20

Introduction to the Respiratory System

LEARNING OBJECTIVES

Upon completion of this chapter, the student should be able to answer the following questions:

1. What is the primary function of the upper airways? What is the primary function of the lower airways? What anatomical adaptations exist in the upper and lower respiratory systems to accomplish these functions?
2. How do the pulmonary and bronchial circulatory systems differ in blood flow, blood pressure, and anatomic distribution?
3. How does the autonomic nervous system regulate airway diameter, airway mucus production, and pulmonary circulation? Is regulation of bulk airflow an autonomic process?
4. What are the functional differences between the conducting airways and the respiratory units?
5. What is the response of the respiratory system to stimulation of the parasympathetic nervous system? What is the response of the respiratory system to stimulation of the sympathetic nervous system?
6. At what age is lung development complete?

The primary function of the lung is gas exchange, which consists of movement of oxygen (O_2) into the body and removal of carbon dioxide (CO_2) from the body. This chapter provides an overview of lung anatomical structure/function relationships (i.e., upper and lower airways, the bronchial and pulmonary circulatory systems, innervation, and muscles of respiration), lung development (at the embryonic stage and throughout life), and lung repair. This chapter is designed to provide a broad conceptual understanding of the respiratory system and is not intended to provide a comprehensive understanding of individual components.

Lung Anatomical Structure/Function Relationships

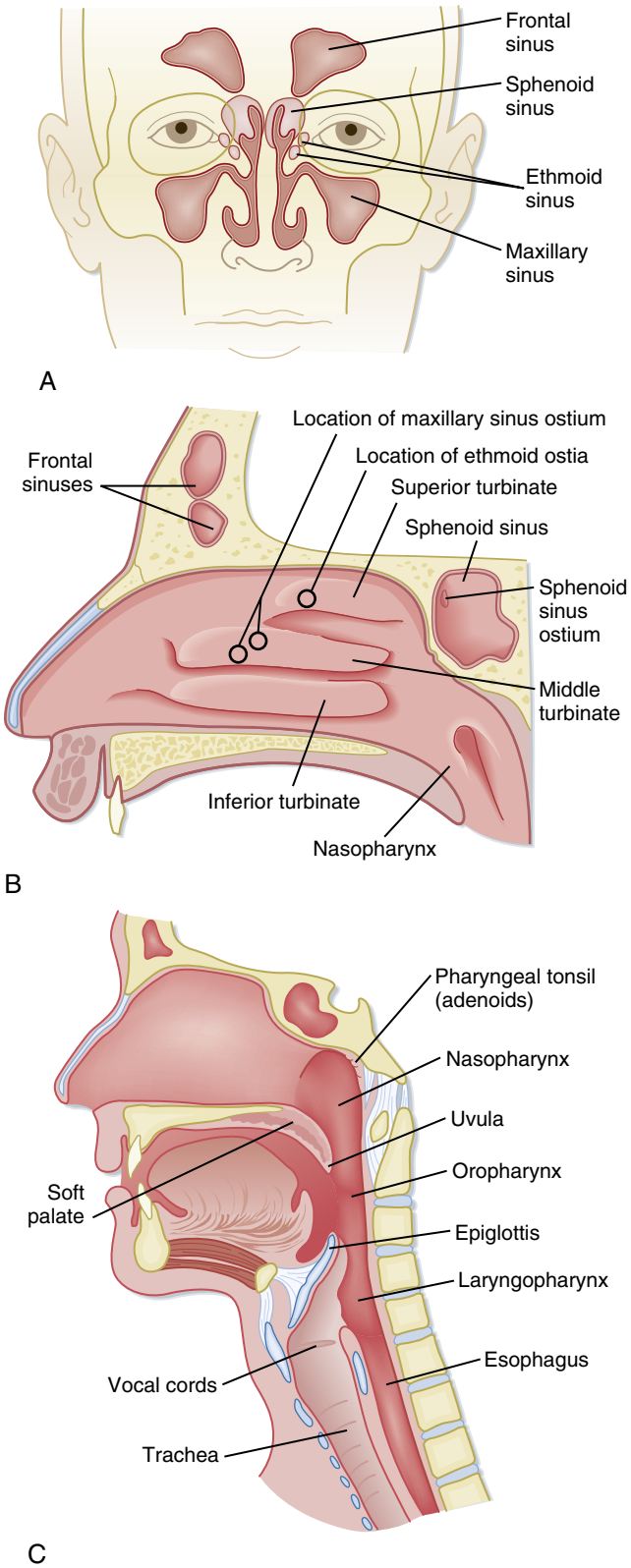
The lungs are contained in the thorax with a volume of approximately 4 L and provide a surface area for gas exchange that is roughly the size of a tennis court (≈85 m^2). This large surface area is composed of millions of independently functioning respiratory units. Unlike the heart, but like the kidneys, the lungs demonstrate functional unity; that is, each respiratory unit is structurally identical and functions like every other respiratory unit. The divisions of the lung and the sites of disease are designated by anatomic location (e.g., right upper lobe, left lower lobe) or radiographic location (e.g., right upper lung field, left lower lung field). It is essential to know pulmonary anatomy in order to understand respiratory physiology and pathophysiologic alterations caused by respiratory disease.

Upper Airways: Nose, Sinuses, and Pharynx

The respiratory system begins at the nose and ends in the most distal **alveolus.** Thus, the **nasal cavity,** the **posterior pharynx,** the **glottis** and **vocal cords,** the **trachea,** and all divisions of the **tracheobronchial tree** are included in the respiratory system. The **upper airways** include all structures from the nose to the vocal cords, including sinuses and the larynx, whereas the **lower airways** consist of the trachea, bronchial airways, and alveoli. The upper airways "condition" inspired air by adding humidity and bringing it to body temperature by the time air reaches the trachea and further into the lower airway. The nose also functions to filter, entrap, and clear inspired particles larger than 10 μm in size. The interior of the nose is lined by respiratory epithelial cells interspersed with surface secretory cells. These secretory cells produce important immunoglobulins, inflammatory mediators, and interferons, which are the first line of host respiratory defense.

The paranasal **sinuses** (**frontal**, **maxillary, sphenoid,** and **ethmoid)** are lined by ciliated epithelial cells and surround the nasal passages (Fig. 20.1*A*). The cilia facilitate the movement of mucus from the upper airways and clear the main nasal passages approximately every 15 minutes. The functions of the sinuses are (1) to lessen the weight of the skull; (2) to protect the brain from frontal trauma; and (3) to offer resonance to the voice. The fluid covering their surfaces is continually being moved from the sinuses into the nose. In some sinuses (e.g., the **maxillary sinus**), the opening **(ostium)** is at the upper edge of the sinus cavity, which makes fluid drainage difficult. The ostia may be narrowed or entirely occluded by nasal edema (swelling). Retention of secretions can result, which may lead to secondary infection **(sinusitis)**.

The volume of the adult nose is approximately 15 to 20 mL, but the surface area is greatly increased by the **nasal turbinates** (a series of three continuous ribbons of tissue that protrude into



• **Fig. 20.1** Illustrations of upper airway anatomy. **A,** Anterior view of the paranasal sinuses. **B,** Lateral view of the nasal passage structures demonstrating the superior, middle, and inferior turbinates and the sinus ostia. **C,** Lateral midsagittal section view of the head and neck, showing the three divisions of the pharynx (nasopharynx, oropharynx, and laryngopharynx) and surrounding upper airway structures.

the nasal cavity, see Fig. 20.1*B*) to approximately 160 cm^2. The nose enables the sense of smell. Neuronal endings in the roof of the nose above the **superior turbinate** carry impulses through the **cribriform plate** to the **olfactory bulb.**

The **pharynx** is divided into three sections: the **nasopharynx**, **oropharynx**, and **laryngopharynx.** Important structures within these regions include the **epiglottis, vocal cords,** and **arytenoid cartilage** that is attached to the vocal cords (see Fig. 20.1*C*). The nasopharynx (2–3 cm wide and 3–4 cm long) is the most anterior and lies behind the nose. It contains small masses of lymphoid tissue (adenoids), also known as *pharyngeal tonsils,* which are a part of the immune system. They represent a drainage pathway of lymphatic fluid between the throat, nose, and ears. This network of structures provides a means of fighting infections but also is a common location for infectious symptoms.

