Nursing Care in Pediatric Respiratory Disease

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Pediatric pulmonary anatomy and physiology

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INTRODUCTION

In ancient Greece, Erasistratus (304–250 BC), an anatomist and royal physician, was among the first to distinguish between veins and arteries. He described the function of the lungs was to bring air into the body to be transferred to the arteries and then into the heart (Mason, 1962). Our understanding of the anatomy and physiology of the human respiratory system has progressed significantly over the past 2,000-plus years. This chapter will explore the structure of the lung and describe the physiological properties that support ventilation and gas exchange through different stages of development of the respiratory system, from fetus to maturity.

ANATOMY OF THE RESPIRATORY SYSTEM

Embryology

To appreciate the complex physiology of breathing, one must understand the events that occur before the first breath is taken at birth. *In utero*, the lung does not participate in gas exchange. The responsibility of fetal oxygenation and elimination of carbon dioxide lies with the placenta until the

lung takes over the process immediately upon transition from prenatal to postnatal life.

Lung growth *in utero* can be divided into five overlapping stages: (1) the embryonic period during the first 5 weeks, (2) the pseudoglandular period from 6 to 16 weeks of gestation, (3) the canalicular period from 16 to 24 weeks of gestation, (4) the saccular period from 24 to 36 weeks, and (5) the alveolar phase from 36 weeks to term and continuing for at least 3 years postnatally (Jeffery, 1998). The alveoli continue to multiply and grow during the first few years of life, following the growth in height of each child.

During the embryonic period, the primitive foregut, seen in the third week of embryogenesis, forms and is the origin of the lung. Over the course of the next 3–4 weeks, branches of the right and left lung form through budding and dividing (see Figure 1.1).

During the pseudoglandular period, there is a differentiation of the primitive airway epithelium (Post & Copland, 2002). At the time of branching, the bronchi are enveloped in the mesenchyme that develops into connective tissue, smooth muscle, and cartilaginous rings, among other things. By the end of the 16th week, the bronchial tree is developed without further formation of airways.

During the canalicular stage, further branching of the bronchioles leads to respiratory bronchioles. The lobules of the lungs start to form, and there is a decrease in interstitial tissue. The differentiation of cuboidal epithelium into types I and II pneumocytes begins at this time (DiFiore & Wilson, 1994). Cartilage starts centrally and proceeds peripherally, ending around the 25th week. It is at this point that the number of bronchial generations with cartilage is the same as the adult lung.

The saccular phase is the period when there is growth of the pulmonary parenchyma, continued development of the surfactant system, and a reduction in the connective tissue between the airspaces. During the alveolar period, branching becomes more extensive. There is an exponential increase in the surface area as saccules, which will eventually form alveoli, develop (Burri, 1984). It is during this time that surface epithelium and blood vessels come into even closer contact, allowing for the future exchange of gases. This process continues for at least 3 years after birth.

The fetal lung is the main source of amniotic fluid in the uterus. Abnormal lungs secondary to poor intrauterine growth are among the many abnormalities associated with a low amount of amniotic fluid. Type II pneumocytes appear in the alveolar epithelium and begin to function around the 24th week of life. These cells go on to produce a surfactant, which is a mixture of phospholipids and proteins. The surfactant decreases the surface tension of the lung, allowing for maturation and, upon delivery, expansion of the lung with the newborn's first breaths. When expectant mothers begin premature labor, administration of glucocorticoids to the mother accelerates the maturation of type II pneumocytes and therefore the production of surfactants (Liggins & Howie, 1972). The molecular
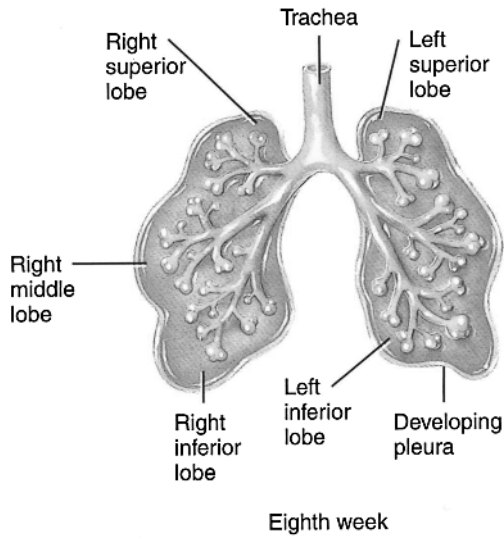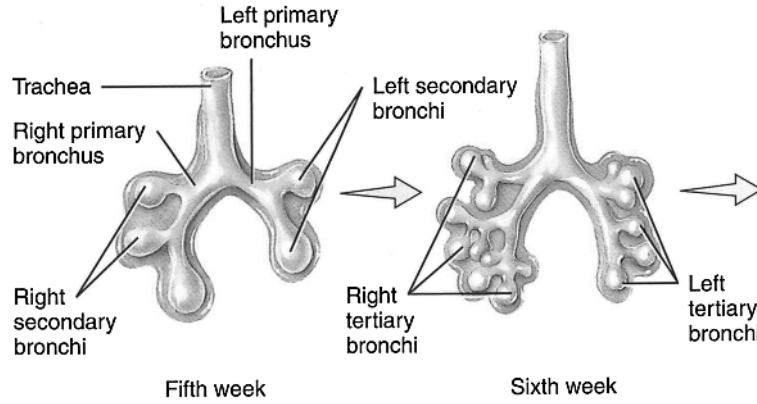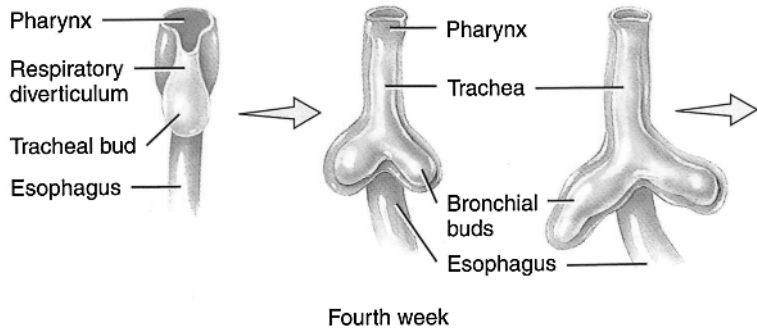
Figure 1.1 Development of the bronchial tubes and lungs. Reprinted from Tortora and Derrickson (2009), with permission from John Wiley & Sons, Inc.

properties of surfactants and the physiological role they play is discussed in the section "Surface Tension Properties of the Lung."

Just before full-term birth, there is approximately 50 mL of surfactant-rich fluid in the lung. This fluid is removed by a combination of active channel transport, lymphatic drainage, and the physics of natural childbirth. Most of the protein-rich portion of this fluid is removed by the lymphatic system. At birth, expansion of the chest cavity with high negative intrathoracic pressures pushes the fluid from the alveoli into the interstitium, then onto the lymphatic channels. By the end of the first few hours after birth, the majority of fluid that was in the lungs during the 9 months of gestation is replaced by air.

During gestation, the lungs do not function as the source of oxygen for the developing organs of the body. That task is completed by the placenta. As a result, the lungs receive poorly oxygenated blood in comparison to the more "vital" fetal organs (see Figure 1.2).

Fetal circulation receives highly oxygenated blood from the placenta through the liver to the right side of the heart. Most of the blood is shunted through the foramen ovale to the left side of the heart. It then either flows through the ascending aorta to the head or through the descending aorta to the systemic circulation. The venous blood that returns from the head flows through the right side of the heart to the pulmonary artery. However, most of this blood is shunted via the ductus arteriosus into the descending aorta to the systemic circulation and the lower part of the body. That blood which does not go through the ductus arteriosus is the blood that oxygenates the lungs. Again, it needs to be pointed out that this blood has already passed through the brain, an organ requiring large amounts of oxygen. As a result, 9 months of this poorly oxygenated circulating blood results from and contributes to the high pulmonary vascular resistance *in utero*.

Replacement of lung fluid by air upon delivery and breathing by the newborn contributes to the decrease in the pulmonary vascular resistance. The subsequent increase in the partial pressure of oxygen (PO_2) and the decrease in the partial pressure of carbon dioxide remove stimuli for vasoconstriction. All of this occurs in association with the reversal of the right-to-left shunt through the ductus arteriosus and foramen ovale present *in utero*. The ductus closes completely during the first few days after birth.

Pulmonary vascular development and the tracheobronchial tree

There are two types of airways based on structure and function: (1) cartilaginous airways (bronchi), which make up the conducting system, and (2) membranous, noncartilaginous airways (bronchioles) (see Figure 1.3). The bronchi and nonrespiratory bronchioles serve as conductors of the gas stream, while the respiratory bronchioles and alveolar ducts (terminal respiratory units) serve as sites of gas exchange. The cartilaginous rings of the trachea, except for the cricoid, are not complete and occur over the

anterior two-thirds of its surface. The posterior portion is membranous and pliable (Johnson, 2008). The conducting airways' blood supply comes from branches of the bronchial arteries and the terminal respiratory units from branches of the pulmonary arteries.

From the trachea to the alveolar sacs, the airway divides 23 times. The first 16 generations form the conducting zone, while the last 7 generations form the transitional and respiratory zone (Sircar, 2008). As stated
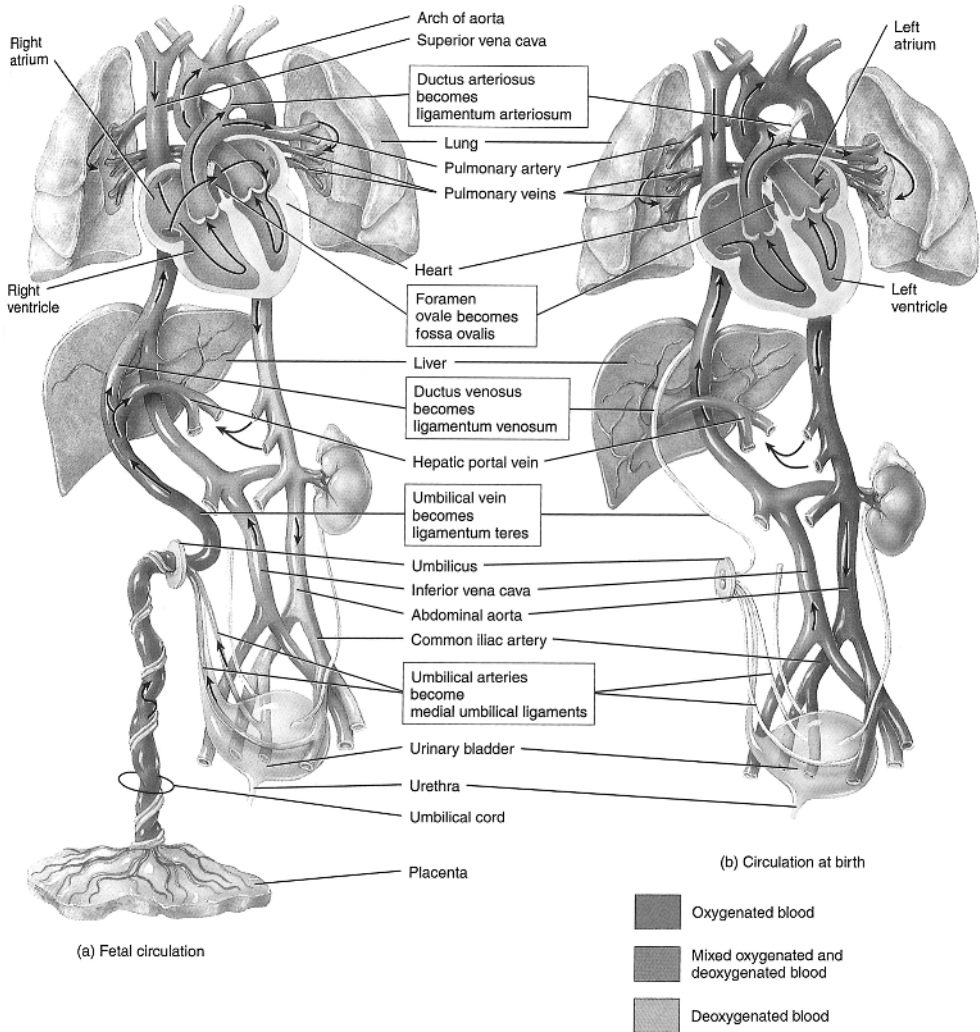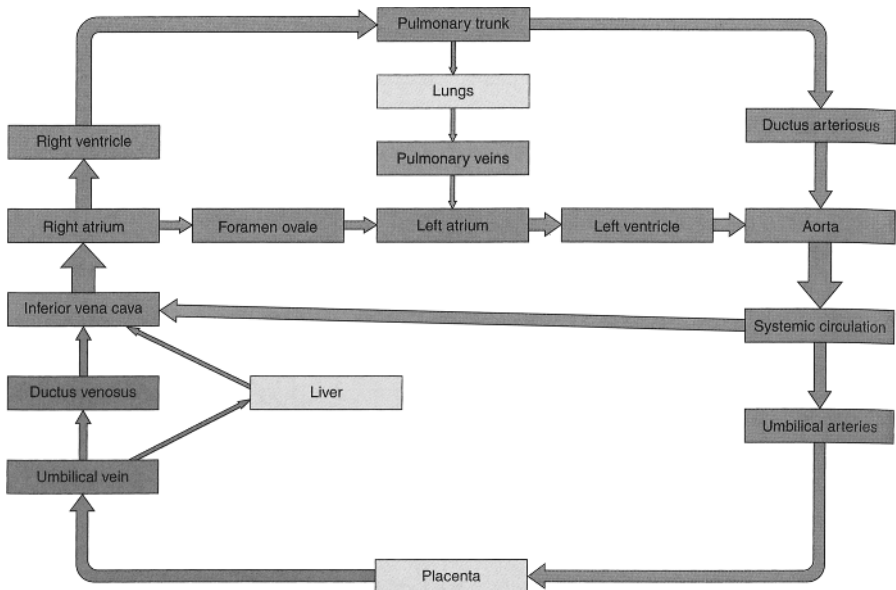

