 The Cycle of Pressure Changes Causing Ventilation of the Lungs. The pressures given here are based on an assumed atmospheric pressure of 760 mmHg (1 atm). Values in parentheses are relative to atmospheric pressure.

Atelectasis can also result from airway obstruction—for example, by a lung tumor, aneurysm, swollen lymph node, or aspirated object. Blood absorbs gases from the alveoli distal to the obstruction, and that part of the lung collapses because it cannot be reventilated.

Resistance to Airflow

In discussing blood circulation (p. 753), we noted that flow = change in pressure/resistance ($F = \Delta P/R$). Resistance affects airflow much the same as it does blood flow. One factor that affects resistance is **pulmonary compliance**—the distensibility of the lungs, or ease with which they expand. More exactly, compliance means the change in lung volume relative to a given change in transpulmonary pressure. The lungs normally inflate with

ease, but compliance can be reduced by degenerative lung diseases that cause pulmonary fibrosis, such as tuberculosis and black lung disease. In such conditions, the thoracic cage expands normally and transpulmonary pressure falls, but the lungs expand relatively little.

Another factor that governs resistance to airflow is the diameter of the bronchioles. Like arterioles, the large number of bronchioles, their small diameter, and their ability to change diameter make bronchioles the primary means of controlling resistance. Their smooth muscle allows for considerable **bronchoconstriction** and **bronchodilation**—changes in diameter that reduce or increase airflow, respectively. Bronchoconstriction is triggered by airborne irritants, cold air, parasympathetic stimulation, or histamine. Many people have died of extreme bronchoconstriction due to asthma or anaphylaxis. Sympathetic nerves and epineph-

rine stimulate bronchodilation. Epinephrine inhalants were widely used in the past to halt asthma attacks, but they have been replaced by drugs that produce fewer side effects.

Alveolar Surface Tension

Another factor that resists inspiration and promotes expiration is the surface tension of the water in the alveoli and distal bronchioles. Although the alveoli are relatively dry, they have a thin film of water over the epithelium that is necessary for gas exchange, yet creates a potential problem for pulmonary ventilation. Water molecules are attracted to each other by hydrogen bonds, creating surface tension, as we saw in chapter 2. If you have ever tried to separate two wet microscope slides, you have felt how strong surface tension can be. Such a force draws the walls of the alveoli inward toward the lumen. If it went unchecked, the alveoli would collapse with each expiration and would strongly resist reinflation.

The solution to this problem takes us back to the great alveolar cells and their surfactant. A *surfactant* is an agent that disrupts the hydrogen bonds of water and reduces surface tension; soaps and detergents are everyday examples. Pulmonary surfactant spreads over the alveolar epithelium and up the alveolar ducts and smallest bronchioles. As these passages contract during expiration, the surfactant molecules are forced closer together; as the local concentration of surfactant increases, it exerts a stronger effect. Therefore, as alveoli shrink during expiration, surface tension decreases to nearly zero. Thus, there is little tendency for the alveoli to collapse. The importance of this surfactant is especially apparent when it is lacking. Premature infants often have a deficiency of pulmonary surfactant and experience great difficulty breathing (see chapter 29). The resulting *respiratory distress syndrome* is often treated by administering artificial surfactant.

Alveolar Ventilation

Air that actually enters the alveoli becomes available for gas exchange, but not all inhaled air gets that far. About 150 mL of it (typically 1 mL per pound of body weight) fills the conducting division of the airway. Since this air cannot exchange gases with the blood, it is called **dead air**, and the conducting division is called the **anatomic dead space**. In pulmonary diseases, some alveoli may be unable to exchange gases with the blood because they lack blood flow or their pulmonary membrane is thickened by edema. **Physiologic (total) dead space** is the sum of anatomic dead space and any pathological alveolar dead space that may exist. In healthy people, few alveoli are nonfunctional, and the anatomic and physiologic dead spaces are identical.

In a state of relaxation, the bronchioles are constricted by parasympathetic stimulation. This minimizes the dead space so that more of the inhaled air ventilates the alveoli. In a state of arousal, by contrast, the sympa-

thetic nervous system dilates the airway, which increases airflow. The increased airflow outweighs the air that is “wasted” by filling the increased dead space.

If a person inhales 500 mL of air and 150 mL of it is dead air, then 350 mL of air ventilates the alveoli. Multiplying this by the respiratory rate gives the **alveolar ventilation rate (AVR)**—for example, $350 \text{ mL/breath} \times 12 \text{ breaths/min} = 4,200 \text{ mL/min}$. Of all measures of pulmonary ventilation, this one is most directly relevant to the body’s ability to get oxygen to the tissues and dispose of carbon dioxide.

Nonrespiratory Air Movements

Breathing serves more purposes than ventilating the alveoli. It promotes the flow of blood and lymph from abdominal to thoracic vessels, as described in earlier chapters. Variations in pulmonary ventilation also serve the purposes of speaking, expressing emotion (laughing, crying), yawning, hiccuping, expelling noxious fumes, coughing, sneezing, and expelling abdominal contents. Coughing is induced by irritants in the lower respiratory tract. To cough, we close the glottis and contract the muscles of expiration, producing high pressure in the lower respiratory tract. We then suddenly open the glottis and release an explosive burst of air at speeds over 900 km/hr (600 mi/hr). This drives mucus and foreign matter toward the pharynx and mouth. Sneezing is triggered by irritants in the nasal cavity. Its mechanism is similar to coughing except that the glottis is continually open, the soft palate and tongue block the flow of air while thoracic pressure builds, and then the uvula (the conical projection of the posterior edge of the soft palate) is depressed to direct part of the airstream through the nose. These actions are coordinated by coughing and sneezing centers in the medulla oblongata.

To help expel abdominopelvic contents during urination, defecation, or childbirth, we often consciously or unconsciously use the **Valsalva¹⁴ maneuver**. This consists of taking a deep breath, holding it, and then contracting the abdominal muscles, thus using the diaphragm to help increase the pressure in the abdominal cavity.

Measurements of Ventilation

Pulmonary function can be measured by having a subject breathe into a device called a **spirometer**,¹⁵ which recaptures the expired breath and records such variables as the rate and depth of breathing, speed of expiration, and rate of oxygen consumption. Four measurements are called **respiratory volumes**: **tidal volume**, **inspiratory reserve**

¹⁴Antonio Maria Valsalva (1666–1723), Italian anatomist

¹⁵*spiro* = breath + *meter* = measuring device

Table 22.2 Respiratory Volumes and Capacities for an Average Young Adult Male

Measurement	Typical Value	Definition
Respiratory Volumes		
Tidal volume (TV)	500 mL	Amount of air inhaled or exhaled in one respiratory cycle
Inspiratory reserve volume (IRV)	3,000 mL	Amount of air in excess of tidal inspiration that can be inhaled with maximum effort
Expiratory reserve volume (ERV)	1,200 mL	Amount of air in excess of tidal expiration that can be exhaled with maximum effort
Residual volume (RV)	1,300 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		
Vital capacity (VC)	4,700 mL	Amount of air that can be exhaled with maximum effort after maximum inspiration (TV + IRV + ERV); used to assess strength of thoracic muscles as well as pulmonary function
Inspiratory capacity (IC)	3,500 mL	Maximum amount of air that can be inhaled after a normal tidal expiration (TV + IRV)
Functional residual capacity (FRC)	2,500 mL	Amount of air remaining in the lungs after a normal tidal expiration (RV + ERV)
Total lung capacity (TLC)	6,000 mL	Maximum amount of air the lungs can contain (RV + VC)

volume, expiratory reserve volume, and residual volume. Four others, called **respiratory capacities**, are obtained by adding two or more of the respiratory volumes: **vital capacity, inspiratory capacity, functional residual capacity, and total lung capacity.** Definitions and representative values for these are given in table 22.2 and figure 22.14. In general, respiratory volumes and capacities are proportional to body size; consequently, they are generally lower for women than for men.

The measurement of respiratory volumes and capacities is important in assessing the severity of a respiratory disease and monitoring improvement or deterioration in a patient's pulmonary function. **Restrictive disorders** of the respiratory system, such as pulmonary fibrosis, stiffen the lungs and thus reduce compliance and vital capacity. **Obstructive disorders** do not reduce respiratory volumes, but they narrow the airway and interfere with airflow; thus, expiration either requires more effort or is less complete than normal. Airflow is measured by having the subject exhale as rapidly as possible into a spirometer and measuring **forced expiratory volume (FEV)**—the percentage of the vital capacity that can be exhaled in a given time interval. A healthy adult should be able to expel 75% to 85% of the vital capacity in 1.0 second (a value called the $FEV_{1.0}$). Significantly lower values may indicate thoracic muscle weakness or obstruction of the airway by mucus, a tumor, or bronchoconstriction (as in asthma). At home, asthma patients and others can monitor their respiratory function by blowing into a handheld meter that measures **peak flow**, the maximum speed at which they can exhale.

The amount of air inhaled per minute is called the **minute respiratory volume (MRV)**. Its primary significance is that the MRV largely determines the alveolar ventilation rate. MRV can be measured directly with a spirometer or obtained by multiplying tidal volume by respiratory rate. For example, if a person has a tidal volume of 500 mL per breath and a rate of 12 breaths per minute, his or her MRV would be $500 \times 12 = 6,000$ mL/min. During heavy exercise, MRV may be as high as 125 to 170 L/min. This is called **maximum voluntary ventilation (MVV)**, formerly called *maximum breathing capacity*.

Patterns of Breathing

Some variations in the rhythm of breathing are defined in table 22.3. You should familiarize yourself with these terms before proceeding further in this chapter, as later discussions assume a working knowledge of these terms.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

1. Name the major muscles and nerves involved in inspiration.
2. Relate the action of the respiratory muscles to Boyle's law.
3. Explain the relevance of compliance and elasticity to pulmonary ventilation, and describe some conditions that reduce compliance and elasticity.
4. Explain how pulmonary surfactant relates to compliance.
5. Define *vital capacity*. Express it in terms of a formula and define each of the variables.

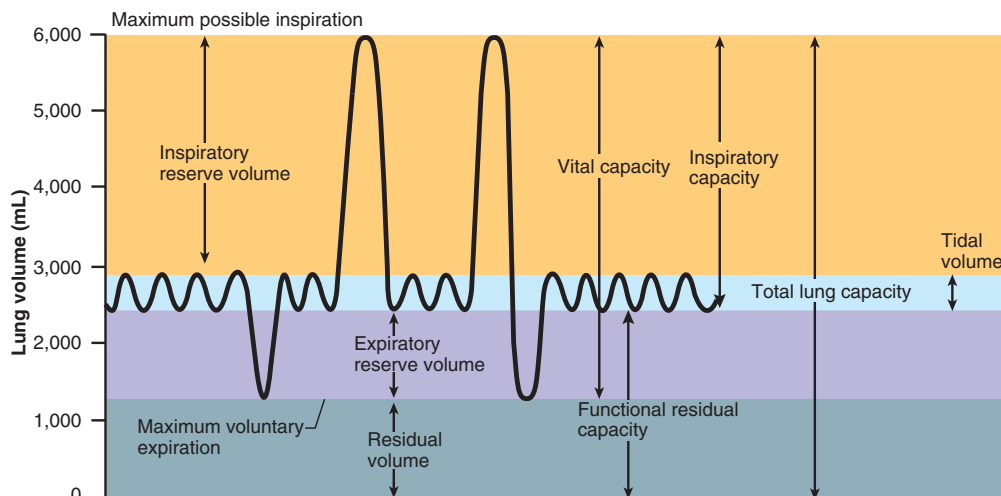


Figure 22.14 Respiratory Volumes and Capacities. The wavy line indicates inspiration when it rises and expiration when it falls. Compare table 22.2.

Table 22.3 Clinical Terminology of Ventilation

<i>Apnea</i> (AP-nee-uh)	Temporary cessation of breathing (one or more skipped breaths)
<i>Dyspnea</i> ¹⁶ (DISP-nee-uh)	Labored, gasping breathing; shortness of breath
<i>Eupnea</i> ¹⁷ (yoop-NEE-uh)	Normal, relaxed, quiet breathing; typically 500 mL/breath, 12 to 15 breaths/min
<i>Hyperpnea</i> (HY-purp-NEE-uh)	Increased rate and depth of breathing in response to exercise, pain, or other conditions
<i>Hyperventilation</i>	Increased pulmonary ventilation in excess of metabolic demand, frequently associated with anxiety; expels CO ₂ faster than it is produced, thus lowering the blood CO ₂ concentration and raising the pH
<i>Hypoventilation</i>	Reduced pulmonary ventilation; leads to an increase in blood CO ₂ concentration if ventilation is insufficient to expel CO ₂ as fast as it is produced
<i>Kussmaul</i> ¹⁸ respiration	Deep, rapid breathing often induced by acidosis, as in diabetes mellitus
<i>Orthopnea</i> (or-thop-NEE-uh)	Dyspnea that occurs when a person is lying down
<i>Respiratory arrest</i>	Permanent cessation of breathing (unless there is medical intervention)
<i>Tachypnea</i> (tack-ip-NEE-uh)	Accelerated respiration

¹⁶dys = difficult, abnormal, painful

¹⁷eu = easy, normal + *pnea* = breathing

¹⁸Adolph Kussmaul (1822–1902), German physician

Neural Control of Ventilation

Objectives

When you have completed this section, you should be able to

- explain how the brainstem regulates respiration;
- contrast the neural pathways for voluntary and automatic control of the respiratory muscles; and
- describe the stimuli that modify the respiratory rhythm and the pathways that these signals take to the brainstem.