The nasopharynx is connected to the middle ear cavity via the Eustachian tubes. These aid in equalizing pressure between the middle ear and the atmospheric (by way of the pharynx). If there is inflammation in the nasopharynx, the Eustachian tubes may become narrowed or blocked. As a result, fluid drainage and air pressure equalization may be impaired, leading to symptoms of Eustachian tube dysfunction.

The soft palate separates the nasopharynx and the oropharynx. The oropharynx ends at the epiglottis. The laryngopharynx begins at the epiglottis and ends at the esophagus. The major role of the laryngopharynx is to help regulate the passage of food into the esophagus and air into the lungs. With some infections or repeated insults, these structures can become **edematous** and contribute significantly to airflow resistance. The epiglottis and arytenoid cartilage (attached to the vocal cords) cover or act as a hood over the vocal cords during swallowing. Thus, under normal circumstances, the epiglottis and arytenoid cartilage function to prevent aspiration of food and liquid into the lower airway. The act of swallowing food after **mastication** (chewing) usually occurs within 2 seconds, and it is closely synchronized with muscle reflexes that coordinate opening and closing of the airway. Air is allowed to enter the lower airway, while food and liquids are kept out. Patients with some neuromuscular diseases have altered muscle reflexes and can lose this coordinated swallowing mechanism. Prescription and recreational drugs may also impair these muscle reflexes. Impairment of this coordinated swallow mechanism increases the risk for aspiration of food and liquid and poses a risk for infection of the lung (**pneumonia**) or lung inflammation (**pneumonitis**).

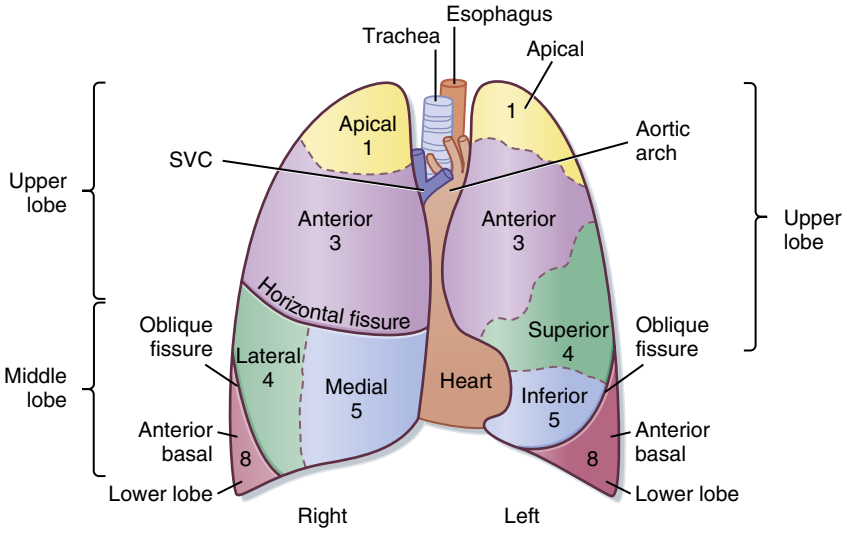
Lower Airway: Trachea, Bronchi, Bronchioles, and Respiratory Unit

The right lung, located in the right **hemithorax,** is divided into three lobes **(upper, middle,** and **lower)** by two interlobular fissures (oblique, horizontal). The left lung, located in the left hemithorax, is divided into two lobes **(upper,** including the **lingula,** a tongue-like projection of the anterior aspect of the upper lobe**,** and **lower)** by an **oblique fissure** (Fig. 20.2). Both the right and left lungs are covered by a thin membrane called

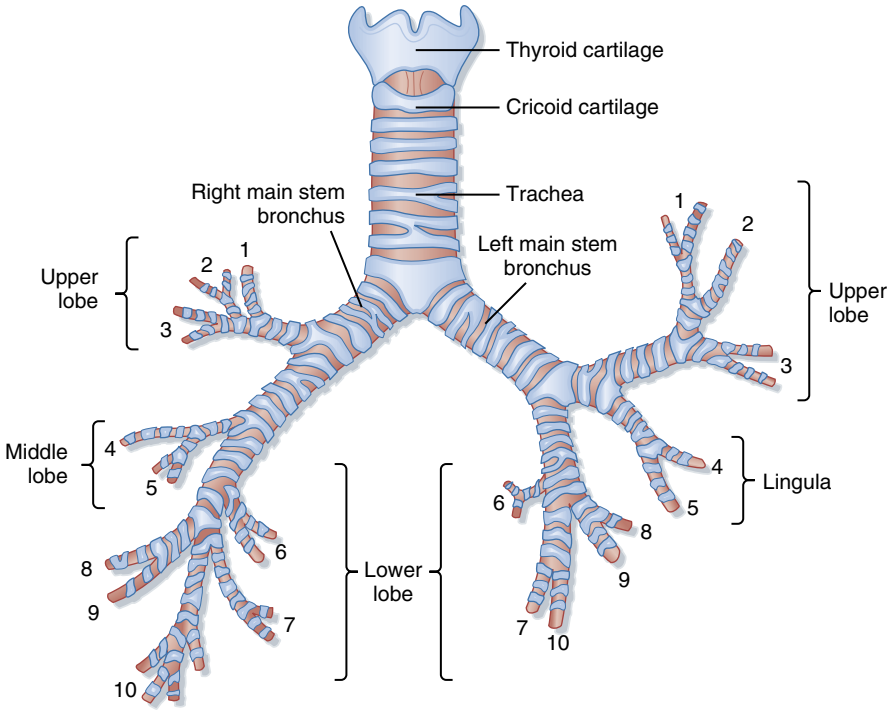
the **visceral pleura.** The interior wall of the chest cavity is lined by another membrane called the **parietal pleura.** The interface of the visceral and parietal pleura allows for smooth gliding of the lung as it expands and contracts in the chest and produces a potential space. Normally this **pleural space** contains less than 5 mL of lubricating **pleural fluid**. Fluid can enter this space by a variety of pathologic mechanisms and create a **pleural effusion** or, if the fluid becomes infected, an **empyema.** Air can also enter the pleural space between the visceral and parietal pleura due to surgery, trauma, or spontaneous rupture of a group of alveoli. Air in the pleural space is called a **pneumothorax.** In either pneumothorax or pleural effusion, the muscles of respiration cannot efficiently create a negative intrathoracic pressure gradient, and work of breathing increases. In severe cases, respiratory distress or respiratory failure may occur.