Figure 1.2 (a–c) Fetal circulation and changes at birth. The boxes between parts (a) and (b) describe the fate of certain fetal structures once postnatal circulation is established. Reprinted from Tortora and Derrickson (2009), with permission from John Wiley & Sons, Inc.

(c) Scheme of fetal circulation

Figure 1.2 (*Continued*)

Branching of bronchial tree

Trachea
↓
Primary bronchi
↓
Secondary bronchi
↓
Tertiary bronchi
↓
Bronchioles
↓
Terminal bronchioles

Larynx

Trachea

Visceral pleura

Parietal pleura

Pleural cavity

Right primary bronchus

Right secondary bronchus

Right tertiary bronchus

Right bronchiole

Right terminal bronchiole

Location of carina

Left primary bronchus

Left secondary bronchus

Left tertiary bronchus

Left bronchiole

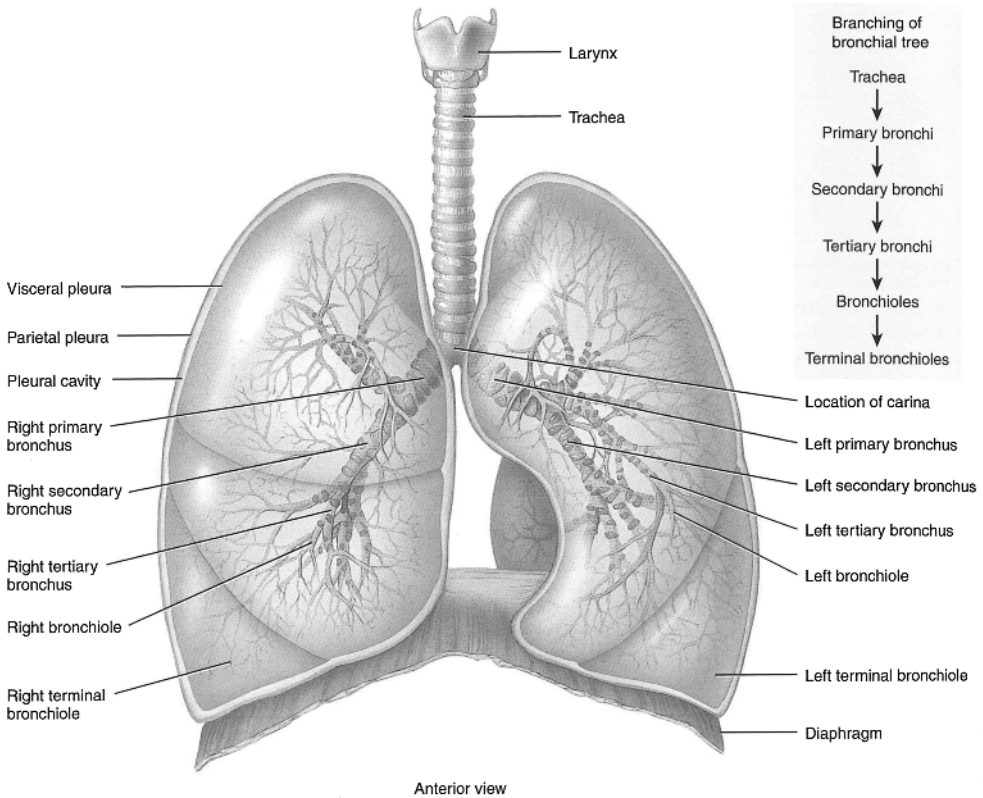Left terminal bronchiole

Diaphragm

Anterior view

Figure 1.3 Branching of airways from the trachea: the bronchial tree. Reprinted from Tortora and Derrickson (2009), with permission from John Wiley & Sons, Inc.

previously, the conducting airways are in place and are fully formed by birth. However, alveoli are just starting to develop at this point.

While the lung bud is forming, the right and left pulmonary arteries are growing as well; branches of the pulmonary arteries follow branches of the bronchi. By the end of the pseudoglandular period, the conducting airways are complete and have an adult pattern, as are all conventional and supernumerary arteries leading to the terminal respiratory units. The pattern of veins from the sites of gas exchange to the hilum, similar to the conducting airways, is complete halfway through gestation. Conversely, just as alveolar formation continues after birth, the arteries within the terminal unit continue to form for several years after birth.

RESPIRATORY AND NONRESPIRATORY FUNCTIONS OF THE LUNG

Nongas exchange functions

The upper airway and tracheobronchial tree do not participate in gas exchange; however, they provide other very important functions. The upper airway warms and humidifies the inspired air and filters out particulate matter. By the time the air reaches the alveoli, it is near body temperature. The hairs in the nostril filter particles larger than 10 μm in diameter. Most of the smaller particles do not travel past the pharynx and are trapped by the tonsils and adenoids. Cilia, which line the respiratory tract down to the terminal bronchioles, pick up any particles between 2–10 μm in size that may have passed through the conducting airways. The cilia are covered in a layer of mucus produced by mucus glands and goblet cells. The cilia move in a synchronized beat carrying these particles up to the larynx where they are swept up to the hypopharynx and swallowed. An abnormality in structure or function of the cilia results in primary ciliary dysfunction, a condition that results in buildup of secretions and a subsequent propensity of bacterial growth in this medium (Johnson, 2008). A similar picture is seen in the lungs of patients with cystic fibrosis, not because of an abnormality of the cilia but because of an abnormality of the mucus layer.

Gases and gas exchange

Transfer of gases through the airways

In humans, as the airway branches from the trachea, the branches become smaller and more numerous. Initially from the trachea, the right and left main bronchi divide to lobar (secondary) followed by segmental (tertiary) bronchi and finally to terminal (0.5 mm in diameter) bronchioles. The walls of the primary bronchi are constructed like the trachea, but as the branches
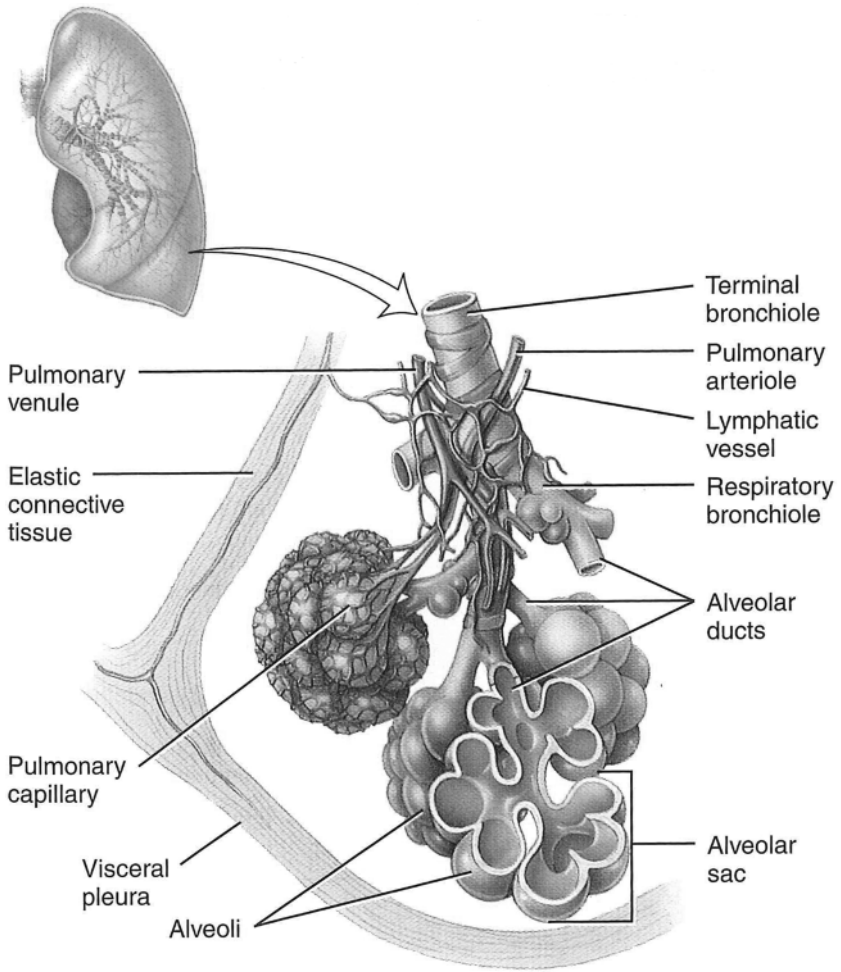
Diagram of a portion of a lobule of the lung

Figure 1.4 Microscopic anatomy of a lobule of the lungs. Reprinted from Tortora and Derrickson (2009), with permission from John Wiley & Sons, Inc.

of the tree decrease in size, the cartilaginous rings and the mucosa are replaced by smooth muscle. To this point, there are no alveoli. As a result, this portion of the lung is anatomical dead space, as there is no participation in gas exchange. These branches mark the first 16 generations of airways and, based on their main function in the lung, are referred to as the conducting airways. This would be analogous to the branches of a tree (see Figure 1.4).

The area where gas exchange occurs is known as the respiratory zone. The occasional alveoli off the walls of the respiratory bronchioles are the

first site of gas exchange in the respiratory tree. Alveoli, which is Latin for little cavities, are particular to mammalian lungs. They contain collagen and elastic fibers and are lined with epithelium. The elastic fibers allow the alveoli to stretch with inhalation and retract during exhalation (this is explained in more detail in the section "Control of Ventilation"). Further distal are alveolar ducts and alveolar sacs, which are completely lined with alveoli. Harkening back to the earlier analogy, the respiratory zone would be the leaves on the tree.

Each human lung contains about 300 million alveoli. Each alveolus is wrapped in a fine mesh of capillaries. The alveoli in the respiratory zone of the lungs constitute a total surface area of about $75\,m^2$ (Pavelka & Roth, 2005). The gas exchange tissue is referred to as the pulmonary parenchyma, while the nonparenchyma consists of the conducting airways, lymphatics, noncapillary blood vessels, and the supplying structures.