The heartbeat and breathing are the two most conspicuously rhythmic processes in the body. The heart has an internal pacemaker and goes on beating even if all nerves to it are severed. Breathing, by contrast, depends on repetitive stimuli from the brain. There are two reasons for this: (1) Skeletal muscles do not contract without nervous stimulation. (2) Breathing involves the coordinated action of multiple muscles and thus requires a central coordinating mechanism to ensure that they all work together.

858 Part Four Regulation and Maintenance

This section describes the neural mechanisms that regulate pulmonary ventilation. Neurons in the medulla oblongata and pons provide automatic control of unconscious breathing, whereas neurons in the motor cortex of the cerebrum provide voluntary control.

Control Centers in the Brainstem

The medulla oblongata contains **inspiratory (I) neurons**, which fire during inspiration, and **expiratory (E) neurons**, which fire during forced expiration (but not during eupnea). Fibers from these neurons travel down the spinal cord and synapse with lower motor neurons in the cervical to thoracic regions. From here, nerve fibers travel in the phrenic nerves to the diaphragm and intercostal nerves to the intercostal muscles. No pacemaker neurons have been found that are analogous to the autorhythmic cells of the heart, and the exact mechanism for setting the rhythm of respiration remains unknown despite intensive research.

The medulla has two respiratory nuclei (fig. 22.15). One of them, called the **inspiratory center**, or **dorsal respiratory group (DRG)**, is composed primarily of I neurons, which stimulate the muscles of inspiration. The more frequently they fire, the more motor units are recruited and the more deeply you inhale. If they fire longer than usual, each breath is prolonged and the respiratory rate is slower. When they stop firing, elastic recoil of the lungs and thoracic cage produces passive expiration.

The other nucleus is the **expiratory center**, or **ventral respiratory group (VRG)**. It has I neurons in its rostral and caudal ends. It is not involved in eupnea, but its E neurons inhibit the inspiratory center when deeper expiration is needed. Conversely, the inspiratory center inhibits the expiratory center when an unusually deep inspiration is needed.

The pons regulates ventilation by means of a *pneumotaxic center* in the upper pons and an *apneustic center* in the lower pons. The role of the apneustic center is still unclear, but it seems to prolong inspiration. The **pneumotaxic** (NEW-mo-TAX-ic) **center** sends a continual stream of inhibitory impulses to the inspiratory center of the medulla. When impulse frequency rises, inspiration lasts as little as 0.5 second and the breathing becomes faster and shallower. Conversely, when impulse frequency declines, breathing is slower and deeper, with inspiration lasting as long as 5 seconds.

Think About It

Do you think the fibers from the pneumotaxic center produce EPSPs or IPSPs at their synapses in the inspiratory center? Explain.

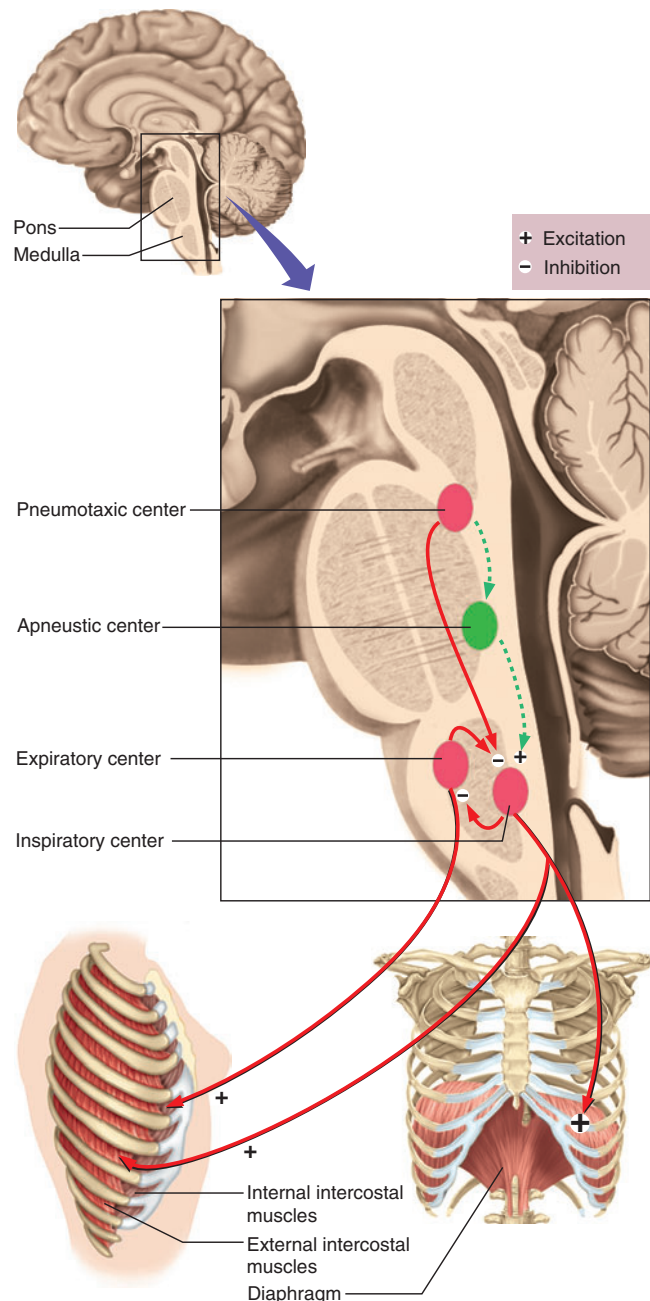


Figure 22.15 Respiratory Control Centers. Functions of the apneustic center are hypothetical and its connections are therefore indicated by broken lines. As indicated by the plus and minus signs, the apneustic center stimulates the inspiratory center, while the pneumotaxic center inhibits it. The inspiratory and expiratory centers inhibit each other.

Afferent Connections to the Brainstem

The brainstem respiratory centers receive input from the limbic system, hypothalamus, chemoreceptors, and lungs themselves. Input from the limbic system and hypothalamus allows pain and emotions to affect respiration—for example, in gasping, crying, and laughing. Anxiety often triggers an uncontrollable bout of hyperventilation. This expels CO₂ from the body faster than it is produced. As blood CO₂ levels drop, the pH rises and causes the cerebral arteries to constrict. The brain thus receives less perfusion, and dizziness and fainting may result. Hyperventilation can be brought under control by having a person rebreathe the expired CO₂ from a paper bag.

Chemoreceptors in the brainstem and arteries monitor blood pH, CO₂, and O₂ levels. They transmit signals to the respiratory centers that adjust pulmonary ventilation to keep these variables within homeostatic limits. Chemoreceptors are later discussed more extensively.

The vagus nerves transmit sensory signals from the respiratory system to the inspiratory center. Irritants in the airway, such as smoke, dust, noxious fumes, or mucus, stimulate vagal afferent fibers. The medulla then returns signals that result in bronchoconstriction or coughing. Stretch receptors in the bronchial tree and visceral pleura monitor inflation of the lungs. Excessive inflation triggers the **inflation (Hering-Breuer¹⁹) reflex**, a protective somatic reflex that strongly inhibits the I neurons and stops inspiration. In infants, this may be a normal mechanism of transition from inspiration to expiration, but after infancy it is activated only by extreme stretching of the lungs.

Voluntary Control

Although breathing usually occurs automatically, without our conscious attention, we obviously can hold our breath, take a deep breath, and control ventilation while speaking or singing. This control originates in the motor cortex of the frontal lobe of the cerebrum, which sends impulses down the corticospinal tracts to the respiratory neurons in the spinal cord, bypassing the brainstem respiratory centers.

There are limits to voluntary control. Temperamental children may threaten to hold their breath until they die, but it is impossible to do so. Holding one's breath lowers the O₂ level and raises the CO₂ level of the blood until a *breaking point* is reached where automatic controls override one's will. This forces a person to resume breathing even if he or she has lost consciousness.

¹⁹Heinrich Ewald Hering (1866–1948), German physiologist; Josef Breuer (1842–1925), Austrian physician

Insight 22.2 Clinical Application

Ondine's Curse

In German legend, there was a water nymph named Ondine who took a mortal lover. When he was unfaithful to her, the king of the nymphs put a curse on him that took away his automatic physiological functions. Consequently, he had to remember to take each breath, and he could not go to sleep or he would die of suffocation—which, as exhaustion overtook him, was indeed his fate.

Some people suffer a disorder called *Ondine's curse*, in which the automatic respiratory functions are disabled—usually as a result of brainstem damage from poliomyelitis or as an accident of spinal cord surgery. Victims of Ondine's curse must remember to take each breath and cannot go to sleep without the aid of a mechanical ventilator.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

- Which of the brainstem respiratory nuclei is (are) indispensable to respiration? What do the other nuclei do?
- Where do voluntary respiratory commands originate? What pathways do they take to the respiratory muscles?

Gas Exchange and Transport

Objectives

When you have completed this section, you should be able to

- define *partial pressure* and discuss its relationship to a gas mixture such as air;
- contrast the composition of inspired and expired air;
- discuss how partial pressure affects gas transport by the blood;
- describe the mechanisms of transporting O₂ and CO₂;
- describe the factors that govern gas exchange in the lungs and systemic capillaries; and
- explain how gas exchange is adjusted to the metabolic needs of different tissues.

We now consider the stages in which oxygen is obtained from inspired air and delivered to the tissues, while carbon dioxide is removed from the tissues and released into the expired air. First, however, it is necessary to understand the composition of air and the behavior of gases in contact with water.

Composition of Air

Air is a mixture of gases, each of which contributes a share, called its **partial pressure**, to the total atmospheric pressure (table 22.4). Partial pressure is abbreviated P followed

860 Part Four Regulation and Maintenance

by the formula of the gas. The partial pressure of nitrogen is P_{N_2} , for example. Nitrogen constitutes about 78.6% of the atmosphere; thus at 1 atm of pressure, $P_{N_2} = 78.6\% \times 760 \text{ mmHg} = 597 \text{ mmHg}$. **Dalton's law** states that *the total pressure of a gas mixture is the sum of the partial pressures of the individual gases*. That is, $P_{N_2} + P_{O_2} + P_{H_2O} + P_{CO_2} = 597.0 + 159.0 + 3.7 + 0.3 = 760.0 \text{ mmHg}$. These partial pressures are important because they determine the rate of diffusion of a gas and therefore strongly affect the rate of gas exchange between the blood and alveolar air.

Alveolar air can be sampled with an apparatus that collects the last 10 mL of expired air. Its gaseous makeup differs from that of the atmosphere because of three influences: (1) the airway humidifies it, (2) the air exchanges O_2 and CO_2 with the blood, and (3) freshly inspired air mixes with residual air left from the previous respiratory cycle. These factors produce the composition shown in table 22.4.

Think About It

Expired air, considered as a whole (not just the last 10 mL), contains about 116 mmHg O_2 and 32 mmHg CO_2 . Why do these values differ from the values for alveolar air?

The Air-Water Interface

When air and water are in contact with each other, as in the pulmonary alveolus, gases diffuse down their concentration gradients until the partial pressure of each gas in the air is equal to its partial pressure in the water. If a gas is more abundant in the water than in the air, it diffuses into the air; the smell of chlorine near a swimming pool is evidence of this. If a gas is more abundant in the air, it diffuses into the water.

Henry's law states that *at the air-water interface, for a given temperature, the amount of gas that dissolves in the water is determined by its solubility in water and its partial pressure in the air* (fig. 22.16). Thus, the greater the

Table 22.4 Composition of Inspired (atmospheric) and Alveolar Air

Gas	Inspired Air*		Alveolar Air	
N_2	78.62%	597.0 mmHg	74.9%	569.0 mmHg
O_2	20.84%	159.0 mmHg	13.6%	104.0 mmHg
H_2O	0.50%	3.7 mmHg	6.2%	47.0 mmHg
CO_2	0.04%	0.3 mmHg	5.3%	40.0 mmHg
Total	100.00%	760.0 mmHg	100.0%	760.0 mmHg

*Typical values for a cool clear day; values vary with temperature and humidity. Other gases present in small amounts are disregarded.

PO_2 in the alveolar air, the more O_2 the blood picks up. And, since the blood arriving at an alveolus has a higher PCO_2 than air, the blood releases CO_2 into the air. At the alveolus, the blood is said to *unload* CO_2 and *load* O_2 . Each gas in a mixture behaves independently; the diffusion of one gas does not influence the diffusion of another.