The **trachea** branches into two mainstem bronchi (Fig. 20.3). These mainstem bronchi then divide (like the branches of a tree) into lobar bronchi (one for each lobe), which in turn divide into **segmental bronchi** (Fig. 20.4; see also Fig. 20.3) and then into smaller and smaller branches **(bronchioles)** until ending in the **alveolus** (Fig. 20.5). Bronchi and bronchioles differ not only in size but also by the presence of cartilage, the type of epithelium, and their blood supply (Table 20.1). Beyond the segmental bronchi, the airways divide in a dichotomous or asymmetrical branching pattern. Bronchi, distinguished by their size and the presence of cartilage, eventually become **terminal bronchioles,** which are the smallest airways without alveoli. Each branching of an airway results in an increase in the number of airways with smaller diameters; as a result, the total surface area for the next generation of branches increases. Terminal bronchioles end in an opening (duct) to a group of alveoli and are called **respiratory bronchioles.**

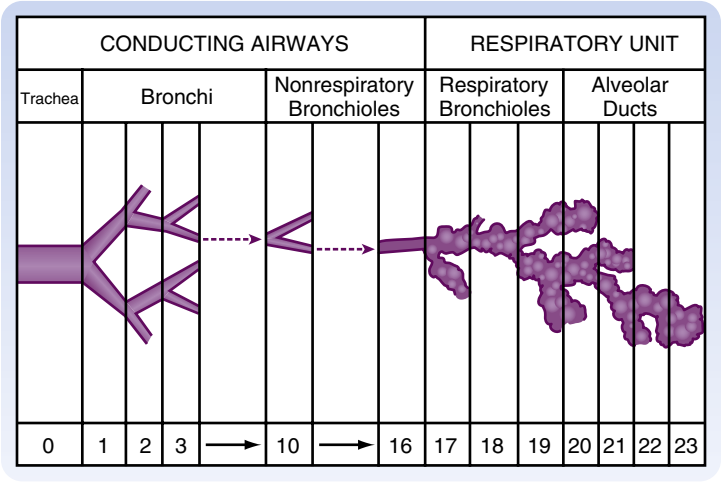
The region of the lung supplied by a segmental bronchus is called a **bronchopulmonary segment** and is the



• **Fig. 20.2** Illustrations of the topography of the lung with anterior and posterior views, demonstrating the lobes, segments, and fissures. The fissures (or chasms) demarcate the lobes in each lung. *Numbers* refer to specific bronchopulmonary segments, as depicted in Fig. 20.3. *SVC*, Superior vena cava.

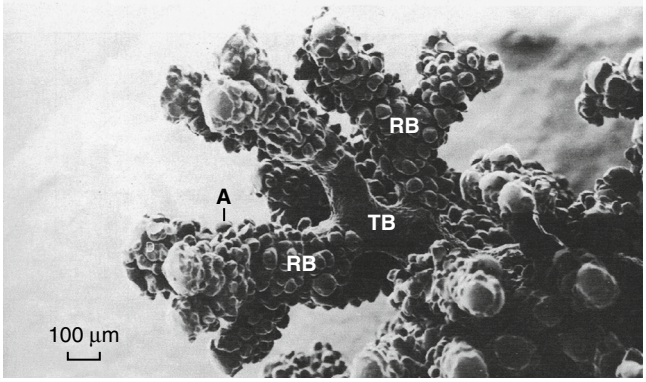


• **Fig. 20.3** Illustration of bronchopulmonary segments, anterior view. The *numbers* correspond to those in Fig. 20.2:*1*, apical; *2*, posterior; *3*, anterior; *4*, lateral (superior); *5*, medial (inferior); *6*, superior; *7*, medial basal; *8*, anterior basal; *9*, lateral basal; *10*, posterior basal. The medial basal regions *(7)* are located in the upper region of the posterior basal regions *(10)* in Fig. 20.2.



• **Fig. 20.4** Illustration of conducting airways and alveolar units of the lung. The relative size of the alveolar unit is greatly enlarged. *Numbers* at the bottom indicate the approximate number of generations from trachea to alveoli, which may vary from as few as 10 to as many as 23. (From Weibel ER. *Morphometry of the Human Lung.* Heidelberg: Springer-Verlag; 1963.)

functional **anatomical** unit of the lung. Because of their structure, bronchopulmonary segments that have become irreversibly diseased can easily be removed surgically. The basic **physiological** unit of the lung is the gas-exchanging unit **(respiratory unit),** which consists of the respiratory bronchioles, the alveolar ducts, and the alveoli (see Figs. 20.4 and 20.5). The bronchi, which contain cartilage, and the terminal bronchioles (i.e., lacking alveoli), in which cartilage is absent, serve to move gas from the airways to the alveoli and are referred to as the **conducting airways.** This area of the lung (≈150 mL in volume) does not participate in gas exchange and is referred to as **anatomical dead space**. This region may further condition inspired air if the capacity of the upper airway to do so is exceeded. The area beginning with the respiratory bronchioles extending to the alveoli is where all gas exchange occurs. This region is only approximately 5 mm long, but it is the largest volume of the lung, at a volume of approximately 2500 mL and with a surface area of 70 m^2 when the lung and chest wall are at the resting volume (see Table 20.1).



• **Fig. 20.5** The airway from the terminal bronchiole to the alveolus. Note the absence of alveoli in the terminal bronchiole. *A*, Alveolus; *RB*, respiratory bronchiole; *TB*, terminal bronchiole.

The alveoli are polygonal in shape and approximately 250 µm in diameter. **Alveolar spaces** are responsible for most of the lung volume; these spaces are divided by tissue known collectively as the **interstitium.** The interstitium is composed primarily of lung collagen fibers and is a space in which fluid and cells can potentially accumulate. An adult has approximately 5×10^8 alveoli (Fig. 20.6), which are composed of **type I** and **type II** epithelial cells. Under normal conditions, type I and type II cells exist in a 1:1 ratio.

The type I cell occupies 96% to 98% of the surface area of the alveolus, and it is the primary site for gas exchange. The thin cytoplasm of type I cells is ideal for optimal gas diffusion. In addition, the basement membrane of type I cells and the capillary endothelium are fused, which minimizes the distance for gas diffusion and thereby facilitates gas exchange.

Type II cells are cuboidal and usually found in the "corners" of the alveolus, where they occupy 2% to 4% of the surface area. During embryonic development, the alveolar epithelium is composed entirely of type II cells, and only very late in gestation do they differentiate into type I cells and form the "normal" alveolar epithelium for optimal gas exchange. Also, type II cells synthesize **pulmonary surfactant** (see Chapter 21). Pulmonary surfactant reduces alveolar surface tension, decreasing fluid cohesive forces that would otherwise lead to deaeration and collapse of the alveoli. Gas exchange occurs in the alveoli through a dense mesh-like network of capillaries and alveoli called the **alveolar-capillary network.** The barrier between gas in the alveoli and the red blood cell is only 1 to 2 µm thick and consists of type I alveolar epithelial cells, capillary endothelial cells, and their respective basement membranes. O_2 and CO_2 passively diffuse across this barrier. Oxygen diffuses into blood and subsequently into red blood cells (see Chapter 24) where it can bind with hemoglobin. Red blood cells pass through the network in 0.75 to 1.0 second, which is sufficient time for CO_2 and O_2 gas exchange. In conditions shortening capillary transit time (e.g., increased cardiac output) or conditions impairing function of the alveolar-capillary network (e.g., emphysema, interstitial lung disease) the transit time may be insufficient for adequate oxygen diffusion.