Transfer of gas in the parenchyma

Diffusion

Inspired fresh air moves via bulk movement through the conducting airways. Here, different gases move together along a total pressure gradient. Because of the vast branching of the bronchi and the subsequent increase in the cross-sectional area of the respiratory zone, the velocity of the bulk flow rapidly decreases. As a result, once in the respiratory zone, further movement occurs via diffusion. Diffusion, the movement from an area of high to low pressure, is the principle by which oxygen and carbon dioxide move in different directions between the air and blood. Unicellular organisms do not require respiratory structures for diffusion. However, for more complex organisms, specialized organs have evolved, including gills in fish and lungs in humans (Rhoades & Planzer, 1996). In all these organisms, the underlying basis for the diffusion of gas is the presence of thin walls and a rich supply of blood vessels to allow for exchange and transport of gases.

Different gases move according to each of their partial pressure gradients. From the alveolar sacs, oxygen diffuses into the pulmonary capillary blood. An important concept to discuss here is Fick's law, which describes diffusion through tissues. Essentially, the rate of transfer of a gas across a surface is directly proportional to the product of the tissue surface area and the difference in gas partial pressure between the two sides of a tissue and is inversely proportional to the thickness of the tissue:

$$V_{gas} = [A \times (P_1 - P_2)]/T,$$

where V_{gas} = volume of gas diffusing through a tissue per time;
  A = surface area of the tissue;
  $P_1 - P_2$ = partial pressure difference of gas across the tissue; and
  T = thickness of the tissue.

Based on these relationships, it becomes clear how the human lung is ideal for gas transfer: The gas exchange surface is very thin (0.2–0.5 μm) and the surface area vast.

After diffusing through the alveolar–capillary interface, that is, the air–blood barrier, the oxygen molecule enters the red blood cell in the pulmonary capillary, combining with hemoglobin (Hb). The exchange of oxygen from the alveolus into the pulmonary capillary blood occurs rapidly with the pressures equalizing in the two areas in 0.25 second. However, the blood requires 0.75 second to move through the pulmonary capillary bed under resting conditions. Approximately 85–95% of the alveolar surface is intertwined with pulmonary capillaries, with 280 billion capillaries supplying 300 million alveoli (Levitzky, 2007).

Because the PO_2 in a red blood cell entering a pulmonary capillary equals the PO_2 in the alveolus one-third of the way through the capillary, the transfer of oxygen is defined as perfusion limited. In other words, the amount of oxygen taken up by the blood is dependent on the amount of blood flow through the capillaries. The fact that under normal circumstances oxygen transfer is perfusion limited does not do justice to the enormous diffusion reserve of the human lung. The PO_2 in the red blood cell at the initial portion of the pulmonary capillary is 40 mmHg. Across the thin alveolar wall, the PO_2 is 100 mmHg. Now, applying Fick's law, consider the enormous surface area of the respiratory zone, the microscopic thickness of the blood–gas barrier, and the large pressure gradient between the barrier. It becomes obvious under normal conditions why the PO_2 in the red cell approximates the PO_2 of the alveolar gas in 0.25 second.

As with much of physiology, abnormal conditions, or pathophysiology sheds more light on normal conditions. Perfusion limitation is most often seen in disease states where there is decreased surface area and/or increased thickness of the alveolar–capillary interface. The rate of diffusion will be slowed, but the PO_2 of the end capillary red cell is still able to equal the PO_2 of alveolar gas. However, with vigorous and prolonged exercise, there is up to a threefold increase in cardiac output and pulmonary blood flow (West, 2003). With the increase in transit time through the pulmonary capillary bed, blood runs through the pulmonary capillaries in less than 0.75 second. In conditions where there is an increased thickness or a decreased surface area, the PO_2 in the capillaries is unable to equalize the partial pressure in the alveolus, leading to diffusion limitation. Disease states in which there is an increased thickness of the alveolar–capillary interface include neonatal chronic lung disease and interstitial lung disease. A decrease in the surface area is seen in emphysema (Bates, 1962). In someone without lung disease, the increase in transit time through the pulmonary circulation will not affect end-capillary PO_2. Clinically, this is part of the explanation for decreased exercise tolerance in these disease states.

Now take for example persons without lung disease, but place them in an abnormal environment. Again, according to Fick's law, one of the factors in the diffusion of a gas is the difference in partial pressures. The atmo-

spheric PO_2, that is, the pressure that determines the pressure gradient, is assumed to be constant, which at sea level it is. However, the pressure gradient changes in a location of higher altitude. Elevations of 6,500 ft (2,000 m) are classified as high altitude because of this difference in the PO_2, but depending on the person, this effect of altitude may be experienced at lower elevations.

At sea level, oxygen has a partial pressure of 159 mmHg. In Mexico City, it is approximately 125 mmHg, while at the top of Everest, it drops to 48 mmHg (Wilmore & Costill, 2005). Therefore, at the top of Everest, the PO_2 is nearly equal to the PO_2 at the initial portion of the pulmonary capillary, markedly decreasing the pressure gradient that is the driving force for the transfer of oxygen into Hb (Peacock, 1998) (see Figure 1.5).

The human body attempts to overcome the difference in the pressure gradient of oxygen by controlling what it can, in this case, increasing the transportation capability of oxygen. Erythropoietin (EPO) is a glycoprotein released by the kidney that increases the production of red blood cells in the bone marrow. Within hours at high altitudes, EPO levels increase, and 4 days later, new red blood cells are produced (Harris, Terrio, Miser, & Yetter,
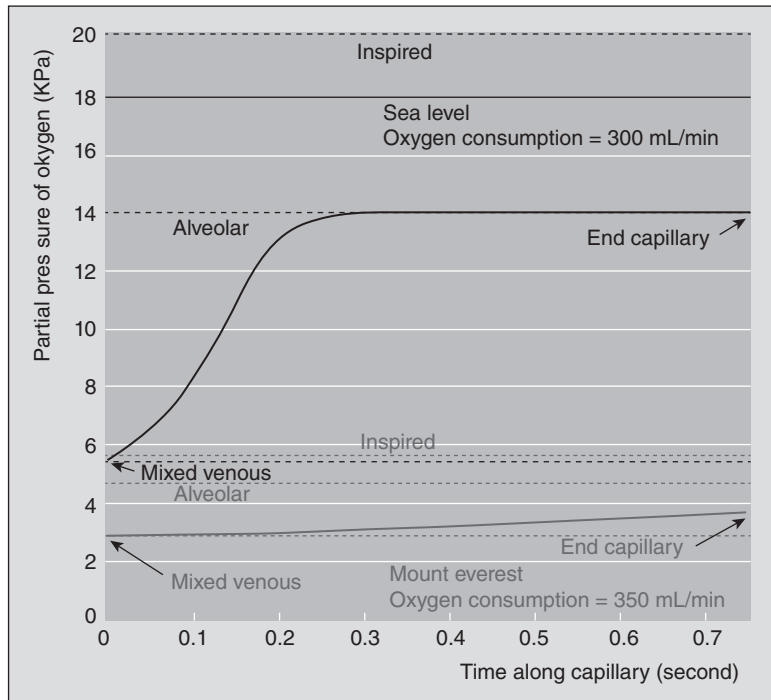

Figure 1.5 Calculated time course for change in partial pressure of oxygen in the pulmonary capillary. At sea level, oxygen pressure reaches almost alveolar levels in a third of available time. At the summit of Mount Everest, the mixed venous oxygen pressure is lower and never reaches alveolar levels. Reprinted from Peacock (1998), with permission from BMJ Publishing Group, Ltd.

1998). This leads to 75% acclimatization at 7–10 days and 100% acclimatization by 15–20 days. Synthetic EPO has been used by athletes as a performance-enhancing drug to increase Hb and, therefore, oxygen carrying capacity. This has most notably been seen in the Tour de France cycling event.

In individuals accustomed to high altitudes, the concentration of 2,3-diphosphoglycerate (2,3-DPG) in the blood is increased. 2,3-DPG allows these individuals to deliver a larger amount of oxygen to tissues under conditions of lower oxygen tension. This is further explored in the section "Oxyhemoglobin."

In 1968, the Olympics were held in Mexico City. These were the first games staged at a high altitude (7,349 ft [2,300 m]). The number of world records set and the categories in which they were set in fueled extensive research. The higher altitude led to reduced wind resistance and drag upon the competitors' bodies. This explained why records in almost every short distance track event from the 100 to 1,500 m were set. However, this was not the case with long-distance events. Athletes in events that involved prolonged aerobic activity and, subsequently, dependency upon maximal amounts of oxygen were adversely affected by the decrease in the atmospheric PO_2 (Jenkins, 2005). Because of this, the International Association of Athletic Federations specifically denotes track and field records that have been broken at altitudes greater than 1,000 m.

A significant amount of research was conducted in the wake of the Mexico City Olympics. As a result, the initial United States Olympic Training Center was built in 1978 on an Air Force base in Colorado Springs, Colorado, to take advantage of the physiological principles of high-altitude training.

As stated previously, under normal conditions, the diffusion of oxygen in the human lung is perfusion limited. In contrast, the diffusion of carbon monoxide (CO) is diffusion limited. This is because carbon monoxide bonds very strongly to Hb. This diffusion can occur with a large amount of carbon monoxide without a significant increase in the partial pressure of carbon monoxide (PCO) (Levitzky, 2007).

These gas properties were utilized in developing a pulmonary function test that measures diffusion in the lung. Because the diffusion of oxygen is not measurable, CO is used for testing. This test, the diffusing capacity of the lung for carbon monoxide (DL_{CO}), is based on the high affinity of Hb for CO and on the negligible partial pressure for CO in Hb. Again using Fick's law, the diffusing capacity of the lung is equal to the volume of carbon monoxide transferred divided by the alveolar PCO. The single-breath DL_{CO} test uses this calculation. A single inspiration of dilute CO is made, and after a 10-second breath hold, the rate of disappearance of CO is measured allowing the difference in partial pressures of inspired and expired carbon monoxide to be determined. The enormity of the surface area of the lung and the inability to measure the thickness of the blood–gas barrier precludes using these two factors in the above-mentioned calculation. However, both of these aspects impact the volume of CO transferred

and the PCO. Therefore, abnormalities in these areas will lead to abnormal DL_{CO} measurements.

Conditions that *decrease* alveolar surface area and therefore *decrease* DL_{CO} include (1) uneven distribution of oxygen in the lung as seen in emphysema and (2) lung injury secondary to bleomycin administration. Conditions that *increase* the alveolar–capillary barrier and therefore decrease DL_{CO} include (1) interstitial or alveolar edema and (2) interstitial or alveolar fibrosis as seen with vasculitis, such as sarcoidosis and scleroderma. Conditions that *increase* DL_{CO} include (1) polycythemia, (2) increased pulmonary blood volume as occurs in exercise or congestive heart failure, and (3) alveolar hemorrhage. The increase in Hb available to bind CO is common to all of these conditions, explaining higher DL_{CO} measurements.

TRANSPORT OF GAS IN THE RED BLOOD CELL

Oxyhemoglobin

The movement of oxygen from the outside environment down the respiratory tract into the alveoli has been discussed. The following explains the mechanisms by which oxygen moves from the alveolus into the pulmonary capillaries and, more specifically, the physiology of the binding of oxygen to Hb.

Heme is an iron compound that is bound to globin, a protein made up of four polypeptides. The iron atom at the center of the heme group is bound to four symmetrically arranged pyrroles and one of four polypeptide chains. The combination of alpha and beta polypeptide chains and the difference in amino acid sequences determines the type of Hb, including normal adult hemoglobin (HbA), fetal hemoglobin (HbF), and hemoglobin S (HbS) (sickle), among others. Each of the four polypeptide chains can bind a molecule of oxygen, though with different affinity (Levitzky, 2007).

HbF has two alpha chains and two gamma chains and has a higher affinity for oxygen than does normal HbA, which has two alpha chains and two beta chains. This distinction is important for oxygen transportation from the placenta *in utero*, where HbF is the predominant form. Beta chains begin to be produced toward the end of the saccular phase, approximately 6 weeks before birth. HbF all but disappears from circulation by 4 months of age in the infant without hemoglobinopathies.