Alveolar Gas Exchange

Alveolar gas exchange is the process of O_2 loading and CO_2 unloading in the lungs. Since both processes depend on erythrocytes (RBCs), their efficiency depends on how long an RBC spends in an alveolar capillary compared to how long it takes for O_2 and CO_2 to reach equilibrium concentrations in the capillary blood. An RBC passes through an alveolar capillary in about 0.75 second at rest and 0.3 sec-

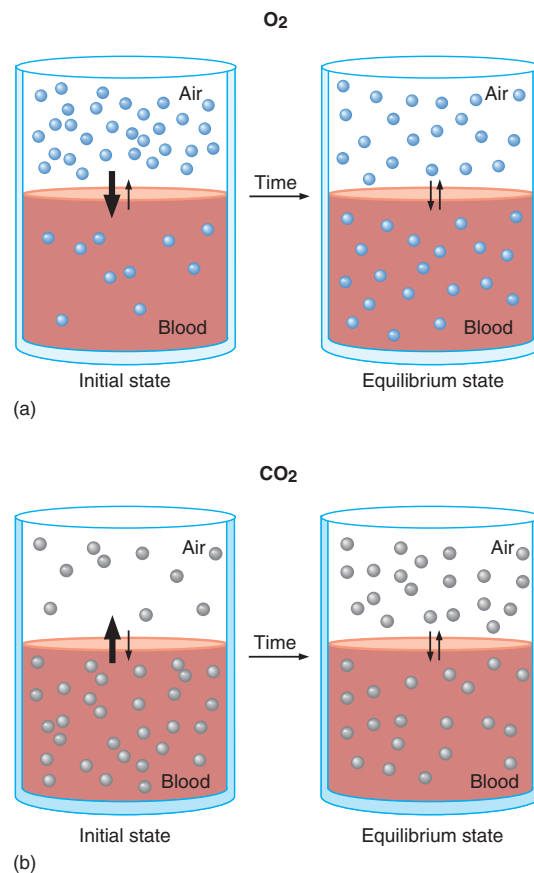


Figure 22.16 Henry's Law and Its Relationship to Alveolar Gas Exchange. (a) The PO_2 of alveolar air is initially higher than the PO_2 of the blood arriving at an alveolus. Oxygen diffuses into the blood until the two are in equilibrium. (b) The PCO_2 of the arriving blood is initially higher than the PCO_2 of alveolar air. Carbon dioxide diffuses into the alveolus until the two are in equilibrium. It takes about 0.25 second for both gases to reach equilibrium.

and during vigorous exercise, when the blood is flowing faster. But it takes only 0.25 second for the gases to equilibrate, so even at the fastest blood flow, an RBC spends enough time in a capillary to load as much O_2 and unload as much CO_2 as it possibly can.

The following factors especially affect the efficiency of alveolar gas exchange:

- **Concentration gradients of the gases.** The PO_2 is about 104 mmHg in the alveolar air and 40 mmHg in the blood arriving at an alveolus. Oxygen therefore diffuses from the air into the blood, where it reaches a PO_2 of 104 mmHg. Before the blood leaves the lung, however, this drops to about 95 mmHg because blood in the pulmonary veins receives some oxygen-poor blood from the bronchial veins by way of anastomoses.

The PCO_2 is about 46 mmHg in the blood arriving at the alveolus and 40 mmHg in the alveolar air. Carbon dioxide therefore diffuses from the blood to the alveoli. These changes are summarized here and at the top of figure 22.17:

Blood Entering Lungs		Blood Leaving Lungs	
PO_2	40 mmHg	PO_2	95 mmHg
PCO_2	46 mmHg	PCO_2	40 mmHg

These gradients differ under special circumstances such as high altitude and *hyperbaric oxygen therapy* (treatment with oxygen at greater than 1 atm of pressure) (fig. 22.18). At high altitudes, the partial pressures of all atmospheric gases are lower. Atmospheric PO_2 , for example, is 159 mmHg at sea level and 110 mmHg at 3,000 m (10,000 ft). The O_2 gradient from air to blood is proportionately less, and as we can predict from Henry's law, less O_2 diffuses into the blood. In a hyperbaric oxygen chamber, by contrast, a patient is exposed to 3 to 4 atm of oxygen to treat such conditions as gangrene (to kill anaerobic bacteria) and carbon monoxide poisoning (to displace the carbon monoxide from hemoglobin). The PO_2 ranges between 2,300 and 3,000 mmHg. Thus, there is a very steep gradient of PO_2 from alveolus to blood and diffusion into the blood is accelerated.

- **Solubility of the gases.** Gases differ in their ability to dissolve in water. Carbon dioxide is about 20 times as soluble as oxygen, and oxygen is about twice as soluble as nitrogen. Even though the concentration gradient of O_2 is much greater than that of CO_2 across the respiratory membrane, equal amounts of the two gases are exchanged because CO_2 is so much more soluble and diffuses more rapidly.
- **Membrane thickness.** The respiratory membrane between the blood and alveolar air is only 0.5 μm thick in most places—much less than the 7 to 8 μm diameter of a single RBC. Thus, it presents little

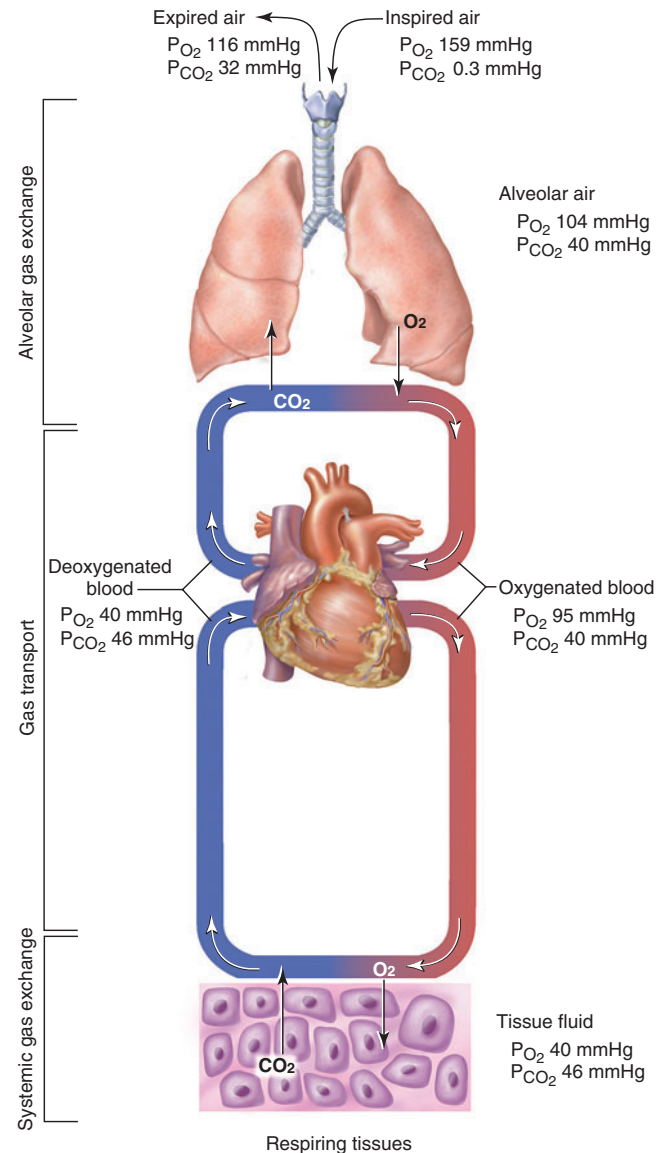


Figure 22.17 Changes in PO_2 and PCO_2 Along the Circulatory Route. Trace the partial pressure of oxygen from inspired air to expired air and explain each change in PO_2 along the way. Do the same for PCO_2 .

obstacle to diffusion (fig. 22.19a). In such heart conditions as left ventricular failure, however, blood pressure backs up into the lungs and promotes capillary filtration into the connective tissues, causing the respiratory membranes to become edematous and thickened (fig. 22.19b). The gases have farther to travel between blood and air and cannot equilibrate fast enough to keep pace with blood flow. Under these circumstances, blood leaving the lungs has an unusually high PCO_2 and low PO_2 .

862 Part Four Regulation and Maintenance

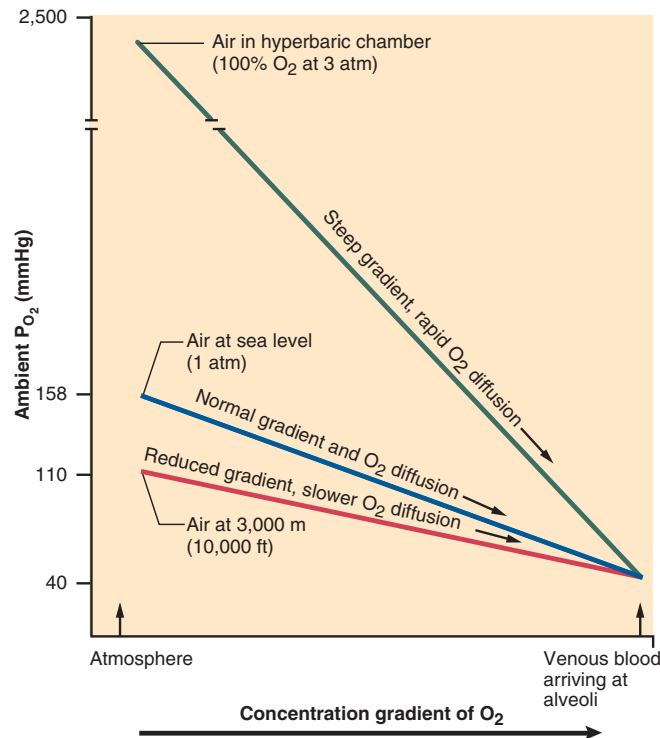


Figure 22.18 Alveolar Oxygen Loading in Relationship to Concentration Gradient. The rate of loading depends on the steepness of the gradient from alveolar air to the venous blood arriving at the alveolar capillaries. Compared to the oxygen gradient at sea level (*blue line*), the gradient is less steep at high altitude (*red line*) because the PO_2 of the atmosphere is lower. Thus oxygen loading of the pulmonary blood is slower. In a hyperbaric chamber with 100% oxygen, the gradient from air to blood is very steep (*green line*) and oxygen loading is correspondingly rapid. This is an illustration of Henry's law and has important effects in diving, aviation, mountain climbing, and oxygen therapy.

- **Membrane area.** In good health, each lung has about 70 m^2 of respiratory membrane available for gas exchange. Since the alveolar capillaries contain a total of only 100 mL of blood at any one time, this blood is spread very thinly. Several pulmonary diseases, however, decrease the alveolar surface area and thus lead to low blood PO_2 —for example, emphysema (fig. 22.19c), lung cancer, and tuberculosis.
- **Ventilation-perfusion coupling.** Gas exchange not only requires good ventilation of the alveolus but also good perfusion of its capillaries. As a whole, the lungs have a *ventilation-perfusion ratio* of about 0.8—a flow of 4.2 L of air and 5.5 L of blood per minute (at rest). The ratio is somewhat higher in the apex of the lung and lower in the base because more blood is drawn toward the base by gravity. **Ventilation-perfusion coupling** is the ability to match ventilation and

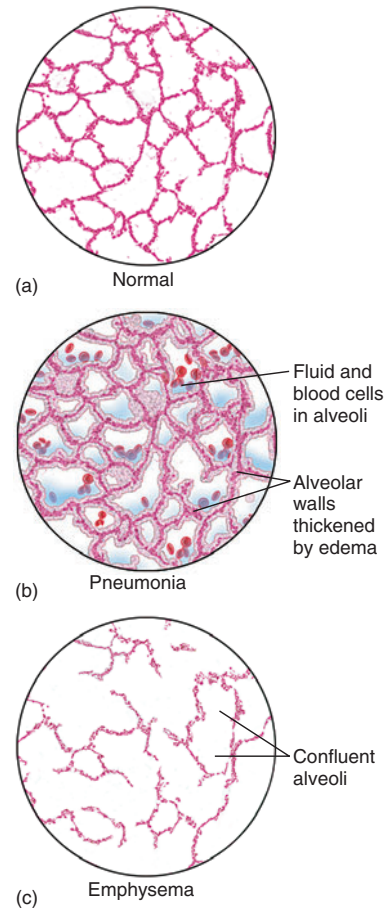


Figure 22.19 Pulmonary Alveoli in Health and Disease.

(a) In a healthy lung, the alveoli are small and have thin respiratory membranes. (b) In pneumonia, the respiratory membranes (alveolar walls) are thick with edema, and the alveoli contain fluid and blood cells. (c) In emphysema, alveolar membranes break down and neighboring alveoli join to form larger, fewer alveoli with less total surface area.

perfusion to each other (fig. 22.20). If part of a lung is poorly ventilated because of tissue destruction or airway obstruction, there is little point in directing much blood there. This blood would leave the lung carrying less oxygen than it should. But poor ventilation causes local constriction of the pulmonary arteries, reducing blood flow to that area and redirecting this blood to better ventilated alveoli. Good ventilation, by contrast, dilates the arteries and increases perfusion so that most blood is directed to regions of the lung where it can pick up the most oxygen. This is opposite from the reactions of systemic arteries, where hypoxia causes vasodilation so that blood flow to a tissue will increase and reverse the hypoxia.