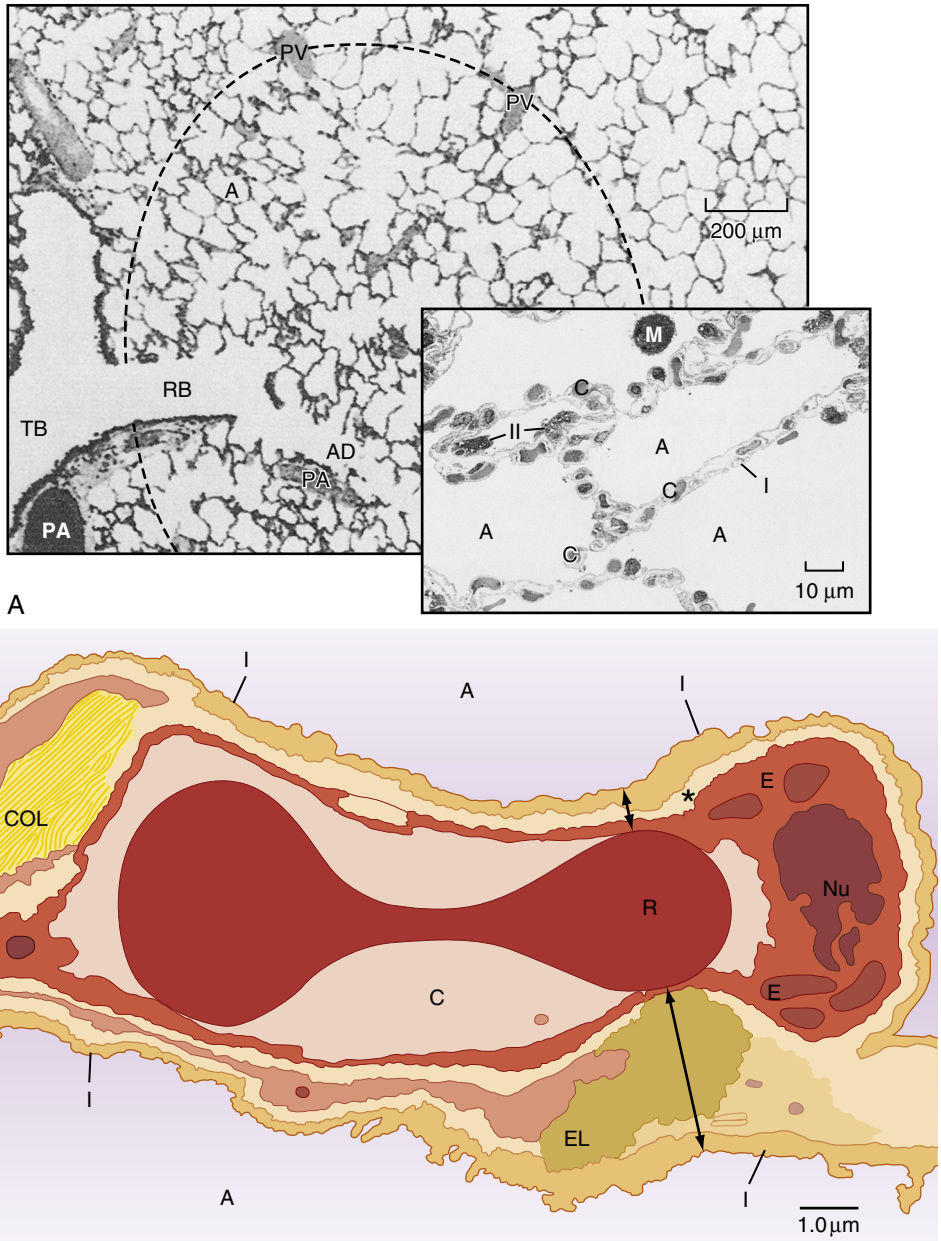
IN THE CLINIC

The conducting airways are involved in several major pulmonary diseases collectively referred to as **obstructive pulmonary disease.** Obstructive pulmonary diseases include asthma, bronchiolitis, chronic bronchitis, cystic fibrosis, and emphysema. Obstruction of airflow through the airways is commonly caused by increased amounts of mucus, airway inflammation, and smooth muscle constriction. Loss of cartilaginous support may also occur. **Asthma** is a chronic inflammatory disease of the large and small airways, mediated predominantly by lymphocytes and eosinophils. Asthma is associated with increased amounts of mucus in the airways and with reversible constriction of the airway smooth muscle (bronchospasm). **Bronchiolitis** is a disease of the bronchioles that usually occur in young infants and is caused by viruses, primarily **respiratory syncytial virus. Chronic bronchitis,** a disease typically of people who smoke, is associated with an increased number of mucus-secreting cells in the airways, an increase in mucus production, and recurrent airway infections. **Cystic fibrosis** is an autosomal recessive genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that codes for a chloride ion channel. Mutations in the *CFTR* gene cause a reduction in chloride and water secretion into the mucus overlying the epithelia cells, which increases the viscosity of mucus. This situation results in mucus accumulation and chronic pulmonary infections, primarily by *Pseudomonas aeruginosa.*

Not every important obstructive lung disease involves the airways directly. **Emphysema** is an irreversible, obstructive lung disease. It is strongly linked to cigarette smoke inhalation. The pathogenesis involves a progressive destruction of the elastic tissues in the lung with a loss of alveolar/capillary structure. The mechanisms of tissue destruction are unclear but may involve proteolytic enzymes released by activated inflammatory cells and by toxic compounds present in cigarette smoke. Emphysema can occur in nonsmoking individuals with occupational or environmental exposures to lung irritants. Individuals with the genetic disorder **α_1-antitrypsin deficiency** may also develop emphysema due to reduced tissue breakdown of proteolytic enzymes, such as elastase.

TABLE 20.1 Anatomical Characteristics of Bronchi and Bronchioles

Anatomical Site	Cartilage	Diameter (mm)	Epithelium	Blood Supply	Alveoli	Volume (mL)
Bronchi	Present	>1	Pseudostratified Columnar	Bronchial	Absent	—
Terminal bronchioles	Absent	<1	Cuboidal	Bronchial	Absent	>150
Respiratory bronchioles	Absent	<1	Cuboidal/alveolar	Pulmonary	Present	2500



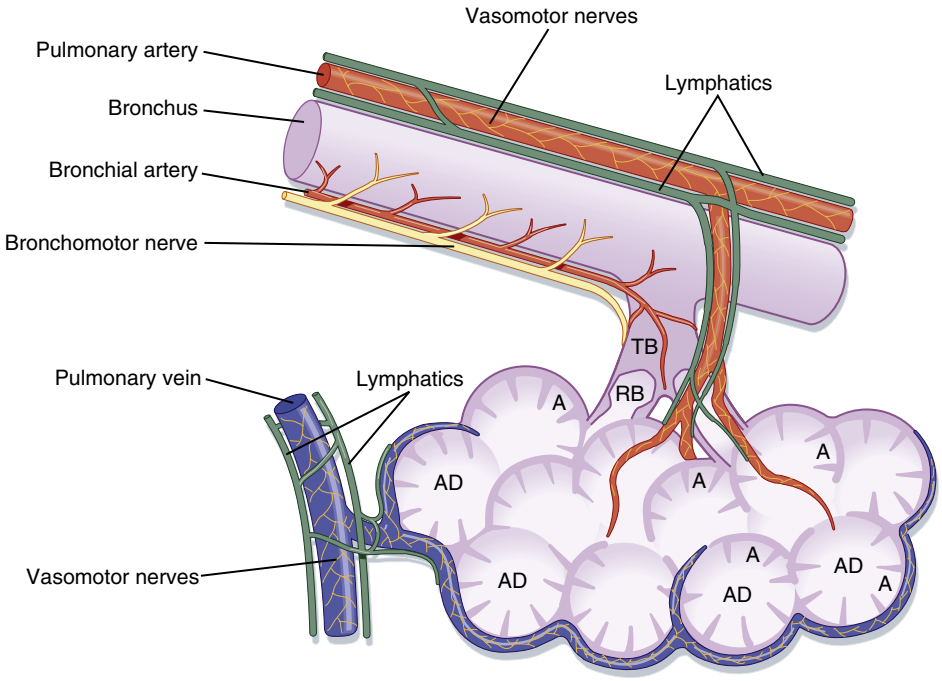
• **Fig. 20.6** Alveoli. **A,** The terminal respiratory unit consists of the alveoli *(A)* and the alveolar ducts *(AD)* arising from a respiratory bronchiole *(RB)*. Each unit is approximately spherical, as suggested by the *dashed outline.* Pulmonary venous vessels *(PV)* have a peripheral location. *PA*, Pulmonary artery; *TB*, terminal bronchiole. *Inset*, type I and type II alveolar epithelial cells. A large fraction of the alveolar wall consists of capillaries *(C)* and their contents. **B**, Illustration of a cross-section of an alveolar wall, showing the path of diffusion of O_2 and CO_2. The thin side of the alveolar wall barrier *(short double arrow)* consists of type I epithelium *(I)*, interstitium *(asterisk)* formed by the fused basal laminae of the epithelial and endothelial cells, capillary endothelium *(E)*, plasma in the alveolar capillary *(C)*, and the cytoplasm of the red blood cell *(R)*. The thick side of the gas-exchange barrier *(long double arrow)* has an accumulation of elastin *(EL)*, collagen *(COL)*, and matrix that jointly separate the alveolar epithelium from the alveolar-capillary endothelium. *Nu*, Nucleus of the capillary endothelial cell.