Oxygen combines with Hb to form oxyhemoglobin. One gram of Hb can combine with 1.39 mL of oxygen (Dominguez de Villota, Ruiz Carmona, Rubio, & de Andrés, 1981). However, some Hb exists as methemoglobin, or is combined with carbon monoxide. Therefore, the oxygen capacity, the maximum amount of oxygen that can combine with Hb, under normal conditions, is 1.34 mL O_2/g Hb. Using the example of a person with an Hb concentration of 15 g/dL, the oxygen carrying capacity would be

$$\frac{15\,\text{g Hb}}{100\,\text{mL of blood}} \times \frac{1.34\,\text{mL O}_2}{\text{g Hb}} = \frac{20.1\,\text{mL O}_2}{100\,\text{mL blood}}.$$

The oxygen saturation of Hb is the amount of oxygen attached to Hb divided by the oxygen capacity. The normal oxygen saturation for arterial blood is over 97%, while in venous blood, it is about 75%.

Oxygen in the blood is transported in two forms: bound to Hb and dissolved in the plasma. While the majority of the oxygen is bound to Hb, a small proportion is dissolved, with the amount dependent on the PO_2. For each $1\,\text{mmHg}$ PO_2, there is $0.003\,\text{mL}$ O_2 dissolved in $100\,\text{mL}$ of plasma. Therefore, the total oxygen concentration of blood (mL O_2/100 mL of blood) is equal to the summation of these two forms:

$$(1.34 \times \text{Hb} \times \text{percentage saturation of Hb}) + 0.003\ PO_2.$$

These relationships explain how one can have normal saturation of Hb and PO_2 but still have a low oxygen concentration of blood if there is severe anemia.

The relationship of the PO_2 of plasma and the Hb saturation is represented graphically by the oxygen dissociation curve (see Figure 1.6).

At normal conditions (pH 7.4, PCO_2 40 mmHg, and 37°), a sigmoid curve describes the relationship between PO_2 on the x-axis and the percent
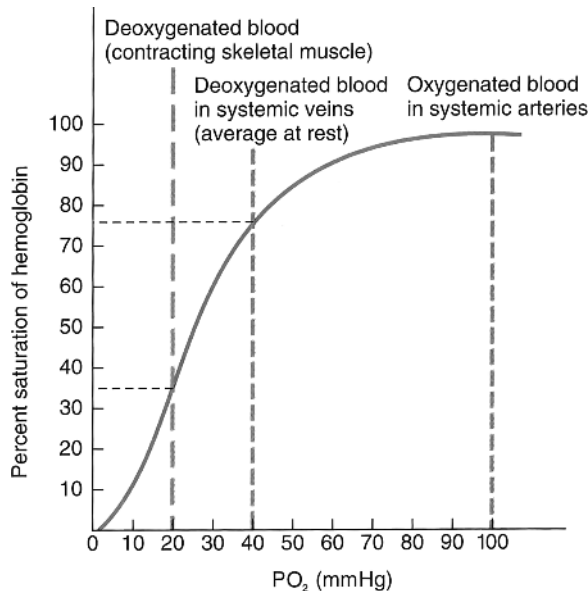

Figure 1.6 Oxygen–hemoglobin dissociation curve showing the relationship between hemoglobin saturation and PO_2 at normal body temperature. Reprinted from Tortora and Derrickson (2009), with permission from John Wiley & Sons, Inc.

saturation of Hb on the y-axis. This figure helps in understanding much of the physiology of Hb and its ability to carry oxygen to the tissues, dissociate with it, and then carry CO_2 back to the lungs.

The oxygen dissociation curve demonstrates why the Hb molecule is the ideal vehicle for combining and dissociating with oxygen. As discussed earlier, the PO_2 at the initial portion of the pulmonary capillary is 40 mmHg, while across the alveolar wall, the PO_2 is 100 mmHg. On the curve, between 40 and 60 mmHg there is steep increase in oxygen saturation. Under normal circumstances, oxygen is transferred rapidly from the alveolus to the red blood cell, and Hb is saturated with oxygen one-third of the way through the pulmonary capillary. The reason for this speed is the continued difference in PO_2 between the alveolar and the pulmonary capillary even after the oxygen has been transferred (100 mmHg vs. 60 mmHg).

Above approximately 60 mmHg, the curve flattens, indicating that the oxygen concentration and Hb saturation do not increase as much for a given increase in the PO_2. This allows for the circumstance when the alveolar PO_2 falls, without causing a significant decrease in the capillary uptake of oxygen. How then can the oxygen concentration of blood increase past this point? Looking back at the formula, it would require (1) an increase in the Hb concentration via transfusion or (2) supplemental oxygen to increase the amount of oxygen dissolved in plasma.

At the lower portion of the curve, below PO_2 of 50 mmHg, the curve is very steep, denoting a decreased affinity of Hb for oxygen. PO_2 levels in this range are found in peripheral tissues, facilitating the unloading of oxygen from Hb in this environment. The steep slope for this range of PO_2 allows for the transfer of large amounts of oxygen for small decreases in capillary PO_2. The PO_2 at which Hb is 50% saturated is known as the P50. For a healthy adult, P50 is 26.6 mmHg and can be visualized by drawing a line from 50% Hb saturation down to the x-intercept.

There are a variety of abnormal conditions that will affect the oxyhemoglobin dissociation curve. Conditions that decrease the affinity of Hb for oxygen will shift the curve to the right, indicating that it will be more difficult for Hb to bind oxygen (see Figures 1.7 and 1.8). As a corollary, a shift to the right leads to more unloading of oxygen for a given PO_2. This situation occurs with an increase in PCO_2, hydrogen ion concentration, temperature, and the concentration of 2,3-DPG (an end product of red cell metabolism). Physiologically, this occurs in exercising muscles, where the environment is acidic, hot, and hypercarbic and is most in need of oxygen. 2,3-DPG is increased in chronic hypoxia, chronic lung disease, anemia and (as stated previously) at high altitudes. These are all instances in which the unloading of oxygen would ideally be maximized.

On the other hand a decrease in the PCO_2, which is mostly secondary to a decrease in the hydrogen ion concentration (this will be discussed further in the section "Acid–Base Balance"), leads to a left shift and an increased affinity for oxygen. Naturally, this is what is seen in the lungs.
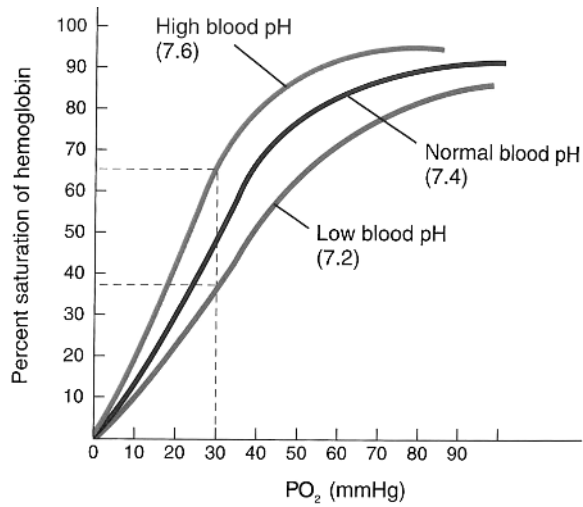
(a) Effect of pH on affinity of hemoglobin for oxygen
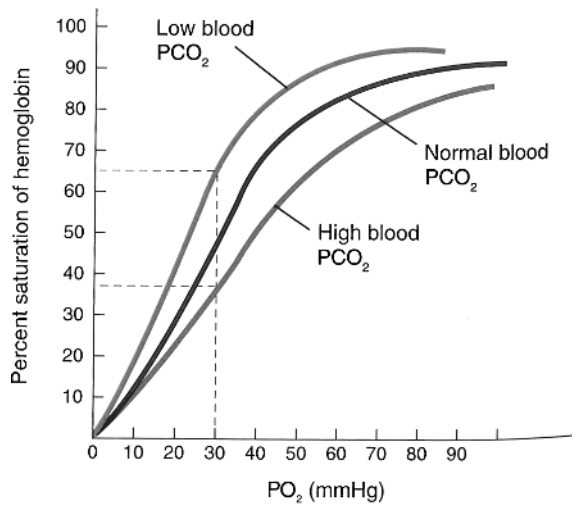
(b) Effect of PCO_2 on affinity of hemoglobin for oxygen

Figure 1.7 Oxygen–hemoglobin dissociation curves showing the relationship of (a) pH and (b) PCO_2 to hemoglobin saturation at normal body temperature. As pH increases or PCO_2 decreases, O_2 combines more tightly with hemoglobin so that less is available to tissues. The broken lines emphasize these relationships. Reprinted from Tortora and Derrickson (2009), with permission from John Wiley & Sons, Inc.
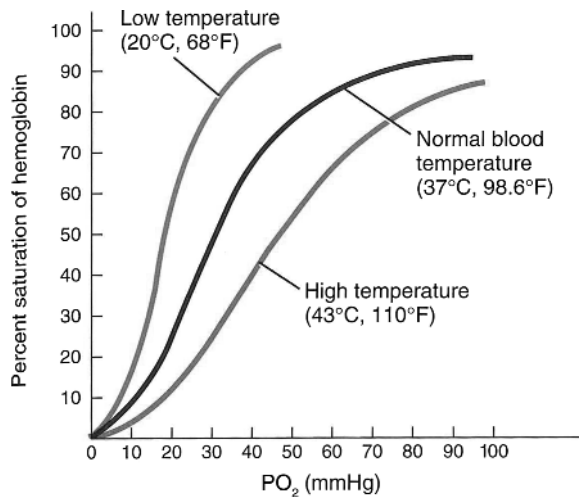
Figure 1.8 Oxygen–hemoglobin dissociation curves showing the effect of temperature changes. Reprinted from Tortora and Derrickson (2009), with permission from John Wiley & Sons, Inc.

Hb binds with carbon monoxide 240 times more readily than with oxygen. The presence of carbon monoxide on one of the four heme sites causes a stronger binding of oxygen on the other sites. Even small amounts of CO make it difficult for Hb to release oxygen to the tissues, leading to a leftward shift of the curve. A CO concentration as low as 667 ppm can cause up to 50% conversion of Hb to carboxyhemoglobin (Tikuisis, Kane, McLellan, Buick, & Fairburn, 1992). This will lead to severe hypoxemia despite a normal Hb concentration and PO_2 of blood (see Figure 1.9).

As mentioned earlier, there are different types of Hb, the most common of which are HbA, HbF, and HbS. Their properties are highlighted by their individual oxygen dissociation curve. HbA is the normal adult Hb, while HbS has a difference in the beta chain with a valine substituted for glutamic acid. HbS is the Hb chain seen in sickle cell disease. The dissociation curve for HbS is shifted to the right in comparison to HbA. HbF has a dissociation curve that is shifted to the left relative to HbA. This makes sense physiologically, as fetal arterial oxygen pressures are low and the leftward shift enhances the placental uptake of oxygen. At the placenta, there is also a higher concentration of 2,3-DPG, which causes the HbA to release more oxygen, to be taken up by the fetus.

Carboxyhemoglobin

The uptake and delivery of oxygen from the lungs to the tissues is one-half of the equation. The other half has to do with the tissues' production of carbon dioxide (CO_2) and its transport to the lungs for elimination via exhalation. Like oxygen, carbon dioxide is found dissolved in blood, but
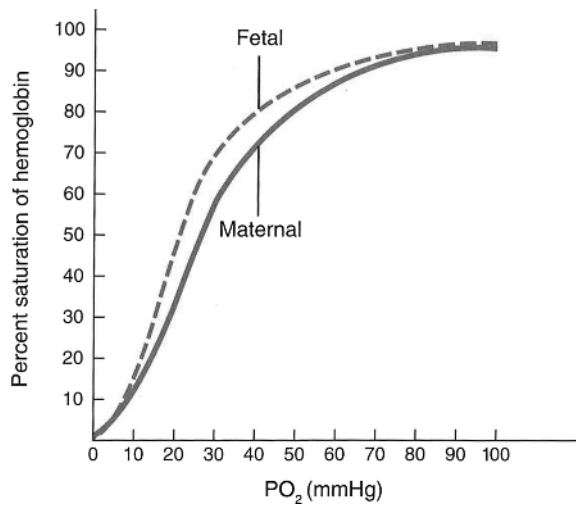
Figure 1.9 Oxygen–hemoglobin dissociation curves comparing fetal and maternal hemoglobin. Reprinted from Tortora and Derrickson (2009), with permission from John Wiley & Sons, Inc.

for carbon dioxide, this makes up a much more significant portion. CO_2 is 20 times as soluble as O_2, leading to 10% of CO_2 exhaled from the lungs coming from the dissolved form of CO_2 (see Figure 1.10).