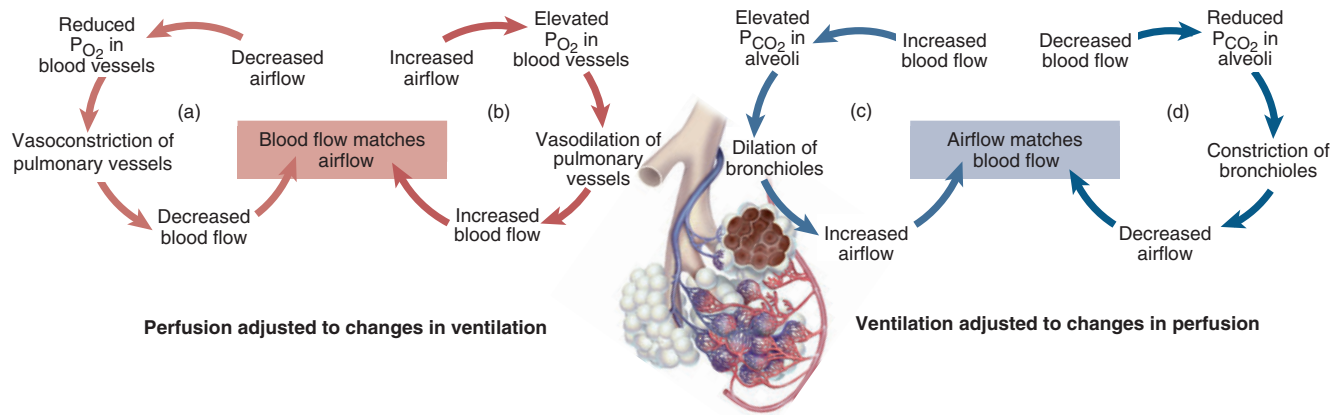


Figure 22.20 Negative Feedback Loops in the Adjustment of Ventilation-Perfusion Ratio. (a) Effect of reduced ventilation on perfusion. (b) Effect of increased ventilation on perfusion. (c) Effect of increased perfusion on ventilation. (d) Effect of reduced perfusion on ventilation.

Ventilation is also adjustable. Poor ventilation causes local CO_2 accumulation, which stimulates local bronchodilation and improves airflow. Low PCO_2 causes local bronchoconstriction.

Gas Transport

Gas transport is the process of carrying gases from the alveoli to the systemic tissues and vice versa. This section explains how the blood loads and transports oxygen and carbon dioxide.

Oxygen

The concentration of oxygen in arterial blood, by volume, is about 20 mL/dL. About 98.5% of this is bound to hemoglobin and 1.5% is dissolved in the blood plasma. Hemoglobin consists of four protein (globin) chains, each with one heme group (see fig. 18.10, p. 690). Each heme group can bind 1 O_2 to the ferrous ion at its center; thus, one hemoglobin molecule can carry up to 4 O_2 . If even one molecule of O_2 is bound to hemoglobin, the compound is called **oxyhemoglobin (HbO_2)**, whereas hemoglobin with no oxygen bound to it is **deoxyhemoglobin (HHb)**. When hemoglobin is 100% saturated, every molecule of it carries 4 O_2 ; if it is 75% saturated, there is an average of 3 O_2 per hemoglobin molecule; if it is 50% saturated, there is an average of 2 O_2 per hemoglobin; and so forth. The poisonous effect of carbon monoxide stems from its competition for the O_2 binding site (see insight 22.3).

The relationship between hemoglobin saturation and PO_2 is shown by an *oxyhemoglobin dissociation curve* (fig. 22.21). As you can see, it is not a simple linear relationship. At low PO_2 , the curve rises slowly; then there is a

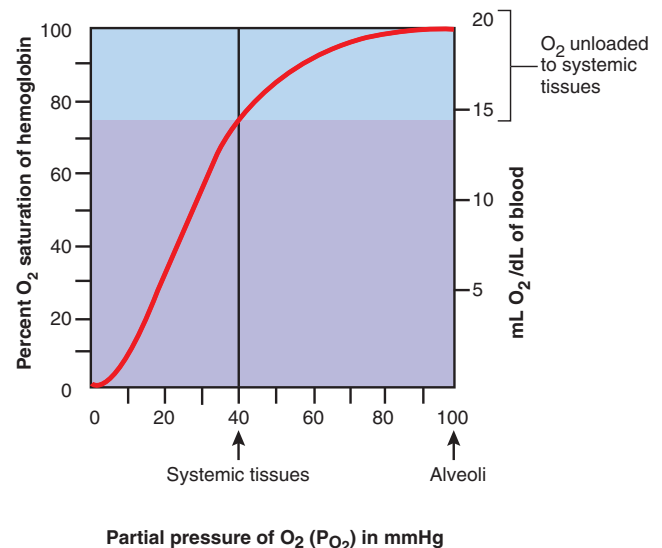


Figure 22.21 The Oxyhemoglobin Dissociation Curve. This curve shows the relative amount of hemoglobin that is saturated with oxygen (y-axis) as a function of ambient (surrounding) oxygen concentration (x-axis). As it passes through the alveolar capillaries where the PO_2 is high, hemoglobin becomes saturated with oxygen. As it passes through the systemic capillaries where the PO_2 is low, it typically gives up about 22% of its oxygen (color bar at top of graph). **What would be the approximate utilization coefficient if the systemic tissues had a PO_2 of 20 mmHg?**

rapid increase in oxygen loading as PO_2 rises further; finally, at high PO_2 , the curve levels off as the hemoglobin approaches 100% saturation. This reflects the way hemoglobin loads oxygen. When the first heme group binds a molecule of O_2 , hemoglobin changes shape in a way that

864 Part Four Regulation and Maintenance

facilitates uptake of the second O₂ by another heme group. This, in turn, promotes the uptake of the third and then the fourth O₂—hence the rapidly rising midportion of the curve.

Think About It

Is oxygen loading a positive feedback process or a negative feedback process? Explain.

Insight 22.3 Clinical Application

Carbon Monoxide Poisoning

The lethal effect of carbon monoxide (CO) is well known. This colorless, odorless gas occurs in cigarette smoke, engine exhaust, and fumes from furnaces and space heaters. It binds to the ferrous ion of hemoglobin to form *carboxyhemoglobin* (HbCO). Thus, it competes with oxygen for the same binding site. Not only that, but it binds 210 times as tightly as oxygen. Thus, CO tends to tie up hemoglobin for a long time. Less than 1.5% of the hemoglobin is occupied by carbon monoxide in most nonsmokers, but this figure rises to as much as 3% in residents of heavily polluted cities and 10% in heavy smokers. An atmospheric concentration of 0.1% CO, as in a closed garage, is enough to bind 50% of a person's hemoglobin, and an atmospheric concentration of 0.2% is quickly lethal.

Carbon Dioxide

Carbon dioxide is transported in three forms—as carbonic acid, carbamino compounds, and dissolved gas:

1. About 90% of the CO₂ is hydrated (reacts with water) to form **carbonic acid**, which then dissociates into bicarbonate and hydrogen ions:



More will be said about this reaction shortly.

2. About 5% binds to the amino groups of plasma proteins and hemoglobin to form **carbamino compounds**—chiefly, **carbaminohemoglobin** (HbCO₂). The reaction with hemoglobin can be symbolized $\text{Hb} + \text{CO}_2 \rightarrow \text{HbCO}_2$. Carbon dioxide does not compete with oxygen because CO₂ and O₂ bind to different sites on the hemoglobin molecule—oxygen to the heme moiety and CO₂ to the polypeptide chains. Hemoglobin can therefore transport both O₂ and CO₂ simultaneously. As we will see, however, each gas somewhat inhibits transport of the other.
3. The remaining 5% of the CO₂ is carried in the blood as dissolved gas, like the CO₂ in soda pop.

The relative amounts of CO₂ exchanged between the blood and alveolar air differ from the percentages just given.

About 70% of the *exchanged* CO₂ comes from carbonic acid, 23% from carbamino compounds, and 7% from the dissolved gas. That is, blood gives up the dissolved CO₂ gas and CO₂ from the carbamino compounds more easily than it gives up the CO₂ in bicarbonate.

Systemic Gas Exchange

Systemic gas exchange is the unloading of O₂ and loading of CO₂ at the systemic capillaries (see fig. 22.17, *bottom*, and fig. 22.22).

Carbon Dioxide Loading

Aerobic respiration produces a molecule of CO₂ for every molecule of O₂ it consumes. The tissue fluid therefore contains a relatively high PCO₂ and there is typically a CO₂ gradient of 46 → 40 mmHg from tissue fluid to blood. Consequently, CO₂ diffuses into the bloodstream, where it is carried in the three forms noted (fig. 22.23). Most of it reacts with water to produce bicarbonate (HCO₃[−]) and hydrogen (H⁺) ions. This reaction occurs slowly in the blood plasma but much faster in the RBCs, where it is catalyzed by the enzyme *carbonic anhydrase*. An antiport called the *chloride-bicarbonate exchanger* then pumps most of the HCO₃[−] out of the RBC in exchange for Cl[−] from the blood plasma. This exchange is called the **chloride shift**. Most of the H⁺ binds to hemoglobin or oxyhemoglobin, which thus buffers the intracellular pH.

Oxygen Unloading

When H⁺ binds to oxyhemoglobin (HbO₂), it reduces the affinity of hemoglobin for O₂ and tends to make hemoglobin release it. Oxygen consumption by respiring tissues keeps the PO₂ of tissue fluid relatively low, and so there is typically a concentration gradient of 95 → 40 mmHg of oxygen from the arterial blood to the tissue fluid. Thus, the liberated oxygen—along with some that was carried as dissolved gas in the plasma—diffuses from the blood into the tissue fluid.

As blood arrives at the systemic capillaries, its oxygen concentration is about 20 mL/dL and the hemoglobin is about 97% saturated. As it leaves the capillaries of a typical resting tissue, its oxygen concentration is about 15.6 mL/dL and the hemoglobin is about 75% saturated. Thus, it has given up 4.4 mL/dL—about 22% of its oxygen load. This fraction is called the **utilization coefficient**. The oxygen remaining in the blood after it passes through the capillary bed provides a **venous reserve** of oxygen, which can sustain life for 4 to 5 minutes even in the event of respiratory arrest. At rest, the circulatory system releases oxygen to the tissues at an overall rate of about 250 mL/min.

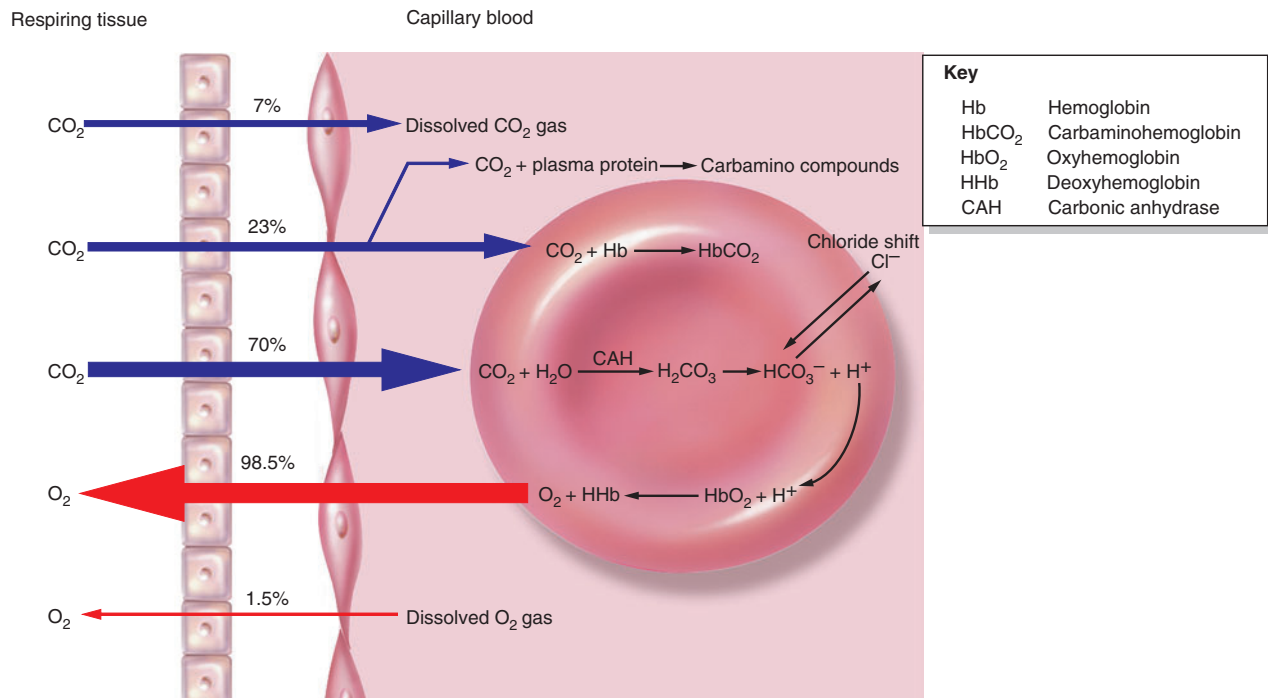


Figure 22.22 Systemic Gas Exchange. Blue arrows show the three mechanisms of CO₂ loading and transport; their thickness represents the relative amounts of CO₂ transported in each of the three forms. Red arrows show the two mechanisms of O₂ unloading; their thickness indicates the relative amounts unloaded by each mechanism. Note that CO₂ loading releases hydrogen ions in the erythrocyte, and hydrogen ions promote O₂ unloading.