Circulatory Systems in the Lung

The circulation to the lung is unique in its duality and ability to accommodate large volumes of blood at low pressure. The lung has two separate blood supplies, one for the uptake of O_2 from the lung and removal of CO_2 from the body (pulmonary circulation) and the other to supply O_2 to lung tissue (bronchial circulation; Fig. 20.7).

Pulmonary Circulation

The pulmonary circulation begins in the right atrium of the heart. Deoxygenated blood from the right atrium



• **Fig. 20.7** Illustration of the anatomical relationship of the pulmonary artery, the bronchial artery, the airways, and the lymphatic vessels. *A*, Alveoli; *AD*, alveolar ducts; *RB*, respiratory bronchioles; *TB*, terminal bronchioles.

enters the right ventricle via the tricuspid valve and is then pumped under low pressure (9–24 mm Hg) through the pulmonic valve into the pulmonary artery trunk. The pulmonary artery trunk branches into the right and left main pulmonary arteries and supplies deoxygenated blood to the right and left lungs, respectively. The arteries of the pulmonary circulation are the only arteries in the body that carry deoxygenated blood. The deoxygenated blood in the pulmonary arteries passes through a progressively smaller series of branching vessels—arteries (diameter, >500 μm), arterioles (diameter, 10–200 μm), and capillaries (diameter, <10 μm)—that end in a complex mesh-like network of capillaries. The sequential branching pattern of the pulmonary arteries follows the pattern of airway branching.

The functions of the pulmonary circulatory system are (1) to bring blood to the alveolar-capillary network for O_2 and CO_2 diffusion, (2) to aid in fluid balance in the lung, and (3) to distribute metabolic products to and from the lung parenchyma. Red blood cells are oxygenated in the capillaries that surround the alveoli, where the pulmonary capillary bed and the alveoli come together in the alveolar wall in a unique configuration for optimal gas exchange. Gas exchange occurs through this alveolar-capillary network (see Chapter 24).

The total blood volume of the pulmonary circulation is approximately 500 mL, which is approximately 10% of the circulating blood volume. Approximately 75 mL of blood is present in the alveolar-capillary network of healthy adults at any one time. The pulmonary capillary bed is the largest vascular bed in the body. It covers a surface area of 70 to 80 m^2, which is nearly as large as the alveolar surface area. During exercise, the pulmonary capillary blood volume increases from 75 mL to as high as 200 mL because of the recruitment of unused capillaries as the result of an increase in blood pressure and flow in the pulmonary circulation. This recruitment of unused capillaries is a unique feature of the lung. It allows for compensation in periods of physiologic stress, as in the case of exercise.

The oxygenated blood leaves the alveolus through a network of small pulmonary venules (15–500 μm in diameter) and veins. These small vessels quickly coalesce to form larger pulmonary veins (>500 μm in diameter), through which the oxygenated blood returns to the left atrium of the heart. In contrast to arteries, arterioles, and capillaries, which closely follow the branching patterns of the airways, venules and veins run quite distant from the airways. There is considerable anatomic variability as to where the pulmonary veins enter the left atrium.

Structure of the Pulmonary Circulation

The arteries of the pulmonary circulation have thin walls, with minimal smooth muscle. They are seven times more compliant than systemic vessels, and they are easily distensible. This highly compliant state of the pulmonary arterial vessels permits blood to flow through the pulmonary circulation at a lower pressure than that of the systemic circulation. In contrast, the arterial walls of the systemic circulation are more muscular and less compliant. The vessels in the pulmonary circulation, under normal circumstances, are in a dilated state and have larger diameters than do similar arteries in the systemic system. All of these factors contribute to a very compliant, low-resistance circulatory system. This aids in the flow of blood through the pulmonary circulation via the relatively weak pumping action of the right ventricle.

This low-resistance, low-work system also explains why the right ventricle is less muscular than the left ventricle. The pressure gradient differential for the pulmonary circulation from the pulmonary artery to the left atrium is only 6 mm Hg (14 mm Hg in the pulmonary artery minus 8 mm Hg in the left atrium). In comparison, a pressure gradient differential of 87 mm Hg is present in the systemic circulation (90 mm Hg in the aorta minus 3 mm Hg in the right atrium).

Structures of the Extra-Alveolar and Alveolar Vessels and the Pulmonary Microcirculation

Although not well defined anatomically, vessels in the pulmonary circulation can be divided into three categories (extra-alveolar, alveolar, and microcirculation) on the basis of differences in their physiological properties. The extra-alveolar vessels (arteries, arterioles, veins, and venules) are larger than their systemic counterparts. They are not influenced by alveolar pressure changes, but they are affected by intrapleural and interstitial pressure changes. Thus, the caliber of extra-alveolar vessels is affected by lung volume and by lung elastin. At high lung volumes, the decrease in pleural pressure increases the caliber of extra-alveolar vessels, whereas at low lung volumes, an increase in pleural pressure decreases vessel caliber. In contrast, alveolar capillaries reside within the interalveolar septa, and they are very sensitive to changes in alveolar pressure but not to changes in pleural or interstitial pressure. Positive-pressure ventilation (such as provided by mechanical ventilation) increases alveolar pressure and compresses these capillaries, increasing pulmonary arterial pressure and impeding pulmonary blood flow. The pulmonary microcirculation comprises the small vessels that participate in liquid and solute exchange in maintenance of fluid balance in the lung.

Structure of the Alveolar-Capillary Network

The sequential branching of the pulmonary arteries culminates in a dense mesh-like network of capillaries that surround alveoli. This alveolar-capillary network is composed of thin epithelial cells of the alveolus and endothelial cells of the capillaries and their supportive matrix, and it has an alveolar surface area of approximately 85 m^2. The structural matrix and the tissue components of this alveolar-capillary network provide the only barrier between gas in the airway and blood in the capillary. The cells of this 1 to 2 μm thick barrier consist of type I alveolar epithelial cells positioned back-to-back with capillary endothelial cells. They are separated only by their respective basement membranes (see Fig. 20.6*B*). Surrounded mostly by air, this alveolar-capillary network is an ideal environment for gas exchange. Red blood cells pass through the capillary component of this network in single file in less than 1 second, which is sufficient time for CO_2 and O_2 gas exchange. During conditions of increased metabolic activity (e.g., illness, physical activity) cardiac output increases and pulmonary capillary transit time decreases. Blood flows more rapidly through the pulmonary capillary bed. If the alveolar-capillary network is diseased, there may be insufficient time for adequate oxygen exchange. Hypoxemia may result.

In addition to gas exchange, the alveolar-capillary network regulates the amount of fluid within the lung. At the pulmonary capillary level, the balance between hydrostatic and oncotic pressure across the wall of the capillary results in a small net movement of fluid out of the vessels into the interstitial space. The fluid is then removed from the lung interstitium by the lymphatic system and enters the circulation via the vena cava in the area of the lung hilum. In normal adults, an average of 30 mL of fluid per hour is returned to the circulation via this route.