Within the red blood cell is an enzyme, carbonic anhydrase, which catalyzes the combination of CO_2 and water (H_2O) into carbonic acid (H_2CO_3). Carbonic acid quickly dissociates into hydrogen ions (H^+) and bicarbonate (HCO_3^-):

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow HCO_3^- + H^+.$$

This catalyzed reaction is reversed in the lungs, where H^+ reacts with bicarbonate to form carbonic acid and then CO_2, which is exhaled into the outside environment. Approximately 80–90% of carbon dioxide in the blood is carried in the form of bicarbonate. As shown by this reaction, blood with high carbon dioxide levels will result in a higher H^+ concentration and therefore a lower pH (more acidic).

Hb that has unloaded oxygen in peripheral tissues is known as reduced Hb, or deoxyhemoglobin. Deoxyhemoglobin is a weaker acid than oxyhemoglobin and therefore combines with H^+, which is liberated during the dissociation of carbonic acid. This allows for more CO_2 to be transported as bicarbonate ion. The binding of H^+ with amino acids of Hb also lowers the affinity of Hb for oxygen. An acidic environment with more H^+ ion available will result in a shift of the oxygen dissociation curve to the right, where the affinity of Hb for oxygen is lower. Hence, we have the Haldane effect, which states that deoxygenation of blood leads to an increased
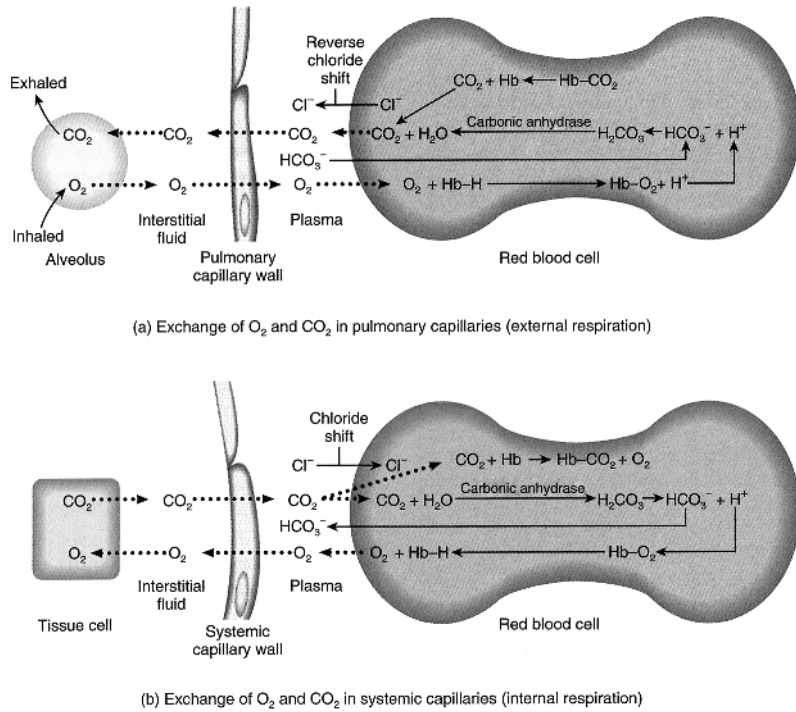
(a) Exchange of O_2 and CO_2 in pulmonary capillaries (external respiration)

(b) Exchange of O_2 and CO_2 in systemic capillaries (internal respiration)

Figure 1.10 Summary of chemical reactions that occur during gas exchange. (a) As carbon dioxide (CO_2) is exhaled, hemoglobin (Hb) inside red blood cells (RBCs) in pulmonary capillaries unloads CO_2 and picks up O_2 from alveolar air. Binding of O_2 to Hb–H releases hydrogen ions (H^+). Bicarbonate ions (HCO_3^-) pass into the RBC and bind to released H^+, forming carbonic acid (H_2CO_3). The H_2CO_3 dissociates into water (H_2O) and CO_2, and the CO_2 diffuses from the blood into alveolar air. To maintain electrical balance, a chloride ion (Cl^-) exits the RBC for each HCO_3^- that enters (reverse chloride shift). (b) CO_2 diffuses out of tissue cells that produce it and enters RBCs, where some of it binds to Hb (Hb–O_2). Other molecules of CO_2 combine with water to produce bicarbonate ions (HCO_3^-) and hydrogen ions (H^+). As Hb buffers H^+, the Hb releases O_2 (Bohr effect). To maintain electrical balance, a chloride ion (Cl^-) enters the RBC for each HCO_3^- that exists (chloride shift). Reprinted from Tortora and Derrickson (2009), with permission from John Wiley & Sons, Inc.

ability of venous blood to carry CO_2 (seen at the tissues) and unload more CO_2 in the presence of oxyhemoglobin (seen at the lungs).

Carbon dioxide binds to Hb at the α-amino group and forms carbaminohemoglobin, the third form CO_2 is carried in the blood (Guyton & Hall, 2006). This causes a change in the protein, which facilitates the release of oxygen, shifting the oxygen dissociation curve to the left, and is known as the Bohr effect. The converse is also true, as more CO_2 can bind to carbaminohemoglobin than HbO_2. As such, the release of O_2 in the peripheral

tissues leads to an increased loading of CO_2. Once in the lung capillaries, deoxyhemoglobin combines with oxygen and releases CO_2.

The carbon dioxide dissociation curve is more linear in comparison with the oxygen dissociation curve. Of particular importance is the increased slope of the curve for CO_2 versus O_2 when plotting partial pressure on the x-axis and concentration on the y-axis of the respective gases. What this demonstrates is in the physiological range of PCO_2, between 40–50 mmHg, there is a greater change in CO_2 concentration per change in PCO_2 than there is change in oxygen concentration per change in PO_2. This is why there is a significantly larger difference in the PO_2 compared to carbon dioxide in the arterial versus venous blood.

ACID–BASE BALANCE

The lungs play a significant role in the precise regulation of the acid–base balance in the human body. Understanding the acid–base balance and the role the lung plays in maintaining it requires reviewing the Henderson–Hasselbach equation. In the context of respiratory physiology where blood is a buffer solution, the equation can be derived as the following:

$$pH = pK_A + log[(HCO_3^-)/(CO_2)].$$

pK_A is the negative logarithm of the dissociation constant of carbonic acid. It can be viewed as a constant and at physiological pH and a temperature of 37°C, it is 6.1. At the same temperature, 0.03 mmol of carbon dioxide dissolves in 1 L of plasma; therefore, the CO_2 concentration is equal to ($PCO_2 \times 0.03$). If the bicarbonate level is normal at 24 mmol/L, inserting these values in the above equation yields

$$7.4 = 6.1 + log[(24)/0.03 \times PCO_2)],$$

a PCO_2 of 40 mmHg, consistent with what is measured by blood gas analysis.

pH is the negative log of the hydrogen ion concentration, and as such, small changes of pH are actually representative of large changes in H^+ concentration ($[H^+]$) in the opposite direction. For example, an increase in pH from 7.4 to 7.7 represents a 50% decrease in $[H^+]$. The normal pH range is 7.35–7.45. A drop leads to acidemia, while an increase renders the blood more basic, resulting in alkalemia. The respiratory system primarily regulates the PCO_2, while the kidney regulates the HCO_3^- concentration. Acidosis is the condition that causes an increase in $[H^+]$ or a decrease in $[HCO_3^-]$, while alkalosis is the condition that causes a decrease in $[H^+]$ or an increase in $[HCO_3^-]$.

The fact that in the above-mentioned Henderson–Hasselbach equation PCO_2 is in the denominator explains why an increase in PCO_2 (outside the normal range of 35–45 mmHg) leads to a fall in pH, that is, an increase in

acidity. This is known as *respiratory acidosis*. Without adequate exhalation, as seen in acute respiratory failure, CO_2 accumulates quickly and respiratory acidosis develops. Short-term changes in PCO_2 (that occur prior to the onset of renal compensation) increase the ratio of CO_2 to HCO_3^-, leading to this acidosis. Causes of acute respiratory acidosis include depression of the central respiratory center by cerebral disease or drugs (including anesthetics and narcotics), or airway obstruction related to asthma or chronic obstructive pulmonary disease (COPD) exacerbation. The body's ability to sense these changes and the control centers of breathing are discussed in the section "Control of Ventilation."

There are also instances of chronic retention of CO_2 often due to neuromuscular disease, either acquired, such as myasthenia gravis, amyotrophic lateral sclerosis, and Guillain–Barré syndrome, or congenital, such as muscular dystrophy. Chronic CO_2 retention also occurs in chronic lung diseases such as neonatal chronic lung disease secondary to extreme prematurity and immaturity of the premature lung. Chronic retention of CO_2 leads to respiratory acidosis. The kidney responds by retaining HCO_3^-. When the kidney is unable to completely reverse the acidosis, a pH below 7.4 will ensue, and this is referred to as compensated respiratory acidosis.

An increase in pH will be secondary to alkalosis. As expected from the Henderson–Hasselbach equation, this can occur because of a decrease in PCO_2, and it is termed *respiratory alkalosis*. Just as respiratory acidosis is caused by hypoventilation, hyperventilation will lead to respiratory alkalosis. Essentially, alveolar ventilation is higher than required for the body's production of carbon dioxide, resulting in a PCO_2 less than 35 mmHg. Hyperventilation is seen with anxiety, fever, and overventilation via a mechanical ventilator. This is also often seen at higher altitudes with hypoxia. One of the body's adjustments to the high altitude will be an increase in the renal excretion of HCO_3^- in an attempt to normalize pH.

In *metabolic acidosis*, the primary problem can be the loss of HCO_3^-, an increase in the production of acid, or a decrease in excretion of H^+ ions all leading to a decrease in the $[(HCO_3^-)/CO_2)]$ ratio. A review of the Henderson–Hasselbach equation demonstrates why a decrease in this ratio will lead to a decrease in the pH. Metabolic acidosis is a common occurrence in the intensive care unit and is present with a variety of disease processes including diabetic ketoacidosis and sepsis leading to tissue hypoxia and lactic acid production. A significant amount of diarrhea leads to loss of bicarbonate. Type I renal tubular acidosis is secondary to a defect in the secretion of H^+ ions in the distal renal tubular and subsequent decrease in reabsorption of bicarbonate.

An increase in HCO_3^- or an excessive loss of acid will lead to an increase in pH and *metabolic alkalosis*. Examples of conditions that result in loss of H+ ions include persistent vomiting with loss of hydrochloric acid and renal loss of hydrogen secondary to high aldosterone levels. Contraction alkalosis is secondary most often to diuretic use, leading to water loss but retention of HCO_3^-, which will bind H^+ ions, increasing blood pH. Excessive

ingestion of bicarbonate, as seen with antacids, also leads to an increase in bicarbonate.

Primary acid–base disturbances are often partially balanced by compensation. When the disturbance is respiratory in nature, be it acidosis or alkalosis, renal compensatory mechanisms take effect. When the disturbances are metabolic, respiratory compensation occurs.

Changes in ventilation that result in changes in PCO_2 and respiratory compensation are controlled via the central and peripheral receptors (see the section "Control of Ventilation"). In metabolic acidosis, with the increase in hydrogen ion concentration, the respiratory system will hyperventilate to increase the exhalation of CO_2 in an attempt to normalize blood pH. Winter's formula allows us to determine if this respiratory compensation for metabolic acidosis is adequate:

$$PCO_2 = [(1.5 \times HCO_3^-) + 8] \pm 2.$$

For a given HCO_3^-, the formula will give the range expected of PCO_2 for adequate respiratory compensation, allowing comparison with the actual PCO_2 measured in the child's blood (Lewis, 2008). In the case of metabolic alkalosis, the respiratory system attempts to compensate by hypoventilating and retaining CO_2, thereby lowering the pH closer to 7.4.