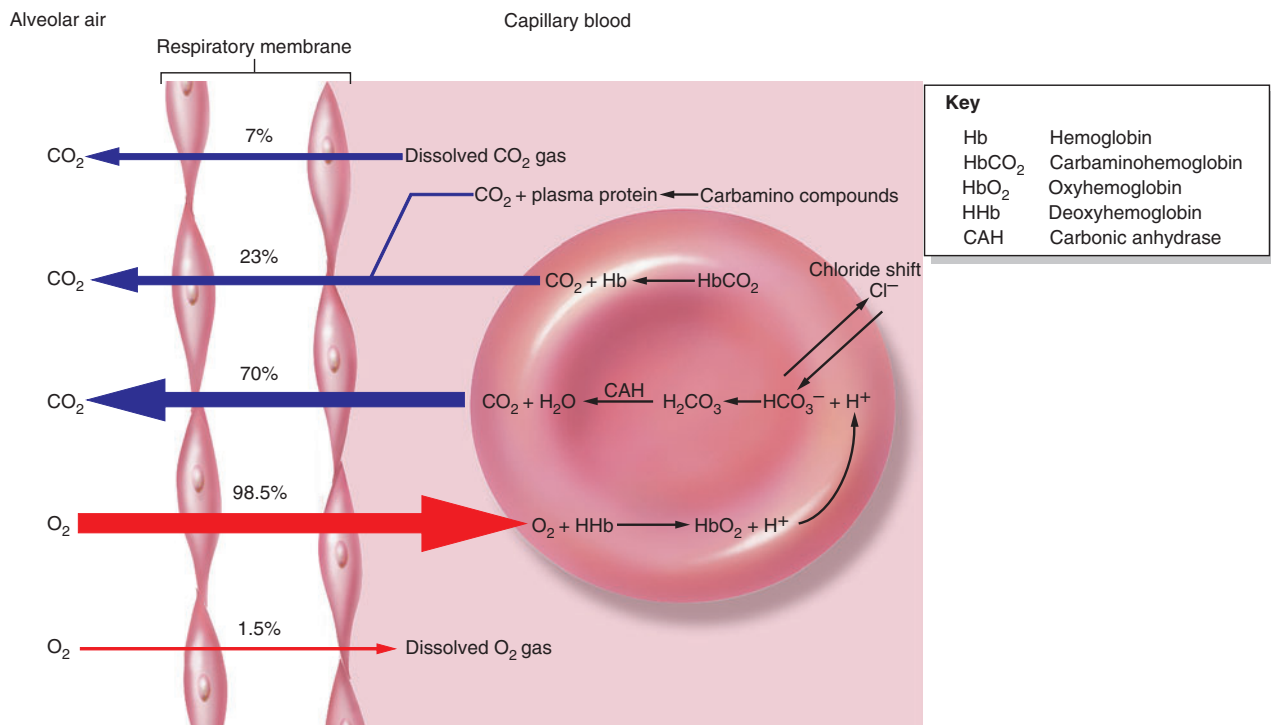


Figure 22.23 Alveolar Gas Exchange.

In what fundamental way does this differ from the preceding figure? Following alveolar gas exchange, will the blood contain a higher or lower concentration of bicarbonate ions than it did before?

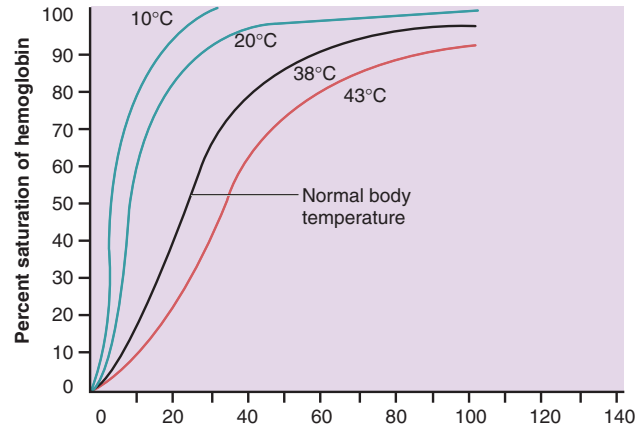
Alveolar Gas Exchange Revisited

The processes illustrated in figure 22.22 make it easier to understand alveolar exchange more fully. As shown in figure 22.23, the reactions that occur in the lungs are essentially the reverse of systemic gas exchange. As hemoglobin loads oxygen, its affinity for H^+ declines. Hydrogen ions dissociate from the hemoglobin and bind with bicarbonate (HCO_3^-) ions transported from the plasma into the RBCs. Chloride ions are transported back out of the RBC (a reverse chloride shift). The reaction of H^+ and HCO_3^- reverses the hydration reaction and generates free CO_2 . This diffuses into the alveolus to be exhaled—as does the CO_2 released from carbaminohemoglobin and CO_2 gas that was dissolved in the plasma.

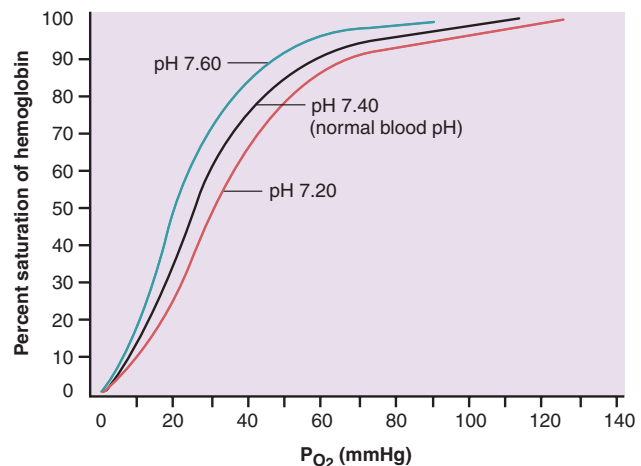
Adjustment to the Metabolic Needs of Individual Tissues

Hemoglobin does not unload the same amount of oxygen to all tissues. Some tissues need more and some less, depending on their state of activity. Hemoglobin responds to such variations and unloads more oxygen to the tissues that need it most. In exercising skeletal muscles, for example, the utilization coefficient may be as high as 80%. Four factors adjust the rate of oxygen unloading to the metabolic rates of different tissues:

1. **Ambient PO_2 .** Since an active tissue consumes oxygen rapidly, the PO_2 of its tissue fluid remains low. From the oxyhemoglobin dissociation curve (see fig. 22.21), you can see that at a low PO_2 , HbO_2 releases more oxygen.
2. **Temperature.** When temperature rises, the oxyhemoglobin dissociation curve shifts to the right (fig. 22.24a); in other words, elevated temperature promotes oxygen unloading. Active tissues are warmer than less active ones and thus extract more oxygen from the blood passing through them.
3. **The Bohr effect.** Active tissues also generate extra CO_2 , which raises the H^+ concentration and lowers the pH of the blood. Like elevated temperatures, a drop in pH shifts the oxygen-hemoglobin dissociation curve to the right (fig. 22.24b) and promotes oxygen unloading. The increase in HbO_2 dissociation in response to low pH is called the **Bohr²⁰ effect**. It is less pronounced at the high PO_2 present in the lungs, so pH has relatively little effect on pulmonary oxygen loading. In the systemic capillaries, however, PO_2 is lower and the Bohr effect is more pronounced.
4. **BPG.** Erythrocytes have no mitochondria and meet their energy needs solely by anaerobic fermentation.



(a)



(b)

Figure 22.24 Effects of Temperature and pH on Oxyhemoglobin Dissociation. (a) For a given PO_2 , hemoglobin unloads more oxygen at higher temperatures. (b) For a given PO_2 , hemoglobin unloads more oxygen at lower pH (the Bohr effect). Both mechanisms cause hemoglobin to release more oxygen to tissues with higher metabolic rates. **Why is it physiologically beneficial to the body that the curves in figure a shift to the right as temperature increases?**

One of their metabolic intermediates is **bisphosphoglycerate (BPG)** (formerly called diphosphoglycerate, DPG), which binds to hemoglobin and promotes oxygen unloading. An elevated body temperature (as in fever) stimulates BPG synthesis, as do thyroxine, growth hormone, testosterone, and epinephrine. All of these hormones thus promote oxygen unloading to the tissues.

The rate of CO_2 loading is also adjusted to varying needs of the tissues. A low level of oxyhemoglobin (HbO_2) enables the blood to transport more CO_2 , a phenomenon

²⁰Christian Bohr (1855–1911), Danish physiologist

known as the **Haldane effect**.²¹ This occurs for two reasons: (1) HbO₂ does not bind CO₂ as well as deoxyhemoglobin (HHb) does. (2) HHb binds more hydrogen ions than HbO₂ does, and by removing H⁺ from solution, HHb shifts the $\text{H}_2\text{O} + \text{CO}_2 \rightarrow \text{HCO}_3^- + \text{H}^+$ reaction to the right. A high metabolic rate keeps oxyhemoglobin levels relatively low and thus allows more CO₂ to be transported by these two mechanisms.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

12. Why is the composition of alveolar air different from that of the atmosphere?
13. What four factors affect the efficiency of alveolar gas exchange?
14. Explain how perfusion of a pulmonary lobule changes if it is poorly ventilated. How is the ventilation of a lobule affected by high PCO₂?
15. Describe how oxygen is transported in the blood, and explain why carbon monoxide interferes with this.
16. What are the three ways in which blood transports CO₂?
17. Describe the role of the chloride shift in CO₂ loading.
18. Give two reasons why highly active tissues can extract more oxygen from the blood than less active tissues.

Blood Chemistry and the Respiratory Rhythm

Objectives

When you have completed this section, you should be able to

- explain how blood gases affect the respiratory centers of the brain; and
- explain how the respiratory centers homeostatically control blood gases and pH.

The most potent stimulus for breathing is the pH of the body fluids, followed by PCO₂ and, least significant, PO₂. These conditions are monitored by chemoreceptors in two general locations: **peripheral chemoreceptors** located outside the central nervous system (CNS) and **central chemoreceptors** located in the brainstem. The peripheral chemoreceptors are **aortic bodies** and **carotid bodies** located in the aortic arch and near the branch of the carotid arteries (fig. 22.25). (These are not to be confused with the aortic and carotid *sinuses*, which harbor the baroreceptors that monitor blood pressure.) Although very small, the aortic and carotid bodies are richly supplied with capillaries and receive almost 40 times as much blood per gram of tissue as the brain does. The aortic bodies send signals to the medulla by way of the vagus

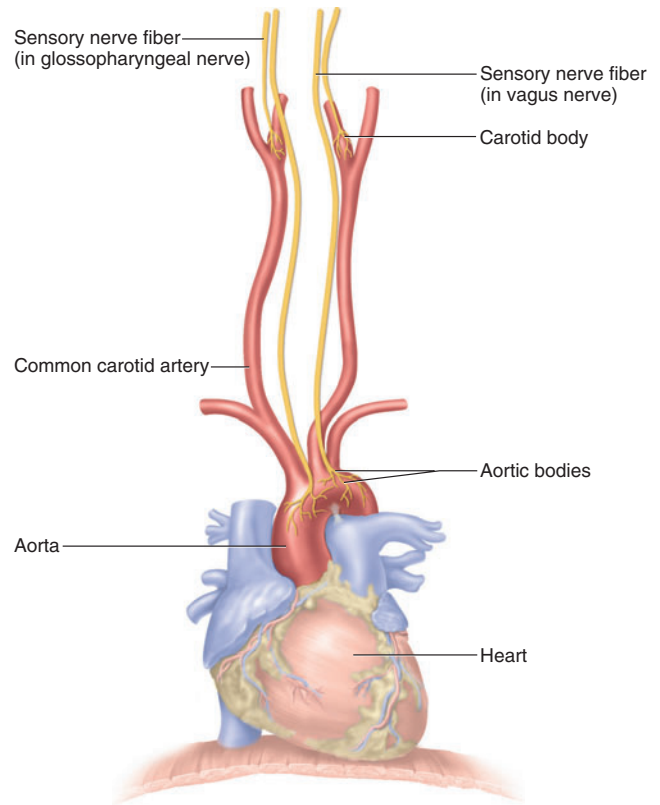


Figure 22.25 Nervous Pathways from the Peripheral Chemoreceptors to the Respiratory Centers of the Medulla Oblongata.

nerves and the carotid bodies transmit by way of the glossopharyngeal nerves. The central chemoreceptors are paired areas close to the surface of the medulla oblongata, ventral to the inspiratory center. They primarily monitor the pH of the cerebrospinal fluid (CSF) and the tissue fluid of the brain.

We now consider how hydrogen ions, carbon dioxide, and oxygen individually affect respiration.

Hydrogen Ions

Ultimately, pulmonary ventilation is adjusted to maintain the pH of the brain. Hydrogen ions cannot freely cross the blood-CSF barrier, but CO₂ does. In the CSF, CO₂ reacts with water and releases H⁺. H⁺ then strongly stimulates the central chemoreceptors, which transmit signals to the inspiratory center.

Normally the blood has a pH of 7.40 ± 0.05 . Deviation from this range is called **acidosis** when the pH falls below 7.35 and **alkalosis** when it rises above 7.45. The normal PCO₂ of the blood is 40 ± 3 mmHg. The most common

²¹John Scott Haldane (1860–1936), British physiologist

868 Part Four Regulation and Maintenance

cause of acidosis is **hypercapnia**,²² a $\text{PCO}_2 > 43$ mmHg; the most common cause of alkalosis is **hypocapnia**, a $\text{PCO}_2 < 37$ mmHg. Whenever there is a CO_2 imbalance in the blood, CO_2 diffusion across the blood-CSF barrier creates a parallel shift in the pH of the CSF. Therefore even though the brain responds primarily to pH changes, it is CO_2 that usually causes those changes. When these pH imbalances are due to a failure of pulmonary ventilation to match the body's rate of CO_2 production, they are called *respiratory acidosis* and *respiratory alkalosis* (see further discussion in chapter 24).