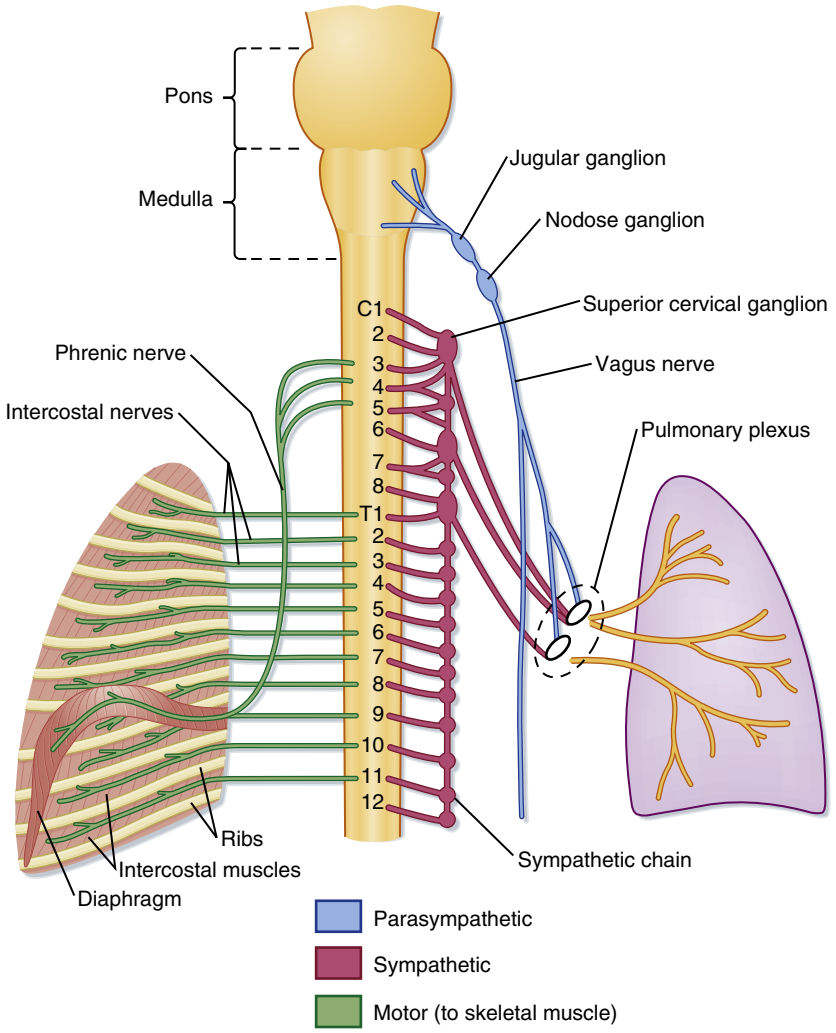
Bronchial Circulation

The bronchial circulation is a distinct system, separate from the pulmonary circulation in the lung, that provides oxygenated systemic arterial blood to the trachea, bronchial tree, surface secretory cells, glands, nerves, visceral pleural surfaces, lymph nodes, pulmonary arteries, and pulmonary veins. The bronchial circulation is similar in structure to the systemic circulatory system and perfuses the upper respiratory tract; it does not reach the terminal or respiratory bronchioles or the alveoli. Venous blood from the capillaries of the bronchial circulation flows to the heart through either true bronchial veins or bronchopulmonary veins. True bronchial veins are present in the region of the lung hilus, and blood flows into the azygos, hemiazygos, or intercostal veins before entering the right atrium. The bronchopulmonary veins are formed through a network of tributaries from the bronchial and pulmonary circulatory vessels that anastomose and form vessels with an admixture of blood from both circulatory systems. Blood from these anastomosed vessels returns to the left atrium through pulmonary veins. Approximately two-thirds of the total bronchial circulation is returned to the heart via the pulmonary veins and this anastomosis route.

The bronchial circulation receives only approximately 1% of total cardiac output from the left heart; in comparison, the pulmonary circulation receives almost 100% from the right heart. In the presence of diseases such as cystic fibrosis, the bronchial arteries increase in size (hypertrophy) and may receive as much as 10% to 20% of the cardiac output. The erosion of inflamed bronchial tissue into these vessels as a result of bacterial infection is responsible for the **hemoptysis** (coughing up blood) that can occur in chronic bronchitis or cystic fibrosis.

Innervation

Breathing is automatic and under control of the central nervous system (CNS). The lungs are innervated by the autonomic nervous system of the peripheral nervous system (PNS), which is under CNS control (Fig. 20.8). The autonomic nervous system has four distinct components: **parasympathetic, sympathetic, nonadrenergic**



• **Fig. 20.8** Innervation of the lung. The autonomic innervation (motor and sensory) of the lung and the somatic (motor) nerve supply to the intercostal muscles and diaphragm are depicted.

noncholinergic inhibitory, and **nonadrenergic noncholinergic stimulatory.**

Stimulation of the parasympathetic system leads to airway smooth muscle constriction, blood vessel dilation, and increased glandular cell secretion, whereas stimulation of the sympathetic system causes relaxation of the airway smooth muscle, constriction of blood vessels, and inhibition of glandular secretion (see Chapter 26, Fig. 26.1). The functional unit of the autonomic nervous system is composed of preganglionic and postganglionic neurons in the CNS and postganglionic neurons in the ganglia of the specific organ. As with most organ systems, the CNS and PNS work in concert to maintain homeostasis. There is no voluntary motor innervation in the lung, nor are there pain fibers. Pain fibers are found only in the parietal pleura, not in the visceral pleura.

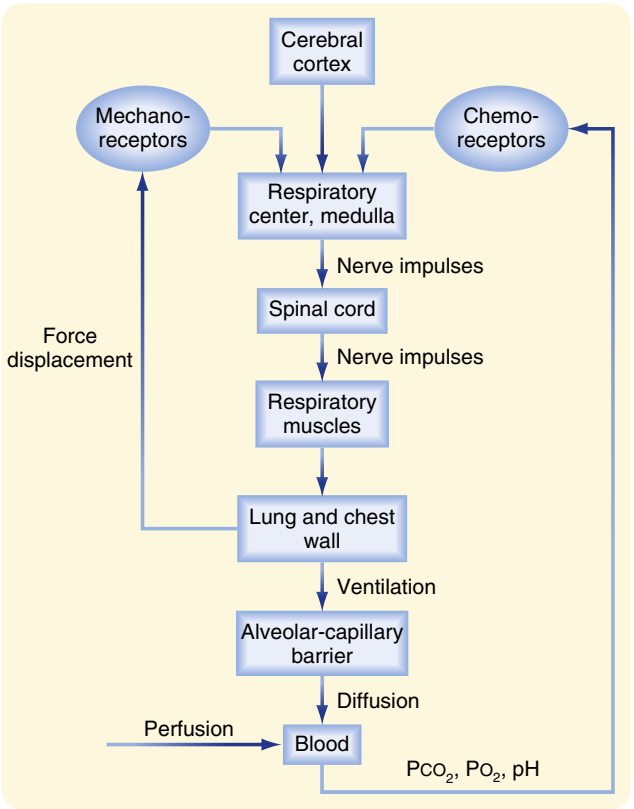
The parasympathetic innervation of the lung originates from the medulla in the brainstem (cranial nerve X, the **vagus nerve**). Preganglionic fibers from the vagal nuclei descend in the vagus nerve to ganglia adjacent to airways and blood vessels in the lung. Postganglionic fibers from the ganglia then complete the network by innervating smooth muscle cells, blood vessels, and bronchial epithelial cells (including goblet cells and submucosal glands). In the lungs, both preganglionic and postganglionic fibers contain excitatory (cholinergic) and inhibitory (noradrenergic) motor neurons. **Acetylcholine** and **substance P** are neurotransmitters of excitatory motor neurons; **dynorphin** and **vasoactive intestinal peptide** are neurotransmitters of inhibitory motor neurons. Parasympathetic stimulation through the vagus nerve is responsible for the slightly constricted smooth muscle tone in a normal resting lung. Parasympathetic fibers also innervate the bronchial glands, and these fibers, when stimulated, increase the synthesis of mucus glycoprotein, which increases the viscosity of mucus. Parasympathetic innervation is greatest in the larger airways and most limited in the smaller conducting airways.