Renal tubular cells actively secrete H^+ ions into the renal tubular fluid, and the proximal tubule of the kidney accounts for the resorption of 80% of all filtered HCO_3^-. Overall, the kidney secretes 70 mEq of H^+ ions and 70 mEq of HCO_3^- ions on a daily basis. However, during respiratory acidosis, the kidney compensates by retaining HCO_3^-, mostly in the proximal tubule of the kidney, and by excreting H^+ ions. The summation of this process allows the pH of the urine to go as low as 4.0, while attempting to increase the blood pH closer to 7.4. In cases of respiratory alkalosis, the renal secretion of H^+ ions is decreased. The reabsorption of HCO_3^- is also decreased, leading to an increase in the secretion of HCO_3^-. The net result is the attempt to decrease the blood pH closer to 7.4.

Whether the respiratory compensation is an attempt to increase or decrease PCO_2 based on the metabolic derangement, compensation occurs rapidly, on the order of minutes. This is in comparison to renal compensatory methods for respiratory derangements. The kidneys compensate for respiratory acid–base derangement by increasing or decreasing the excretion of acids and the retention of bicarbonate. Renal compensation is typically on the order of 3–6 days (Levitzky, 2007).

RESPIRATORY MECHANICS

Oxygen enters the body from the outside environment, through the conducting airways, into the respiratory zone, diffusing into the pulmonary capillaries and combining with Hb. Entry of oxygen requires an expansion of the lungs to accommodate a volume of air from which oxygen is derived.

To understand the process of normal breathing, one needs to understand the inherent properties of the lung and the chest wall. Functionally, the chest wall is made up of the rib cage, diaphragm, and abdominal contents. At baseline, the lung's tendency is to recoil inward, while the chest wall tends to recoil outward. The pleural pressure combines them into a functioning unit. The opposing forces generate a negative intrapleural pressure of −3- to −5-cm H_2O. The lung volume at which the lung and chest wall recoil are balanced is known as functional residual capacity (FRC). At the end of expiration, the muscles of respiration are relaxed and the lung volume is at FRC (see Figure 1.11).

Atmospheric pressure = 760 mmHg

Atmospheric pressure = 760 mmHg

Alveolar pressure = 760 mmHg

Intrapleural pressure = 756 mmHg

Alveolar pressure = 758 mmHg

Intrapleural pressure = 754 mmHg

(1). At rest (diaphragm relaxed)

(2). During inhalation (diaphragm contracting)

Atmospheric pressure = 760 mmHg

Alveolar pressure = 762 mmHg

Intrapleural pressure = 756 mmHg

(3). During exhalation (diaphragm relaxing)

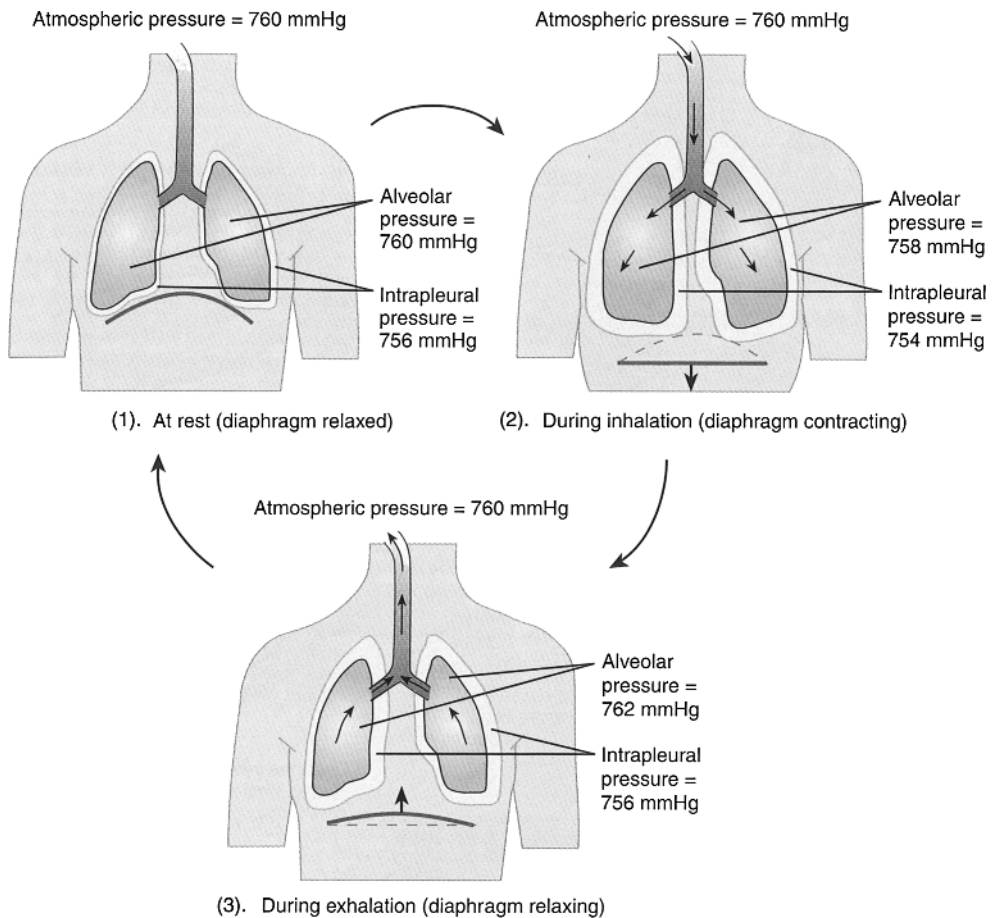**Figure 1.11** Pressure changes in pulmonary ventilation. During inhalation, the diaphragm contracts, the chest expands, the lungs are pulled outward, and the alveolar pressure decreases. During exhalation, the diaphragm relaxes, the lungs recoil inward, and alveolar pressure increases, forcing air out of the lungs. Reprinted from Tortora and Derrickson (2009), with permission from John Wiley & Sons, Inc.

An appreciation of the terminology of the various lung volumes is required prior to understanding the dynamics of ventilation. Chest wall and lung recoil properties determine pressure and volume changes during the breathing cycle. One inhalation produces a tidal volume (V_t), which, when exhaled, leaves a volume (FRC) in the lungs. Performing a maximal inhalation generates the vital capacity (VC), which is the maximal volume of air one can inhale during one breathing maneuver. The volume of air left in the lungs after a forceful exhalation from VC is the residual volume (RV). The summation of RV and VC equals the total lung capacity (TLC) (see Figure 1.12).

During forced inhalation, inspiratory muscles contract, leading to an increase in the thoracic volume. However, these muscles must overcome the inward recoil of the chest wall back to its resting position. TLC is the volume at which inspiration ceases because the muscles of inhalation cannot overcome the inward recoil of the chest wall. In forced exhalation, the contraction of expiratory muscles leads to a decrease in thoracic volume. The pressure needed to empty the lungs must overcome the outward recoil of the chest wall to its resting position. The volume left in the lungs at which the muscles of exhalation cannot overcome this outward recoil is the RV (see Figure 1.13).

The outward recoil out of the chest wall leads to a negative pressure; this negative pressure facilitates inhalation. Inhalation normally occurs via negative pressure; when alveolar pressure falls below atmospheric pressure to the point that it overcomes airway resistance, air flows into the lungs. This is in comparison to positive pressure ventilation, which is commonly utilized in intensive care units as the mode of breathing for children on ventilators.

Static properties: Compliance and elasticity

Compliance is the relationship between changes in volume and changes in pressure. In other words, compliance reflects the "ease" with which an object can be stretched. This contrasts with elasticity, which is a measure of the opposition to stretch. On a volume–pressure curve, the slope of the line is the measure of compliance and is measured as

$$\text{Compliance} = \frac{\text{Change in volume}}{\text{Change in pressure}}.$$

The classic clinical conditions that illustrate this are emphysema and fibrosis. Adult patients with emphysema have lungs that are more distensible and are therefore more compliant with elastic fibers that are easily stretched (Tortora & Derrickson, 2009). The patient with interstitial fibrosis has stiffer, less compliant lungs. The volume–pressure curve for the more compliant lung will be steeper than a normal individual, while the curve for the less compliant lung will be less steep. Conversely, the elastic recoil
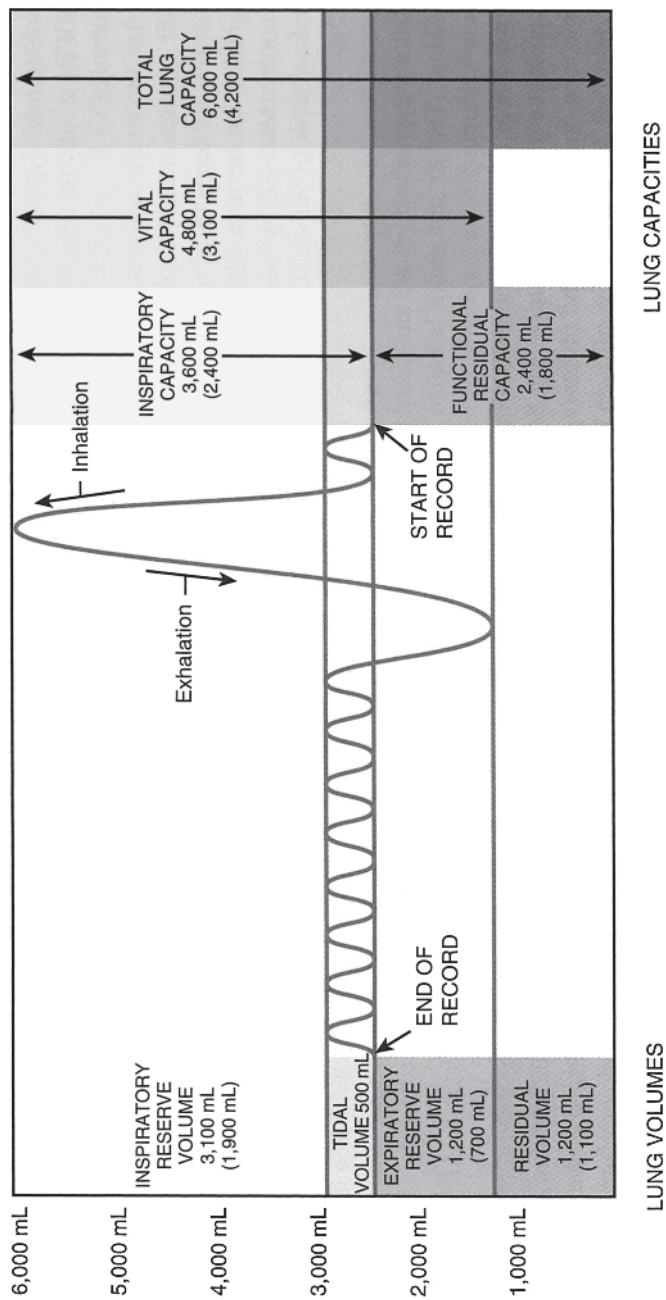
6,000 mL

5,000 mL

4,000 mL

3,000 mL

2,000 mL

1,000 mL

INSPIRATORY RESERVE VOLUME 3,100 mL (1,900 mL)

TIDAL VOLUME 500 mL

EXPIRATORY RESERVE VOLUME 1,200 mL (700 mL)

RESIDUAL VOLUME 1,200 mL (1,100 mL)

Inhalation

Exhalation

START OF RECORD

END OF RECORD

INSPIRATORY CAPACITY 3,600 mL (2,400 mL)

VITAL CAPACITY 4,800 mL (3,100 mL)

TOTAL LUNG CAPACITY 6,000 mL (4,200 mL)

FUNCTIONAL RESIDUAL CAPACITY 2,400 mL (1,800 mL)