The corrective homeostatic response to acidosis is hyperventilation, “blowing off” CO_2 faster than the body produces it. This shifts the carbonic acid reaction to the left:



The CO_2 on the left is expired in the breath. The H^+ on the right is consumed as this reaction proceeds toward the left, and as H^+ concentration declines, the pH rises.

The corrective response to alkalosis is hypoventilation, which allows the body to produce CO_2 faster than it exhales it. Hypoventilation shifts the reaction to the right, raises the H^+ concentration, and lowers the pH to normal:



Although pH changes usually result from PCO_2 changes, they can have other causes. In diabetes mellitus, for example, fat oxidation releases acidic ketone bodies, causing an abnormally low pH called *ketoacidosis* (see chapter 17). Ketoacidosis tends to induce a form of dyspnea called *Kussmaul respiration* (see table 22.3). Hyperventilation cannot reduce the level of ketone bodies in the blood, but by blowing off CO_2 , it reduces the concentration of CO_2 -generated H^+ and compensates to some degree for the H^+ released by the ketone bodies.

Carbon Dioxide

Although the arterial PCO_2 has a strong influence on respiration, we have seen that it is mostly an indirect one, mediated through its effects on the pH of the CSF. Yet CO_2 has some effect even when pH remains stable. At the beginning of exercise, the rising blood CO_2 level may directly stimulate the peripheral chemoreceptors and trigger an increase in ventilation more quickly than the central chemoreceptors do.

Oxygen

Oxygen concentration usually has little effect on respiration. Even in eupnea, the hemoglobin is 97% saturated with O_2 ; therefore, increased ventilation cannot add very much. Only if the arterial PO_2 drops below 60 mmHg

does it significantly affect ventilation, and such a low PO_2 seldom occurs even in prolonged holding of the breath. A moderate drop in PO_2 does stimulate the peripheral chemoreceptors, but another effect overrides this: as the level of HbO_2 falls, hemoglobin binds more hydrogen ions (see fig. 22.22). This raises the blood pH, which indirectly inhibits respiration. Only at a $\text{PO}_2 < 60$ mmHg does the stimulatory effect of hypoxemia override the inhibitory effect of the pH increase. Long-term hypoxemia can lead to a condition called **hypoxic drive**, in which respiration is driven more by the low PO_2 than by CO_2 or pH. This occurs in situations such as emphysema and pneumonia, which interfere with alveolar gas exchange, and in mountain climbing of at least 2 or 3 days' duration.

In summary, the main chemical stimulus to pulmonary ventilation is the H^+ in the CSF and tissue fluid of the brain. These hydrogen ions arise mainly from CO_2 diffusing into the CSF and brain and generating H^+ through the carbonic acid reaction. Therefore the PCO_2 of the arterial blood is an important driving force in respiration, even though its action on the chemoreceptors is indirect. Ventilation is adjusted to maintain arterial pH at about 7.40 and arterial PCO_2 at about 40 mmHg. This automatically ensures that the blood is at least 97% saturated with O_2 as well. Under ordinary circumstances, arterial PO_2 has relatively little effect on respiration. When it drops below 60 mmHg, however, it excites the peripheral chemoreceptors and stimulates an increase in ventilation. This can be significant at high altitudes and in certain lung diseases.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

- Describe the locations of the chemoreceptors that monitor blood pH and gas concentrations.
- Define *hypocapnia* and *hypercapnia*. Name the pH imbalances that result from these conditions and explain the relationship between PCO_2 and pH.
- Explain how variations in pulmonary ventilation can correct pH imbalances.

Respiratory Disorders

Objectives

When you have completed this section, you should be able to

- describe the forms and effects of oxygen deficiency and oxygen excess;
- describe the chronic obstructive pulmonary diseases and their consequences; and
- explain how lung cancer begins, progresses, and exerts its lethal effects.

²²capn = smoke

The delicate lungs are exposed to a wide variety of inhaled pathogens and debris; thus, it is not surprising that they are prone to a host of diseases. Several already have been mentioned in this chapter.

Oxygen Imbalances

Hypoxia, discussed in previous chapters, is a deficiency of oxygen in a tissue or the inability to use oxygen. It is not a respiratory disease in itself but is often a consequence of respiratory diseases. Hypoxia is classified according to cause:

- **Hypoxemic hypoxia**, a state of low arterial PO_2 , is usually due to inadequate pulmonary gas exchange. Some of its root causes include atmospheric deficiency of oxygen at high altitudes; impaired ventilation, as in drowning; aspiration of foreign matter; respiratory arrest; and the degenerative lung diseases discussed shortly. It also occurs in carbon monoxide poisoning, which prevents hemoglobin from transporting oxygen.
- **Ischemic hypoxia** results from inadequate circulation of the blood, as in congestive heart failure.
- **Anemic hypoxia** is due to anemia and the resulting inability of the blood to carry adequate oxygen.
- **Histotoxic hypoxia** occurs when a metabolic poison such as cyanide prevents the tissues from using the oxygen delivered to them.

Hypoxia is often marked by **cyanosis**, blueness of the skin. Whatever its cause, the primary effect of hypoxia is the necrosis of oxygen-starved tissues. This is especially critical in organs with the highest metabolic demands, such as the brain, heart, and kidneys.

An oxygen excess is also dangerous. You can safely breathe 100% oxygen at 1 atm for a few hours, but **oxygen toxicity** rapidly develops when pure oxygen is breathed at 2.5 atm or greater. Excess oxygen generates hydrogen peroxide and free radicals that destroy enzymes and damage nervous tissue; thus it can lead to seizures, coma, and death. This is why scuba divers breathe a mixture of oxygen and nitrogen rather than pure compressed oxygen (see insight 22.4, p. 871). Hyperbaric oxygen was formerly used to treat premature infants for respiratory distress syndrome, but it caused retinal deterioration and blinded many infants before the practice was discontinued.

Chronic Obstructive Pulmonary Diseases

Chronic obstructive pulmonary disease (COPD) refers to any disorder in which there is a long-term obstruction of airflow and a substantial reduction in pulmonary ventilation. The major COPDs are *asthma*, *chronic bronchitis*, and *emphysema*. In asthma, an allergen triggers the release of

histamine and other inflammatory chemicals that cause intense bronchoconstriction and sometimes suffocation (see p. 828). The other COPDs are almost always caused by cigarette smoking but occasionally result from air pollution or occupational exposure to airborne irritants.

Beginning smokers exhibit inflammation and hyperplasia of the bronchial mucosa. In **chronic bronchitis**, the cilia are immobilized and reduced in number, while goblet cells enlarge and produce excess mucus. With extra mucus and fewer cilia to dislodge it, smokers develop a chronic cough that brings up **sputum** (SPEW-tum), a mixture of mucus and cellular debris. Thick, stagnant mucus in the respiratory tract provides a growth medium for bacteria, while cigarette smoke incapacitates the alveolar macrophages and reduces defense mechanisms against respiratory infections. Smokers therefore develop chronic infection and bronchial inflammation, with symptoms that include dyspnea, hypoxia, cyanosis, and attacks of coughing.

In **emphysema**²³ (EM-fih-SEE-muh), alveolar walls break down and the lung exhibits larger but fewer alveoli (see fig. 22.19c). Thus, there is much less respiratory membrane available for gas exchange. The lungs become fibrotic and less elastic. The air passages open adequately during inspiration, but they tend to collapse and obstruct the outflow of air. Air therefore becomes trapped in the lungs, and over a period of time a person becomes barrel-chested. The overly stretched thoracic muscles contract weakly, which further contributes to the difficulty of expiration. People with emphysema become exhausted because they expend three to four times the normal amount of energy just to breathe. Even slight physical exertion, such as walking across a room, can cause severe shortness of breath.

Think About It

Explain how the length-tension relationship of skeletal muscle (see chapter 11) accounts for the weakness of the respiratory muscles in emphysema.

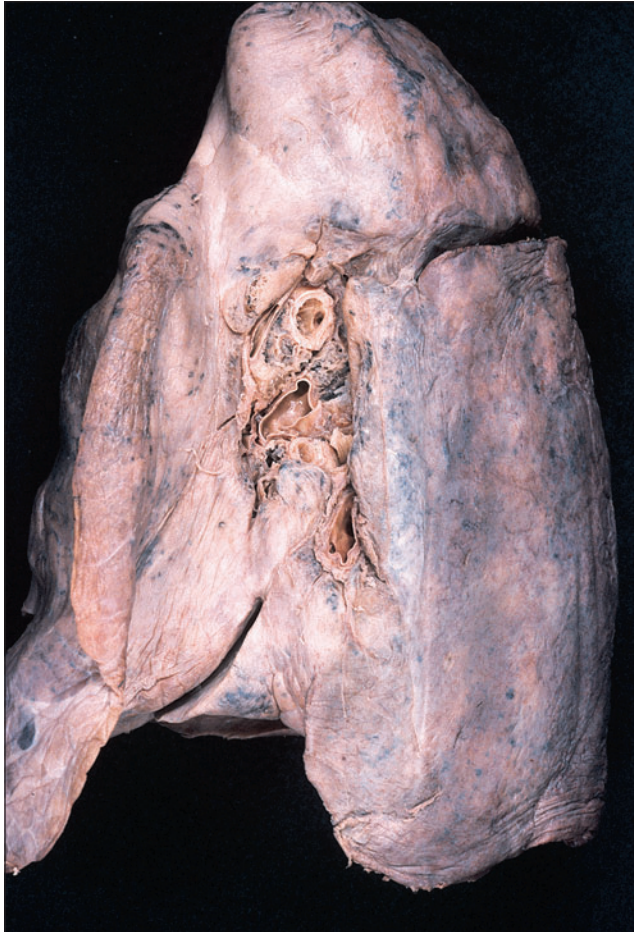
All of the COPDs tend to reduce pulmonary compliance and vital capacity and cause hypoxemia, hypercapnia, and respiratory acidosis. Hypoxemia stimulates the kidneys to secrete erythropoietin, which leads to accelerated erythrocyte production and polycythemia, as discussed in chapter 18. COPD also leads to **cor pulmonale**—hypertrophy and potential failure of the right heart due to obstruction of the pulmonary circulation (see chapter 19).

Smoking and Lung Cancer

Lung cancer (fig. 22.26) accounts for more deaths than any other form of cancer. The most important cause of lung cancer is cigarette smoking, distantly followed by air

²³emphys = inflamed

870 Part Four Regulation and Maintenance



(a)



(b)

Figure 22.26 Effect of Smoking. (a) A healthy adult lung. (b) A smoker's lung with carcinoma.

pollution. Cigarette smoke contains at least 15 carcinogenic compounds. Lung cancer commonly follows or accompanies COPD.

There are three forms of lung cancer, the most common of which is **squamous-cell carcinoma**. This form begins with the multiplication of basal cells of the bronchial epithelium and transformation of the ciliated pseudostratified columnar epithelium into the stratified squamous type. As the dividing epithelial cells invade the underlying tissues of the bronchial wall, the bronchus develops bleeding lesions. Dense swirled masses of keratin appear in the lung parenchyma and replace functional respiratory tissue. A second form of lung cancer, nearly as common, is **adenocarcinoma**,²⁴ which originates in

mucous glands of the lamina propria. The least common (10%–20% of malignancies) but most dangerous form is **small-cell (oat-cell) carcinoma**, named for clusters of cells that resemble oat grains. This originates in the primary bronchi but invades the mediastinum and metastasizes quickly to other organs.

Over 90% of lung tumors originate in the mucous membranes of the large bronchi. As a tumor invades the bronchial wall and grows around it, it compresses the airway and may cause atelectasis (collapse) of more distal parts of the lung. Growth of the tumor produces a cough, but coughing is such an everyday occurrence among smokers it seldom causes much alarm. Often, the first sign of serious trouble is the coughing up of blood. Lung cancer metastasizes so rapidly that it has usually spread to other organs by the time it is diagnosed. Common sites of

²⁴adeno = gland + carcino = cancer + oma = tumor

Table 22.5 Some Disorders of the Respiratory System

<i>Acute rhinitis</i>	The common cold. Caused by many types of viruses that infect the upper respiratory tract. Symptoms include congestion, increased nasal secretion, sneezing, and dry cough. Transmitted especially by contact of contaminated hands with mucous membranes; not transmitted orally.		
<i>Adult respiratory distress syndrome</i>	Acute lung inflammation and alveolar injury stemming from trauma, infection, burns, aspiration of vomit, inhalation of noxious gases, drug overdoses, and other causes. Alveolar injury is accompanied by severe pulmonary edema and hemorrhage, followed by fibrosis that progressively destroys lung tissue. Fatal in about 40% of cases under age 60 and in 60% of cases over age 65.		
<i>Pneumonia</i>	A lower respiratory infection caused by any of several viruses, fungi, or protozoans (most often the bacterium <i>Streptococcus pneumoniae</i>). Causes filling of alveoli with fluid and dead leukocytes and thickening of the respiratory membrane, which interferes with gas exchange and causes hypoxemia. Especially dangerous to infants, the elderly, and people with compromised immune systems, such as AIDS and leukemia patients.		
<i>Sleep apnea</i>	Cessation of breathing for 10 seconds or longer during sleep; sometimes occurs hundreds of times per night, often accompanied by restlessness and alternating with snoring. Can result from altered function of CNS respiratory centers, airway obstruction, or both. Over time, may lead to daytime drowsiness, hypoxemia, polycythemia, pulmonary hypertension, congestive heart failure, and cardiac arrhythmia. Most common in obese people and in men.		
<i>Tuberculosis (TB)</i>	Pulmonary infection with the bacterium <i>Mycobacterium tuberculosis</i> , which invades the lungs by way of air, blood, or lymph. Stimulates the lung to form fibrous nodules called tubercles around the bacteria. Progressive fibrosis compromises the elastic recoil and ventilation of the lungs. Especially common among impoverished and homeless people and becoming increasingly common among people with AIDS.		
<i>Disorders described elsewhere</i>			
Apnea 857	Decompression sickness 872	Pleurisy 849	
Asthma 828	Dyspnea 857	Pneumothorax 853	
Atelectasis 853	Emphysema 869	Pulmonary edema 861	
Carbon monoxide poisoning 864	Hypoxia 869	Respiratory acidosis 868	
Chronic bronchitis 869	Lung cancer 869	Respiratory alkalosis 868	
Cor pulmonale 740	Ondine's curse 859	Respiratory distress syndrome 855	

metastasis are the pericardium, heart, bones, liver, lymph nodes, and brain. The chance of recovery is poor, with only 7% of patients surviving for 5 years after diagnosis.