The response of the parasympathetic nervous system is very specific and local. In contrast, the response of the sympathetic nervous system tends to be more general. Mucous glands and blood vessels are heavily innervated by the sympathetic nervous system; however, airway smooth muscle

is not. Neurotransmitters of the adrenergic nerves include **norepinephrine** and dopamine. Stimulation of the sympathetic nerves in mucous glands increases water secretion. This disrupts the balanced response of increased water and increased viscosity between the sympathetic and parasympathetic pathways. In addition to those in the sympathetic and parasympathetic systems, afferent nerve endings are present in the epithelium and in smooth muscle cells in the lung.

Central Control of Respiration

Breathing is an automatic, rhythmic, and centrally regulated process with voluntary control. The CNS, particularly the **brainstem,** functions as the main control center for respiration (Fig. 20.9). Regulation of respiration requires (1) generation and maintenance of a respiratory rhythm; (2) modulation of this rhythm by sensory feedback loops and reflexes that allow adaptation to various conditions while minimizing energy costs; and (3) recruitment of respiratory muscles that can contract appropriately for gas exchange. Control of respiration is described in greater detail in Chapter 25 .



• **Fig. 20.9** Block diagram of the respiratory control system, demonstrating relationships between the respiratory control center and muscles of respiration. The respiratory center neurons, dispersed into several groups in the medulla, demonstrate spontaneous cyclic activity but are strongly influenced by stimuli descending from the cerebral cortex (volitional control) and from two sensory loops: mechanoreceptor and chemoreceptor pathways. Ventilation and perfusion occur together near the end of the cycle, and their output determines partial pressures of arterial and alveolar carbon dioxide *(Pco_2)* and oxygen *(Po_2)* and, in part, arterial hydrogen ion concentration *(pH)*. These outputs feed back to the respiratory center via chemoreceptor and mechanoreceptor sensory pathways.

IN THE CLINIC

Individuals with obstructive lung disease often experience episodes of bronchospasm (narrowing of the conducting airways due to bronchial smooth muscle constriction) or excess mucus production. Use of inhaled bronchodilator medications can lead to relaxation of bronchial smooth muscle. Albuterol, a short acting compound, mimics the effects of endogenous activators of the sympathetic nervous system. When inhaled, in can quickly lead to decreased tone of airway smooth muscle and subsequent bronchodilation. Inhaled anticholinergic agents such as ipratropium block acetylcholine receptors decreasing bronchoconstriction and airway mucus secretion.

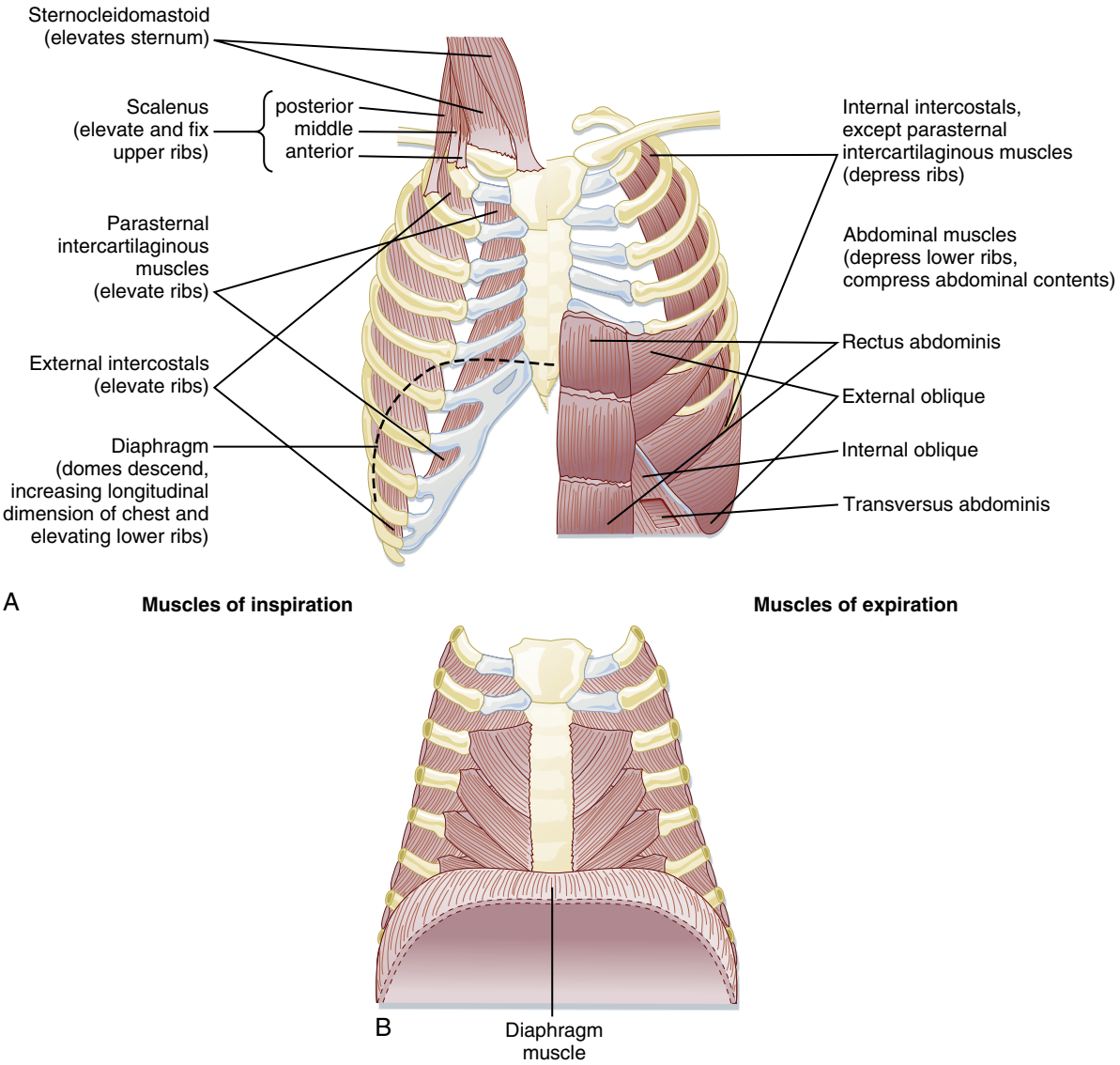
Muscles of Respiration

The major muscles of respiration include the **diaphragm,** the **external intercostal muscles,** and the **scalene muscles,** all of which are skeletal muscles. Skeletal muscles provide the driving force for ventilation; the force of contraction increases when they are stretched and decreases when they are shortened. The force of contraction of respiratory muscles increases at larger lung volumes.

The diaphragm is the major muscle of respiration, and it divides the thoracic cavity from the abdominal cavity (Fig. 20.10). Contraction of the diaphragm forces the abdominal contents downward and forward. This increases the vertical dimension of the chest cavity and creates a pressure difference between the thorax and abdomen. In adults, the diaphragm can generate airway pressures of up to 150 to 200 cm H_2O during maximal inspiratory effort. During quiet breathing (tidal breathing), the diaphragm moves approximately 1 cm. During deep breathing maneuvers, the diaphragm can move as much as 10 cm. The diaphragm is innervated by the right and left phrenic nerves whose origins are at the third to fifth cervical segments of the spinal cord (C3–C5).

The other important muscles of inspiration are the external intercostal muscles, which pull the ribs upward and forward during inspiration (see Fig. 20.10). This causes an increase in both the lateral and anteroposterior diameters of the thorax. Innervation of the external intercostal muscles originates from **intercostal nerves** that arise from the same level of the spinal cord (T1 and T2). Paralysis of these muscles has limited effect on respiration because respiration is dependent primarily on the diaphragm. This is why individuals with injuries to the lower spinal cord can breathe on their own; it is only when the injury is above C3 that an individual is completely dependent on a mechanical ventilator for breathing support.

Accessory muscles of inspiration (the scalene muscles, which elevate the **sternocleidomastoid muscles;** the **alae nasi,** which cause nasal flaring; and small muscles in the neck and head) do not contract during normal breathing.