LUNG VOLUMES

LUNG CAPACITIES

Figure 1.12 Spirogram of lung volumes and capacities. The average values for a healthy adult male and female are indicated, with the values for a female in parentheses. Note that the spirogram is read from right (start of record) to left (end of record). Reprinted from Tortora and Derrickson (2009), with permission from John Wiley & Sons, Inc.
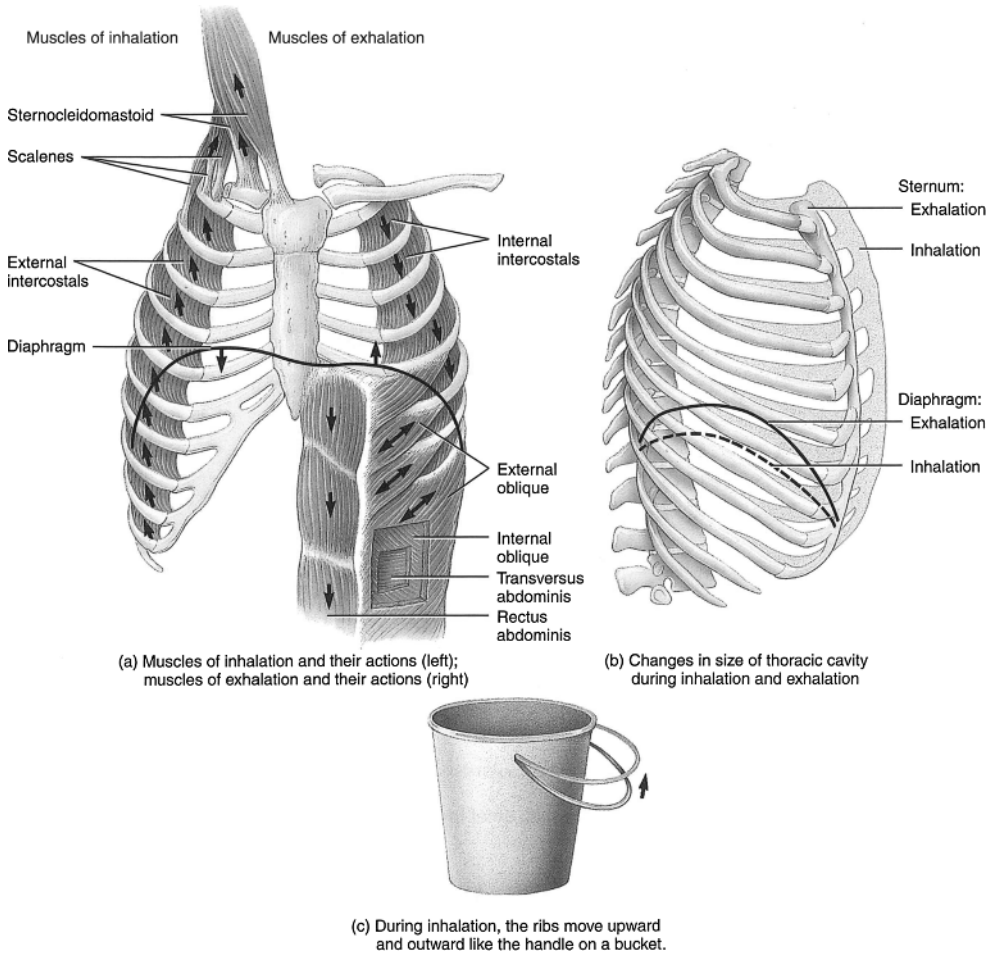
Muscles of inhalation   Muscles of exhalation

Sternocleidomastoid

Scalenes

External intercostals

Diaphragm

Internal intercostals

External oblique

Internal oblique
Transversus abdominis
Rectus abdominis

(a) Muscles of inhalation and their actions (left); muscles of exhalation and their actions (right)

Sternum:
Exhalation
Inhalation

Diaphragm:
Exhalation
Inhalation

(b) Changes in size of thoracic cavity during inhalation and exhalation

(c) During inhalation, the ribs move upward and outward like the handle on a bucket.

Figure 1.13 Muscles of inhalation and exhalation and their actions. Reprinted from Tortora and Derrickson (2009), with permission from John Wiley & Sons, Inc.

for the more compliant lung will be less, while the less compliant lung will have higher elastic recoil.

Muscles of breathing

Inspiration

As stated previously, breathing normally takes places via negative pressure; the decrease in pleural and hence alveolar pressure to below atmospheric pressure is secondary to contraction of the muscles of inspiration. The most important muscle of inspiration is the diaphragm. The diaphragm is a thin muscle that delineates the thorax from the abdomen, attaching to

the lower ribs on each side. The diaphragm contracts during inspiration, forcing abdominal contents down and thereby increasing the cephalad/caudal dimensions of the thorax. This lifts the ribs up and out, increasing the transverse dimension of the thorax. Also involved in inspiration are the external intercostal muscles that connect adjacent ribs. When they contract, the ribs are pulled upward and forward, increasing anterior–posterior and lateral diameters of the thorax, commonly referred to as the "bucket-handle" movement of the ribs (see Figure 1.13).

Paralysis of the diaphragm leads to paradoxical movement, with the diaphragm moving up on inspiration with the fall in intrathoracic pressure. Paralysis of the intercostal muscle has little effect on breathing. Other muscles that play more of a role during exercise include the scalene muscles, which elevate the first two ribs, and the sternocleidomastoid muscles, which raise the sternum. Neuronal inputs and brainstem control of inspiration are discussed in the section "Control of Ventilation."

As previously stated, prior to the initiation of inspiration, the intrapleural pressure is between −3- and −5-cm H_2O. The transmural pressure is equal to the alveolar pressure minus the intrapleural pressure. The muscles of inspiration increase thoracic cavity volume, thereby decreasing the alveolar pressure (making more negative) and the transmural pressure. An increase in the transmural pressure gradient distends the alveolar walls, increasing the alveolar volume and allowing for the inspiration of air until, once again, alveolar pressure is not less than atmospheric pressure.

Expiration

Expiration during regular tidal breathing is passive. At the end of inspiration, the elastic properties of the distended alveoli are such that the alveolar pressure is greater than atmospheric pressure, allowing for the flow of air out of the lung (see Figure 1.11). During hyperventilation, whether done voluntarily or with exercise, expiration becomes active, as the lungs attempt to overcome the outward recoil of the chest. The muscles that make up the abdominal wall are key to this movement. They contract, leading to an increase in intra-abdominal pressure as the diaphragm is pushed up. The Valsalva maneuver is a variation on this theme, where expiration is forced against a closed glottis, increasing abdominal pressure. This occurs in coughing, sneezing, and defecation (Levitzky, 2007).

Surface tension properties of the lung

In addition to the physical and mechanical properties that allow lung expansion and ventilation, the lung has specific properties that facilitate the ease with which it can be inflated and deflated. These are related to the alveolar cell types and alveolar surface tension. There are two types of alveolar epithelial cells, conveniently named type I and type II cells. Type I cells are squamous epithelial alveolar cells that have long cytoplasmic

extensions that spread out over the alveolar walls and help form the structure of the wall. Type II cells are compact with microvilli that extend into the alveoli.

Type II cells produce a surfactant, a phospholipid made in the lung from fatty acids. It coats the surface of the alveolus and decreases its surface tension. Eighty-five to ninety percent of a surfactant consists of lipids of which 85% is phospholipids. Along with the phospholipids, a surfactant has four different types of surfactant proteins: The hydrophilic proteins SP-A and SP-D and the hydrophobic proteins SP-B and SP-C. Seventy-five percent of the phospholipids are dipalmitoyl phosphatidylcholine (DPCC), or lecithin. DPCC's molecular properties allow surfactants to reduce elastic recoil secondary to surface tension, thereby increasing compliance. DPCC has one hydrophobic molecular end, while the other end is hydrophilic. Normally, liquid surface molecules are attracted to each other leading to surface tension. However, the repulsive forces of the two ends of DPCC oppose this attractive force, decreasing the surface tension. A surfactant's surface tension decreases to a higher degree as the surface area layer is reduced because the molecules of DPCC are brought closer together, leading to an increase in the repulsive force.

As a result of the properties of surfactants, smaller alveoli have lower surface tensions, normalizing the alveolar pressure throughout the lung. Overall, the reduction in elastic recoil and the increase in compliance lead to a decrease in the work of breathing of inspiration. By allowing the surface tension to decrease as lung volume decreases, surfactants stabilize the lung and prevent atelectasis. Surface tension forces lead to transudation of fluid from the capillaries into the alveolar spaces, but by decreasing surface tension, surfactants also keep the alveoli dry. Furthermore, surfactants protect the lung against epithelial injury and provides a barrier against infection (Anandarajan, Paulraj, & Tubman, 2009).

Surfactant production begins in the fourth month of gestation but is not fully functional until after the seventh month (Levitzky, 2007). Infants born during this gestational period develop classic respiratory distress syndrome (RDS). Problems include difficulty inflating alveoli because the lungs are stiff, secondary to the decrease in pulmonary compliance. In those alveoli that are inflated, there are areas of collapse secondary to instability associated with lack of surfactant. This leads to the classic heterogenous picture of RDS: areas of hyperinflation and pockets of atelectasis. Current strategies to prevent RDS include antenatal maternal treatment with steroids to enhance fetal lung maturation or postnatal treatment with synthetic surfactant to the newborn.

Antenatal glucocorticoid therapy administered to women at risk for preterm delivery has reduced the incidence of RDS and overall mortality in the offspring (Liggins & Howie, 1972). Antenatal glucocorticoid therapy causes maturation of the lung architecture (Ballard & Ballard, 1995; Smolders-de Haas et al., 1990). In essence, the maternal treatment with glucocorticoids allows for a swift pulmonary maturation through the sac-

cular phase into the alveolar stage. The decreased severity and incidence of RDS lead to a decrease in the need for surfactant therapy, supplemental oxygen, and mechanical ventilation (National Institute of Child Health and Human Development, 1994).

A similar clinical picture is seen in term infants who have inherited surfactant deficiencies secondary to mutations of the surfactant proteins SP-B and SP-C. This leads to intracellular accumulation of proteins and extracellular deficiency of surfactant proteins. These mutations are a cause of both familial and sporadic interstitial lung disease. Mutations in the adenosine triphosphate (ATP)-binding cassette gene (ABCA3) in newborns result in fatal surfactant deficiency. ABCA3 is critical for proper surfactant function.

Airway resistance

In addition to the properties of the muscles of breathing and the lung parenchyma, properties of the conducting airways are important determinants of airflow into the lungs. In straight tubes, flow is described as laminar, which is flow that occurs at a low rate in parallel streams through a tube. With laminar flow, the resistance is inversely proportional to the radius of the tube to the fourth power. As a result, a decrease in the radius by half will increase the resistance 16-fold.

In the human lung, laminar flow occurs in the smallest airways; hence, one would expect that a decrease in radius in these airways, as might occur with an infection, would result in a large increase in airway resistance to airflow. However, the main areas of resistance are not in these smallest airways. This is because despite the remarkably narrow radius of the small airways, the exponential number of these airways greatly reduces the overall effect of the radius in terms of resistance. It is the medium-sized bronchi (up to the seventh generation) that are the site of 80% of the resistance in the human lung (West, 2003).

At low lung volumes, the small airways can collapse, especially at the base of the lung. Though this area ventilates more efficiently, it is not well expanded. It is thought that children who have increased airway resistance, a hallmark of poorly controlled asthma, breathe at higher lung volumes to decrease airway resistance. Understanding this pathophysiology helps to understand the mainstays of asthma treatment.

Bronchial airway smooth muscles have receptors that, when stimulated, lead to contraction or relaxation of the muscles. In some children, airway smooth muscle contraction can be stimulated by certain triggers, including environmental (pollen, grass, etc.), viral, or exercise. Beta adrenergic receptors, found in the airway smooth muscle, lead to relaxation of the smooth muscle when stimulated by a beta adrenergic agonist. This is the means by which albuterol sulfate, a beta adrenergic agonist, acts as a rescue medicine during an asthma exacerbation and provides relief by increasing airway radius and decreasing resistance.