Some infectious diseases and other disorders of the respiratory system are briefly described in table 22.5. The effects of aging on the respiratory system are described on p. 1111.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

- Describe the four classes of hypoxia.
- Name and compare two COPDs and describe some pathological effects that they have in common.
- In what lung tissue does lung cancer originate? How does it kill?

Insight 22.4 Clinical Application

Diving Physiology and Decompression Sickness

Because of the rise in popularity of scuba diving in recent years, many people now know something about the scientific aspects of breathing under high pressure. But diving is by no means a new fascination. As early as the fifth century B.C.E., Aristotle described divers using snorkels and taking containers of air underwater in order to stay down longer. Some Renaissance artists depicted divers many meters deep breathing from tubes to the water surface. In reality, this would be physically impossible. For one thing, such tubes would have so much dead space that fresh air from the surface would not reach the diver. The short snorkels used today are about the maximum length that will work for surface breathing. Another reason snorkels cannot be used at greater depths is that water pressure doubles for every 11 m of depth, and even at 1 m the pressure is so great that a diver cannot expand the chest muscles without help. This is one reason why scuba divers use pressurized air tanks. The tanks create a positive intrapulmonary pressure and enable the diver to inhale with only slight assistance from the thoracic muscles. Scuba tanks also have regulators that adjust the outflow pressure to the diver's depth and the opposing pressure of the surrounding water.

But breathing pressurized (hyperbaric) gas presents its own problems. Divers cannot use pure oxygen because of the problem of oxygen toxicity. Instead, they use compressed air—a mixture of 21% oxygen and 79% nitrogen. On land, nitrogen presents no physiological problems; it dissolves poorly in blood and it is physiologically inert. But under hyperbaric conditions, larger amounts of nitrogen dissolve in the blood. (Which of the gas laws applies here?) Even more dissolves in adipose tissue and the myelin of the brain, since nitrogen is more soluble in lipids. In the brain, it causes *nitrogen narcosis*, or what Jacques Cousteau termed “rapture of the deep.” A diver can become dizzy, euphoric, and dangerously disoriented; for every 15 to 20 m of depth, the effect is said to be equivalent to one martini on an empty stomach.

Strong currents, equipment failure, and other hazards sometimes make scuba divers panic, hold their breath, and quickly swim to the surface (a *breath-hold ascent*). Ambient (surrounding) pressure falls rapidly as a diver ascends, and the air in the lungs expands just as rapidly. (Which gas law is demonstrated here?) It is imperative that an ascending diver keep his or her airway open to exhale the expanding gas; otherwise it is likely to cause *pulmonary barotrauma*—ruptured

alveoli. Then, when the diver takes a breath of air at the surface, alveolar air goes directly into the bloodstream and causes air embolism. After passing through the heart, the emboli tend to enter the cerebral circulation because the diver is head-up and air bubbles rise in liquid. The resulting cerebral embolism can cause motor and sensory dysfunction, seizures, unconsciousness, and drowning.

Barotrauma can be fatal even at the depths of a backyard swimming pool. In one case, children trapped air in a bucket 1 m underwater and then swam under the bucket to breathe from the air space. Because the bucket was under water, the air in it was compressed. One child filled his lungs under the bucket, did a “mere” 1-m breath-hold ascent, and his alveoli ruptured. He died in the hospital, partly because the case was mistaken for drowning and not treated for what it really was. This would not have happened to a person who inhaled at the surface, did a breath-hold dive, and then resurfaced—nor is barotrauma a problem for those who do breath-hold dives to several meters. (Why? What is the difference?)

Even when not holding the breath, but letting the expanding air escape from the mouth, a diver must ascend slowly and carefully to allow for decompression of the nitrogen that has dissolved in the tissues. *Decompression tables* prescribe safe rates of ascent based on the depth and the length of time a diver has been down. When pressure drops, nitrogen dissolved in the tissues can go either of two places—it can diffuse into the alveoli and be exhaled, or it can form bubbles like the CO₂ in a bottle of soda when the cap is removed. The diver's objective is to ascend slowly, allowing for the former and preventing the latter. If a diver ascends too rapidly, nitrogen “boils” from the tissues—especially in the 3 m just below the surface, where the relative pressure change is greatest. A diver may double over in pain from bubbles in the joints, bones, and muscles—a disease called the “bends,” or *decompression sickness (DCS)*. Nitrogen bubbles in the pulmonary capillaries cause “chokes”—substernal pain, coughing, and dyspnea. DCS is sometimes accompanied by mood changes, seizures, numbness, and itching. These symptoms usually occur within an hour of surfacing, but they are sometimes delayed for up to 36 hours. DCS is treated by putting the individual in a hyperbaric chamber to be recompressed and then *slowly* decompressed.

DCS is also called *caisson disease*. A caisson is a watertight underwater chamber filled with pressurized air. Caissons are used in underwater construction work on bridges, tunnels, ships' hulls, and so forth. Caisson disease was first reported in the late 1800s among workmen building the foundations of the Brooklyn Bridge.

Connective Issues

Interactions Between the RESPIRATORY SYSTEM and Other Organ Systems

- ← indicates ways in which this system affects other systems
- ➡ indicates ways in which other systems affect this one

All Systems

The respiratory system serves all other systems by supplying O₂, removing CO₂, and maintaining acid-base balance

Integumentary System

- ➡ Nasal guard hairs reduce inhalation of dust and other foreign matter

Skeletal System

- ➡ Thoracic cage protects lungs; movement of ribs produces pressure changes that ventilate lungs

Muscular System

- ➡ Skeletal muscles ventilate lungs, control position of larynx during swallowing, control vocal cords during speech; exercise strongly stimulates respiration because of the CO₂ generated by active muscles

Nervous System

- ➡ Produces the respiratory rhythm, monitors blood gases and pH, monitors stretching of lungs; phrenic, intercostal, and other nerves control respiratory muscles

Endocrine System

- ← Lungs produce angiotensin-converting enzyme (ACE), which converts angiotensin I to the hormone angiotensin II
- ➡ Epinephrine and norepinephrine dilate bronchioles and stimulate ventilation

Circulatory System

- ← Regulates blood pH; thoracic pump aids in venous return; lungs produce blood platelets; production of angiotensin II by lungs is important in control of blood volume and pressure; obstruction of pulmonary circulation leads to right-sided heart failure
- ➡ Blood transports O₂ and CO₂; mitral stenosis or left-sided heart failure can cause pulmonary edema; emboli from peripheral sites often lodge in lungs

Lymphatic/Immune Systems

- ← Thoracic pump promotes lymph flow
- ➡ Lymphatic drainage from lungs is important in keeping alveoli dry; immune cells protect lungs from infection



Urinary System

- ← Valsalva maneuver aids in emptying bladder
- ➡ Disposes of wastes from respiratory organs; collaborates with lungs in controlling blood pH

Digestive System

- ← Valsalva maneuver aids in defecation
- ➡ Provides nutrients for growth and maintenance of respiratory system

Reproductive System

- ← Valsalva maneuver aids in childbirth
- ➡ Sexual arousal stimulates respiration

Chapter Review

Review of Key Concepts

Anatomy of the Respiratory System (p. 842)

1. Respiration includes ventilation of the lungs, gas exchange with the blood, and oxygen use by the tissues.
2. The *conducting division* of the respiratory system consists of the nose, pharynx, larynx, trachea, bronchi, and most bronchioles; it serves only for airflow.
3. The *respiratory division* consists of the alveoli and other distal gas-exchange regions of the lungs.
4. The nose extends from the anterior nares to the posterior nares and is divided by the nasal septum into right and left *nasal fossae*.
5. Each fossa has three scroll-like *nasal conchae* covered with a ciliated mucous membrane. The conchae warm, humidify, and cleanse the air flowing over them.
6. The *pharynx* is a muscular passage divided into nasopharynx, oropharynx, and laryngopharynx.
7. The *larynx* is a cartilaginous chamber beginning superiorly at the *glottis* and ending about 4 cm below this at the trachea. It contains the vocal cords and keeps food and drink out of the airway. Intrinsic muscles of the larynx function in speech and its extrinsic muscles help to close off the larynx during swallowing.
8. The *trachea* is a 12-cm tube, supported by cartilaginous rings, ending where it branches inferiorly into the two primary bronchi. The ciliated mucosa of the trachea acts as a *mucociliary escalator* to remove inhaled debris, stuck in the tracheal mucus, from the respiratory tract.
9. Each lung is a conical organ extending from the superior apex to the inferior, broad base. The left lung is divided into two lobes and the right lung into three.
10. One primary bronchus supplies each lung; it divides into one secondary bronchus for each lobe of the lung, and this divides into smaller tertiary bronchi.

11. *Bronchioles* are finer divisions of the airway lacking cartilage. The smallest members of the conducting division are the terminal bronchioles. Beyond this, thin-walled respiratory bronchioles begin the respiratory division. Respiratory bronchioles have alveoli along their walls and branch distally into alveolar ducts.
12. An alveolus is a thin-walled sac surrounded by a basket of blood capillaries. It is composed of squamous and great alveolar cells and contains alveolar macrophages, the last line of defense against inhaled debris. Alveoli are the primary site of gas exchange with the blood.
13. The surface of each lung is a serous membrane called the *visceral pleura*. It continues as the *parietal pleura*, which lines the inside of the rib cage. The space between the pleurae is the *pleural cavity*, and is lubricated with *pleural fluid*. The pleurae reduce friction during breathing, contribute to the pressure gradients that move air into and out of the lungs, and help compartmentalize the thoracic cavity.

Mechanics of Ventilation (p. 850)

1. Airflow is governed by the relationship of pressure and resistance.
2. The average atmospheric (barometric) pressure at sea level is 760 mmHg (1 atm).
3. *Inspiration* is achieved by a muscular effort that increases the volume of the lungs. This reduces the *intrapulmonary pressure* (according to Boyle's law) to a few mmHg below atmospheric pressure, and air flows down its pressure gradient from the atmosphere into the lungs.
4. *Expiration* occurs when elastic recoil of the thoracic cage reduces lung volume and increases intrapulmonary pressure to a few mmHg above atmospheric pressure. Air then flows down its pressure gradient from the lungs into the atmosphere.

5. Inspiration is achieved primarily by contractions of the diaphragm and external intercostal muscles. Other muscles aid in deep inspiration. Expiration is achieved primarily by elastic recoil of the thoracic cage, but the internal intercostals, abdominal muscles, and other muscles aid in deep or rapid expiration.
6. Airflow is inversely related to resistance in the airway. High pulmonary *compliance* means that the lungs expand easily and resistance is minimal. Compliance is reduced in such diseases as tuberculosis and black lung disease, which stiffen the lungs.
7. Resistance also varies with the diameter of the airway. *Bronchoconstriction* increases resistance and reduces airflow; *bronchodilation* increases airflow. Asthma and anaphylaxis can cause fatal bronchoconstriction.
8. Alveolar surface tension also affects resistance by tending to cause alveolar collapse during expiration and resisting inflation during inspiration; but surface tension is normally minimized by a lipoprotein *pulmonary surfactant* secreted by the great alveolar cells. Surfactant deficiency is the cause of *respiratory distress syndrome* in premature infants.
9. At rest, an average adult inhales about 500 mL of air in one inspiration. About 150 mL of this is *dead air*, filling the conducting division (*anatomic dead space*) where no gas exchange occurs; 350 mL ventilates the alveoli. This quantity times the respiratory rate is the *alveolar ventilation rate* (for example, 350 mL/breath \times 12 breaths/min = 4,200 mL/min).
10. In addition to gas exchange, breathing serves the purposes of speaking, laughing, crying, yawning, hiccupping, expelling noxious fumes, coughing, sneezing, and expelling abdominal contents (by means of the Valsalva maneuver).

11. Pulmonary function is measured with a *spirometer*, which quantifies various respiratory volumes and capacities (see table 22.2) and can help the clinician assess the severity of *restrictive* and *obstructive disorders* of the respiratory system. Restrictive disorders reduce pulmonary compliance and obstructive disorders reduce the speed of airflow.