• **Fig. 20.10** Illustrations of the major respiratory muscles. **A,** The inspiratory muscles are depicted on the *left side*, and the expiratory muscles are depicted on the *right side*. **B,** The diaphragm muscle in relation to the rib cage. (From Garrity ER, Sharp JT. Respiratory muscles: function and dysfunction. In: American College of Chest Physicians. *Pulmonary and Critical Care Update.* Vol 2. Park Ridge, IL: American College of Chest Physicians; 1986.)

However, they do contract vigorously during exercise, and when airway obstruction is significant, they actively pull up the rib cage. During normal breathing, they anchor the sternum and upper ribs. Because the upper airway must remain patent during inspiration, the pharyngeal wall muscles **(genioglossus** and **arytenoid)** are also considered muscles of inspiration. All the rib cage muscles are voluntary muscles that are supplied by intercostal arteries and veins and innervated by motor and sensory intercostal nerves.

Exhalation during normal breathing is passive, but it becomes active during exercise and hyperventilation. The most important muscles of exhalation are those of the abdominal wall (**rectus abdominis, internal** and **external oblique,** and **transversus abdominis**) and the **internal intercostal muscles,** which oppose the external intercostal muscles (i.e., they pull the ribs downward and inward). The inspiratory muscles do the work of breathing. During normal breathing, this workload is low, and the inspiratory muscles have significant reserve. Respiratory muscles can be trained to do more work, but there is a limit to the work that they can perform. Respiratory muscle weakness can impair movement of the chest wall, and respiratory muscle fatigue is a major factor in the development of respiratory failure.

Lung Embryology, Development, Aging, and Repair

The epithelium of the lung arises as a pouch from the primitive foregut at approximately 22 to 26 days after fertilization

IN THE CLINIC

Because respiratory muscles provide the driving force for ventilation, diseases that affect the mechanical properties of the lung affect the muscles of respiration. For example, in **chronic obstructive pulmonary disease (COPD),** the work of breathing is increased secondary to airflow obstruction. Exhalation no longer is passive but instead requires active, expiratory muscle contraction. In addition, total lung capacity is increased (see Chapter 21). The larger total lung capacity forces the diaphragm downward, shortens the muscle fibers, and decreases the radius of curvature of the diaphragm. As a result, the function and efficiency of the diaphragm is decreased. Respiratory muscles can fatigue just as other skeletal muscles do when the workload increases. Diseases impairing nerve signal transmission to the respiratory muscles can also lead to respiratory muscle weakness (e.g., acute inflammatory demyelinating polyneuropathy or **Guillain-Barré syndrome, myasthenia gravis**). In these diseases, sufficient weakness of the respiratory muscles can impair movement of the chest wall and result in respiratory failure, even though the mechanical properties of the lung and chest wall are normal.

of the ovum. This single lung bud branches into primitive right and left lungs. Over the next 2 to 3 weeks, further branching occurs to create the irregular dichotomous branching pattern. The pathologist Lynne Reid described "three laws of lung development": (1) the bronchial tree has developed by week 16 of intrauterine life; (2) alveoli continue to develop after birth, the number of alveoli increases until the age of 8 years, and the size of alveoli increases until growth of the chest wall is completed at adulthood; and (3) the development of preacinar vessels (arteries and veins) parallels that of the airways, whereas that of intraacinar vessels parallels that of the alveoli. Thus, intrauterine events that occur before 16 weeks of gestation will affect the number of airways. A condition known as **congenital diaphragmatic hernia** is an example of a congenital lung disease. It occurs at 6 to 8 weeks of gestation and is due to failure of the pleuroperitoneal canal to close and thereby separate the chest and abdominal cavities; the presence of the abdominal contents in the lung hemithorax results in abnormal lung growth with a decrease in the number of airways and alveoli. Before the birth of an affected infant, the alveolar epithelium is composed solely of type II epithelial cells, and it is not until birth that these cells differentiate into type I epithelial cells.

Growth of the lungs is similar and relatively proportional to growth in body length and stature. The rate of development is fastest in the neonatal and preadolescent periods (≈11 years of age), and girls' lungs mature earlier than boys'. Although the growth rate of the lung slows after adolescence, both body and lung increase in size steadily until adulthood. Improvement in lung function occurs at all stages of growth and development; however, once optimal size has been attained in early adulthood (20–25 years of age), lung function plateaus and starts to decline with age. The decrease in lung function with age, estimated at less than 1% per year, appears to begin earlier and proceed faster in individuals who smoke or are exposed to other toxic environmental factors. The major physiological insufficiencies caused by aging involve ventilatory capacity and responses, especially during exercise, and they result in abnormal ventilation with normal perfusion. In addition, gas diffusion decreases with age, probably as a result of a decrease in alveolar surface area. Age-related decreases in lung function and altered structure parallel increased levels of elastin within the lung, which could explain some of the functional abnormalities.

AT THE CELLULAR LEVEL

Type I cells lack free radical scavengers (i.e., superoxide dismutase) and are susceptible to injury and death induced by toxic O_2 compounds and free radicals (i.e., H_2O_2, OH^-, and O_2^-). In various inflammatory lung diseases, type I cells die, and the alveolar epithelium thereby becomes denuded. This leads to increased vascular permeability, alveolar fluid accumulation (impaired gas exchange), and disruption of the alveolar surfactant system. Type II cells have superoxide dismutase and are thus more resistant to toxic oxygen radicals. They can survive to proliferate and differentiate into type I cells to restore the normal alveolar architecture. This type of response is dependent on an intact basement membrane to support the proliferation of type II cells. If the basement membrane cannot be repopulated, then the body's recourse for repair is collagen deposition and scar formation, which is not conducive to gas exchange. In lung disease that involves scar formation (such as pulmonary fibrosis), the total lung volume decreases as a result of the loss of alveoli and impairment of O_2 diffusion into the capillaries by a thickened, nonpermeable matrix. Historically, idiopathic pulmonary fibrosis has been very difficult to treat because of the lack of specific therapeutics to inhibit collagen deposition. Two therapeutic compounds (pirfenidone and nintedanib) have been shown in clinical trials to slow the progression of the disease and improve outcomes in patients with idiopathic pulmonary fibrosis. Pirfenidone is a small low-molecular-weight compound with anti-inflammatory properties (it decreases procollagen types I and II synthesis), and nintedanib is a tyrosine kinase inhibitor (inhibits vascular endothelial growth factor and fibroblast-derived growth factor).

Key Points

1. The lungs demonstrate anatomical and physiological unity; that is, each unit (bronchopulmonary segment) is structurally identical and functions just like every other unit.
2. The upper airways (nose, sinuses, pharynx) condition inspired air for temperature and humidity, and controls, via the epiglottis, the flow of air into the lungs and food/fluids into the esophagus.
3. Components of the lower airways (trachea, bronchi, bronchioles) are considered conducting airways in which air is transported to the gas-exchanging respiratory units composed of respiratory bronchioles, alveolar ducts, and alveoli.

4. The lungs have unique, dual circulatory systems. The pulmonary circulatory system has the ability to accommodate large volumes of blood at low pressure and brings deoxygenated blood from the right ventricle to the gas-exchanging units in the lung, returning oxygenated blood to the left atrium. The bronchial circulation arises from the aorta and provides nourishment and oxygen to the conducting airways.
5. Breathing is automatic; the lungs are innervated by the autonomic nervous system of the PNS while under the control of the CNS. Parasympathetic stimulation results in constriction of airway smooth muscles (airway narrowing) whereas sympathetic stimulation results in relaxation of airway smooth muscles (airway opening).
6. Inspiration is the active phase of breathing. The diaphragm is the major muscle of respiration, and its contraction creates a pressure difference (mechanoreceptor response) between the thorax and diaphragm (negative pressure in the chest), which induces inspiration.
7. The respiratory center is located in the medulla and regulates respiration with input from sensory (mechanoreceptor and chemoreceptor) feedback loops.