Regional differences of the lung

Alveoli at the top of the lung are more fully expanded at FRC than those at the bottom of the lung. This is secondary to higher transpulmonary pressure at the top of the lung. Factors that lead to this gradient in transpulmonary pressure include the effect of gravity on the chest wall and the effect of the weight of the lung. These downward acting forces on the lung require higher pressure at the lower rather than the higher areas to balance the forces. Therefore, the pressure near the base is less negative than at the apex. Because the transpulmonary pressure at the base is small, the resting volume of the lung in this region is also small; in essence, the basal lung is more compressed.

However, this gradient decreases during inspiration, and at full inspiration, that is, at TLC, the alveoli are virtually uniform in size from the apices to the bases in the lung. As the lung volume increases above FRC, alveoli at the bottom expand more than those at the top of the lung. As a result, during normal breathing at rest, the base of the lungs ventilates more than the uppermost regions of the lung. The lower portion of the lung is on the steeper part of the pressure–volume curve, leading to more expansion on inspiration in comparison to the apex. Lungs with higher volumes (apex vs. basal segments) are more difficult to inflate as they require larger expanding pressure; in essence, they are stiffer.

This regional difference in ventilation coincides with a higher blood flow at the base in comparison to the top of the lungs. The higher rate of ventilation and perfusion leads to a more efficient exchange of gases. This apex/base difference dissipates when in the supine position, but the posterior portion of the lung (now the lower part) is higher than the anterior portion (now the upper part).

CONTROL OF VENTILATION

This section presents the triad of components involved in ventilation: the central and peripheral receptors that sense changes in pH, PCO_2, and PO_2 in the blood and cerebrospinal fluid (CSF); the brainstem neurons that receive the inputs from these receptors; and the muscles of respiration that receive the signals sent out by the neurons.

Breathing is a tightly regulated process that is controlled by the central nervous system. In order to adjust tidal volume and respiratory rate to meet the demands of maintaining normal gas exchange and pH, feedback is needed from the lungs, the respiratory muscles, and the blood. The sensors that detect PO_2 and PCO_2 levels in the blood and CSF are located centrally and peripherally in the body.

The central chemoreceptors are bathed in brain extracellular fluid (ECF) on the ventral surface of the medulla, near cranial nerves 9 and 10. The ventral respiratory group controls voluntary forced expiration and acts to increase the force of inspiration. An increase in H^+ ion concentration will

increase ventilation, as well as the converse; a decrease in H^+ ion concentration will decrease ventilation (Coates, Li, & Nattie, 1984). This is consistent with the Henderson–Hasselbach equation, which shows that a decrease in pH (an increase H^+ ion concentration) is seen with an increase in PCO_2, as might occur in hypoventilation. The result will be an increase in respiratory drive to lower PCO_2 and increase pH. Under normal conditions, the most important factor in the control of ventilation is the arterial PCO_2.

The ECF is composed of and affected by CSF and local blood flow and metabolism. The interactions of these components are dictated by the environment of the brain. The CSF is separated from the blood by the blood–brain barrier (BBB). Unlike H^+ ions, CO_2 is able to diffuse through the BBB. When blood PCO_2 rises, this difference in permeability allows CO_2 to move from the cerebral blood vessels, through the BBB, into the CSF. Once in the CSF, the pH will decrease with an increase in H^+ ions, stimulating chemoreceptors. An increase in PCO_2 increases diffusion because CO_2 causes vasodilation of cerebral blood vessels. Vasodilation is an important effect of CO_2 that allows the close control of ventilation and enables the quick resolution of changes in blood CO_2. How this stimulation leads to an increase in respiration and therefore a decrease in PCO_2 is presented later in this section.

The peripheral chemoreceptors are found in the carotid bodies at the bifurcation of the common carotid arteries and above and below the aortic arch in the aortic bodies (see Figure 1.14). Peripheral chemoreceptors act most importantly to detect arterial decreases in PO_2 and pH and increases in PCO_2. They are the sole means to an increase in ventilation secondary to a decrease in arterial PO_2. In fact, those with bilateral absence of carotid bodies have an absolute loss of hypoxic ventilatory drive. In comparison to central chemoreceptors, carotid bodies play a much smaller role in controlling ventilation secondary to PCO_2. At sea level, carbon dioxide is the main stimulus to ventilation, but at a higher altitude (above 3,000 m), hypoxia plays more of a role in increasing ventilation (Peacock, 1998). There is also a distinction in regard to the peripheral chemoreceptors themselves, as the carotid, but not aortic, bodies respond to a decrease in arterial pH.

The CSF has a lower buffering capacity in comparison with blood due to a lower protein concentration. This allows for a more rapid return of pH in the CSF versus blood when there is an alteration in the concentration of CO_2. This is an important factor when comparing central to peripheral chemoreceptors and their collective import on the control of ventilation.

Various other receptors are present, all with significantly less effect on ventilation. Among these are pulmonary stretch receptors within the airway smooth muscle. These receptors signal distention of the lung, leading to a slowing of the respiratory rate via prolongation of the expiratory phase. Irritant receptors are found in airway epithelial cells and are stimulated by irritants, such as dust, cigarette smoke, and odors, leading to bronchoconstriction (Harries, Parkes, Lessof, & Orr, 1981). As such, they
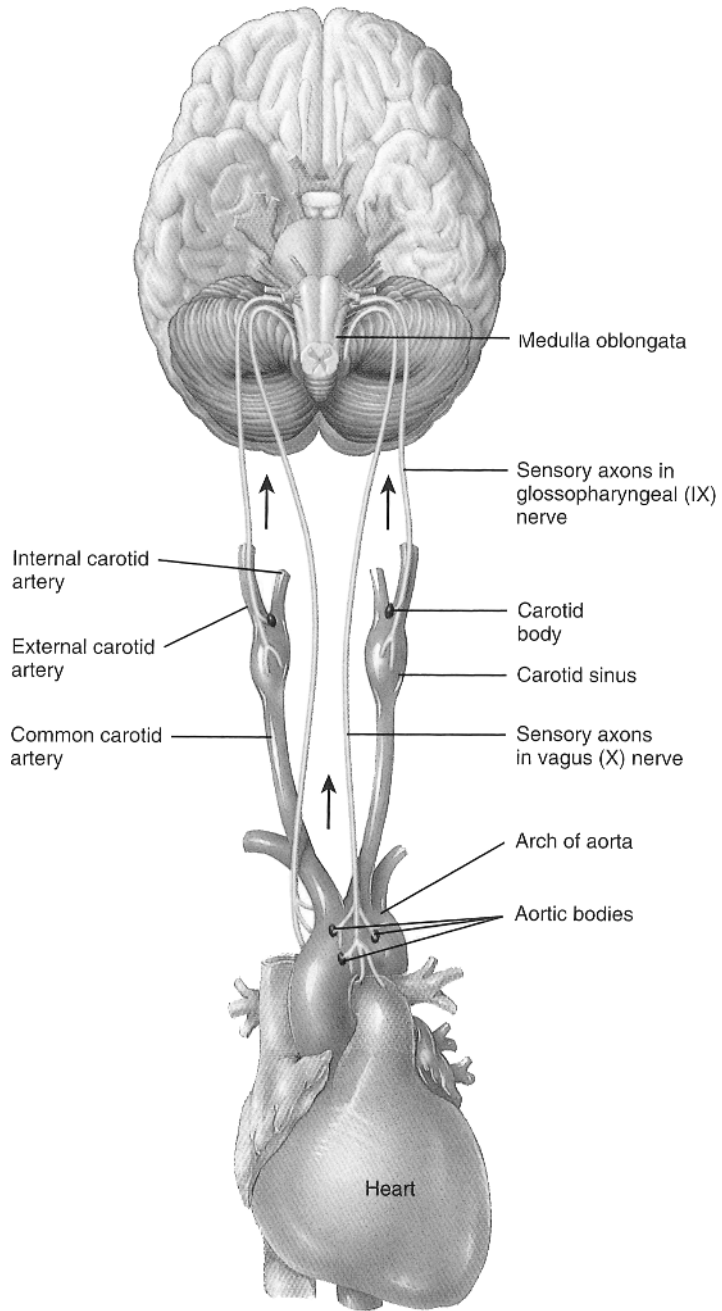
Figure 1.14 Locations of peripheral chemoreceptors. Reprinted from Tortora and Derrickson (2009), with permission from John Wiley & Sons, Inc.

play a role in the bronchospasm seen with asthma exacerbations upon exposure to environmental triggers. J-receptors are believed to be in the alveolar walls, in close proximity to the capillaries. They respond to the accumulation of interstitial fluid in the lung parenchyma, seen in pulmonary edema, and to pulmonary capillary engorgement.

All of these receptors, whether central or peripheral, send signals to the central controller of respiration found in the brain. The brain stem houses groups of neurons known as the respiratory centers. Coordination of the muscles of respiration is orchestrated by the groups of neurons. During studies conducted in the 1960s, the medulla was isolated as the location of respiratory control (Batsel, 1964). This was based on experiments that showed that despite transection of the brain above the pontomedullary junction (pons and medulla in the brain stem), rhythmic respiration continued, but transaction of the medulla and below led to termination of respiration (Levitzky, 2007) (see Figure 1.15).

The region of each collection of neurons has a distinct function. In the medulla, the nuclei in the ventral region control voluntary forced exhalation and can increase the force of inspiration. In the dorsal region of the medulla, the group of neurons controls inspiration.

During normal breathing, the ventral medulla area is quiet, as inspiration is signaled by the dorsal region leading to contraction of inspiratory
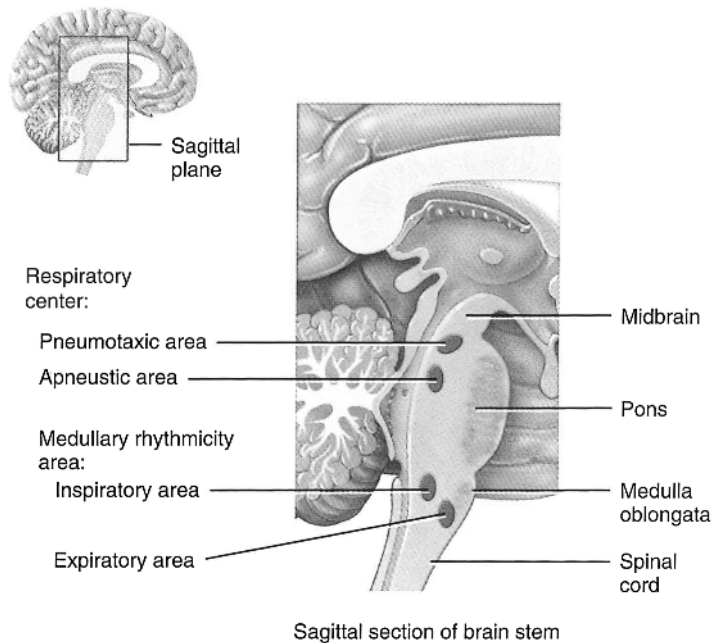

Figure 1.15 Locations of areas of the respiratory center. Reprinted from Tortora and Derrickson (2009), with permission from John Wiley & Sons, Inc.

muscles, and expiration is brought on by the natural chest wall recoil, discussed in the previous section on ventilation. However, as stated in that section, exhalation can become active (e.g., in exercise), during which the ventral medulla fires.

The apneustic center is located in the lower pons and is involved in the transition between inspiration and expiration. Its name is derived from the fact that when it sends stimulatory impulses to the dorsal medulla, it leads to prolongation of inspiration, causing long, deep breaths. This is seen in animal experiments when transection above this area leads to a prolonged inspiratory gasp followed by transient expiratory effort (apnea).

The pneumotaxic center is located in the upper pons and sends inhibitory impulses to the dorsal medulla, shortening inspiration and, as a result, leading to an increase in the respiratory rate. Sometimes it is viewed as an area that allows for small adjustments to respiration as normal rhythmic breathing still occurs with transaction of this area.

The cerebral cortex also has some, though limited, effect on ventilation. This is seen most notably with voluntary hyperventilation. Voluntary hypoventilation cannot be achieved to the same degree as hyperventilation because of the tight regulation of PCO_2 and PO_2.

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