Neural Control of Ventilation (p. 857)

1. The respiratory rhythm is governed by pacemakers in the brainstem which control the respiratory muscles.
2. The medulla oblongata contains two respiratory nuclei. One of these, the *inspiratory center*, consists mostly of inspiratory (I) neurons. Firing of these neurons ultimately stimulates the diaphragm (via the phrenic nerves) and external intercostal muscles (via the intercostal nerves) and causes inspiration.
3. The expiratory center of the medulla has both I neurons and expiratory (E) neurons. It is not employed in normal relaxed breathing (*eupnea*), but inhibits the inspiratory center when deep expiration is needed.
4. The pons contains an *apneustic center* which seems to prolong inspiration, and a *pneumotaxic center* which acts on the inspiratory center of the medulla to vary the rate and depth of breathing.
5. The brainstem respiratory centers receive input from the limbic system, hypothalamus, and frontal lobe of the cerebrum, enabling mental states to affect breathing.
6. They also receive input from chemoreceptors in the arteries and from receptors in the airway and lungs that respond to airborne irritants, stretching of the lungs, and other stimuli.

Gas Exchange and Transport (p. 859)

1. Air is composed of nearly 79% N₂, 21% O₂, 0.5% H₂O, and 0.04% CO₂. The concentrations of these gases are also expressed as *partial pressures*, the fraction that each contributes to the total atmospheric pressure (see Dalton's law).
2. Expired air shows changes that result from what the body adds to and takes from the inhaled air: it is about 75% N₂, 14% O₂, 6% H₂O, and 5% CO₂.

3. At the air-water interface in the alveoli, gases diffuse down their concentration gradients at rates determined by their solubility in water and partial pressures in the alveolar air and blood (see Henry's law). The blood thus unloads CO₂ into the alveolus, to be expired, and loads O₂ to be carried to other tissues of the body.
4. The efficiency of alveolar gas exchange depends on the concentration gradients of the gases (air vs. blood), solubility of the gases in water, thickness of the respiratory membrane between the blood and alveolar air, and ventilation-perfusion coupling.
5. *Ventilation-perfusion coupling* is the tendency of the lungs to direct the most blood to the best-ventilated parts of the lungs, and direct the most air to the best-perfused parts of the lung. The lungs thus minimize wasteful ventilation of poorly perfused areas of the lung and wasteful blood circulation to poorly ventilated areas.
6. About 1.5% of the O₂ in the blood is dissolved in the plasma, and 98.5% is bound to hemoglobin in the RBCs. Each hemoglobin can carry up to 4 O₂. It is called *oxyhemoglobin* (HbO₂) if it carries one or more O₂ molecules.
7. The relationship between oxygen concentration (PO₂) and percent HbO₂ is the *oxyhemoglobin dissociation curve* (fig. 22.21). It shows that binding of the first oxygens to hemoglobin accelerates the binding of more O₂, until the Hb becomes saturated.
8. About 90% of the CO₂ in the blood is carried as bicarbonate (HCO₃⁻) ions, 5% is bound to proteins as carbamino compounds, and 5% is dissolved in the blood plasma.
9. The loading of CO₂ from the tissue fluids is promoted by *carbonic anhydrase*, an enzyme in the RBCs that promotes the reaction of CO₂ and water to form carbonic acid. The carbonic acid breaks down to HCO₃⁻ and H⁺. Most of the H⁺ binds to hemoglobin, while the HCO₃⁻ is exchanged for Cl⁻ from the blood plasma.
10. This binding of H⁺ to hemoglobin promotes the unloading of O₂ to the systemic tissues. In one pass through the capillaries of a resting tissue, the

blood gives up about 22% of its O₂ to the tissue (the *utilization coefficient*).

11. In the alveoli, Hb unloads O₂. This unloading causes H⁺ to dissociate from the Hb and recombine with HCO₃⁻ to produce carbonic acid. The carbonic acid is then broken down by carbonic anhydrase into water and CO₂. The latter is exhaled.
12. Hemoglobin unloads varying amounts of O₂ to different tissues according to their needs. Hemoglobin adjusts O₂ unloading in response to variations in the tissue's PO₂, temperature, and pH (the Bohr effect), and the RBC's own temperature- and hormone-sensitive concentration of bisphosphoglycerate (BPG).

Blood Chemistry and the Respiratory Rhythm (p. 867)

1. Breathing is stimulated especially by the pH of the body fluids, but also by the PCO₂ and to some extent PO₂. These conditions are monitored by *central chemoreceptors* in the brainstem and *peripheral chemoreceptors* in the aortic arch and carotid arteries.
2. Ultimately, breathing is adjusted to maintain a stable pH in the brain. Blood pH is determined largely by PCO₂ because of the reaction of CO₂ and water: CO₂ + H₂O ↔ H₂CO₃ ↔ HCO₃⁻ + H⁺. The more CO₂ is present, the more H⁺ is generated and the lower the pH is; the less CO₂, the higher the pH.
3. Normally, the blood pH ranges from 7.35 to 7.45. A pH below this range is called *acidosis* and a pH above this range is *alkalosis*.
4. Acidosis is usually caused by a CO₂ excess (*hypercapnia*) and can therefore be corrected by increasing pulmonary ventilation to expel more CO₂.
5. Alkalosis is usually caused by a CO₂ deficiency (*hypocapnia*) and can therefore be corrected by reducing pulmonary ventilation to allow for metabolically generated CO₂ to build up in the blood.
6. PCO₂ can also have a direct effect on ventilation even when the pH is stable.
7. PO₂ normally has little effect on ventilation, but long-term hypoxemia (PO₂ < 60 mmHg) can trigger *hypoxic drive*, in which ventilation is driven more by O₂ than CO₂ levels. This can occur in such conditions as emphysema and mountain climbing.

876 Part Four Regulation and Maintenance

Respiratory Disorders (p. 868)

1. Hypoxia, a deficiency of O_2 in the tissues, can be of *hypoxemic*, *ischemic*, *anemic*, or *histotoxic* origin. It can cause cyanosis and, if severe and prolonged, tissue necrosis.
2. Oxygen excess can generate hydrogen peroxide and free radicals that cause *oxygen toxicity*.
3. The *chronic obstructive pulmonary diseases (COPDs)* are asthma, chronic bronchitis, and emphysema. Asthma is an allergic disease while the others are usually caused by tobacco smoke. Chronic bronchitis entails congestion of the airway with thick mucus, and susceptibility to respiratory infection. Emphysema entails destruction of pulmonary alveoli and air retention in expiration.
4. Lung cancer also is usually caused by tobacco smoke. Its variations are squamous-cell carcinoma, adenocarcinoma, and small-cell carcinoma. It tends to metastasize rapidly.

Selected Vocabulary

nasal fossa 843	alveolus 849	tidal volume 855	hypercapnia 868
nasal concha 843	pulmonary surfactant 849	vital capacity 856	hypocapnia 868
pharynx 845	pleura 849	partial pressure 859	hypoxia 869
larynx 845	pleural cavity 849	oxyhemoglobin 863	chronic obstructive pulmonary disease 869
trachea 846	inspiration 851	carbonic acid 864	chronic bronchitis 869
mucociliary escalator 846	expiration 851	chemoreceptor 867	emphysema 869
bronchus 847	bronchoconstriction 854	acidosis 867	lung carcinoma 870
bronchiole 848	bronchodilation 854	alkalosis 867	

Testing Your Recall

1. The nasal cavity is divided by the nasal septum into right and left
 - a. nares.
 - b. vestibules.
 - c. fossae.
 - d. choanae.
 - e. conchae.
2. The intrinsic laryngeal muscles regulate speech by rotating
 - a. the extrinsic laryngeal muscles.
 - b. the corniculate cartilages.
 - c. the arytenoid cartilages.
 - d. the hyoid bone.
 - e. the vocal cords.
3. The largest air passages that engage in gas exchange with the blood are
 - a. the respiratory bronchioles.
 - b. the terminal bronchioles.
 - c. the primary bronchi.
 - d. the alveolar ducts.
 - e. the alveoli.
4. Respiratory arrest would most likely result from a tumor of the
 - a. pons.
 - b. midbrain.
 - c. thalamus.
 - d. cerebellum.
 - e. medulla oblongata.
5. Which of these values would normally be the highest?
 - a. tidal volume
 - b. inspiratory reserve volume
 - c. expiratory reserve volume
 - d. residual volume
 - e. vital capacity
6. The _____ protects the lungs from injury by excessive inspiration.
 - a. pleura
 - b. rib cage
 - c. inflation reflex
 - d. Haldane effect
 - e. Bohr effect
7. According to _____, the warming of air as it is inhaled helps to inflate the lungs.
 - a. Boyle's law
 - b. Charles' law
 - c. Dalton's law
 - d. the Bohr effect
 - e. the Haldane effect
8. Poor blood circulation causes _____ hypoxia.
 - a. ischemic
 - b. histotoxic
 - c. hemolytic
 - d. anemic
 - e. hypoxemic
9. Most of the CO_2 that diffuses from the blood into an alveolus comes from
 - a. dissolved gas.
 - b. carbaminohemoglobin.
 - c. carboxyhemoglobin.
 - d. carbonic acid.
 - e. expired air.
10. CO_2 affects the pH of the CSF more than it does the pH of the blood because
 - a. CSF contains less protein than blood.
 - b. CO_2 cannot cross the blood-brain barrier.
 - c. all CO_2 crosses the blood-brain barrier, so none remains in the blood.
 - d. only the blood contains carbonic anhydrase.
 - e. the chloride shift occurs in the blood.
11. The superior opening into the larynx is called the _____.
12. Within each lung, the airway forms a branching complex called the _____.
13. The great alveolar cells secrete a lipoprotein called _____.
14. Intrapulmonary pressure must be greater than _____ pressure for inspiration to occur, but greater than _____ pressure for expiration to occur.
15. _____ disorders reduce the flow of air through the airway.
16. Some inhaled air does not participate in gas exchange because it fills the _____ of the respiratory tract.
17. Inspiration depends on the ease of pulmonary inflation, called _____,

Chapter 22 The Respiratory System 877

- whereas expiration depends on _____, which causes pulmonary recoil.
18. Inspiration is caused by the firing of I neurons in the _____ of the medulla oblongata.
19. The matching of airflow to blood flow in any region of the lung is called _____.
20. A blood pH > 7.45 is called _____ and can be caused by a CO₂ deficiency called _____.

Answers in Appendix B

True or False

Determine which five of the following statements are false, and briefly explain why.

- The glottis is the opening from the larynx to the trachea.
- The lungs contain more respiratory bronchioles than terminal bronchioles.
- In alveolar capillaries, oncotic pressure is greater than the mean blood pressure.
- If you increase the volume of a given quantity of gas, its pressure increases.
- Pneumothorax is the only cause of atelectasis.
- Obstruction of the bronchial tree results in a reduced FEV.
- At a given PO₂ and pH, hemoglobin carries less oxygen at warmer temperatures than it does at cooler temperatures.
- Most of the air one inhales never makes it to the alveoli.
- The greater the PCO₂ of the blood is, the lower its pH is.
- Most of the CO₂ transported by the blood is in the form of dissolved gas.

Answers in Appendix B

Testing Your Comprehension

- Discuss how the different functions of the conducting division and respiratory division relate to differences in their histology.
- State whether hyperventilation would raise or lower each of the following—the blood PO₂, PCO₂, and pH—and explain why. Do the same for the effects of emphysema.
- Some competitive swimmers hyperventilate before an underwater race, thinking they can “load up on extra oxygen” and hold their breaths longer underwater. While they can indeed hold their breaths longer, it is not for the reason they think. Furthermore, some have fainted and drowned because of this practice. What is wrong with this thinking, and what accounts for the loss of consciousness?
- Consider a man in good health with a 650 mL tidal volume and a respiratory rate of 11 breaths per minute. Report his minute respiratory volume in liters per minute. Assuming his anatomic dead space is 185 mL, calculate his alveolar ventilation rate in liters per minute.
- An 83-year-old woman is admitted to the hospital, where a critical care nurse attempts to insert a nasogastric tube (“stomach tube”) for feeding. The patient begins to exhibit dyspnea, and a chest X ray reveals air in the right pleural cavity and a collapsed right lung. The patient dies 5 days later from respiratory complications. Name the conditions revealed by the X ray and explain how they could have resulted from the nurse’s procedure.

Answers at the Online Learning Center

Answers to Figure Questions

- 22.3 Bacteria can easily travel from the throat up the auditory tube to the middle ear.
- 22.7 The right primary bronchus is more vertical than the left, making it easier for objects to fall into the right.
- 22.21 About 70%
- 22.23 In the alveoli, CO₂ leaves the blood, O₂ enters, and all the chemical reactions are the reverse of those in figure 22.22. The blood bicarbonate concentration will be reduced following alveolar gas exchange.
- 22.24 A higher temperature suggests a relatively high metabolic rate, and thus an elevated demand for oxygen. Comparison of these curves shows that for a given PO₂, hemoglobin gives up more oxygen at warmer temperatures.

www.mhhe.com/saladin3

The Online Learning Center provides a wealth of information fully organized and integrated by chapter. You will find practice quizzes, interactive activities, labeling exercises, flashcards, and much more that will complement your learning and understanding of anatomy and physiology.