Flow of air into and out of the lungs

Because air flows down a pressure gradient, the intra-alveolar pressure must be less than atmospheric pressure for air flow into the lungs during inspiration. Similarly, the intra-alveolar pressure must be greater than atmospheric pressure for air to flow out of the lungs during expiration. Changes in lung volume, and accordingly intra-alveolar pressure, are brought about indirectly by respiratory muscle activity.

The respiratory muscles that accomplish breathing do not act directly on the lungs to change their volume. Instead, these muscles change the volume of the thoracic cavity, causing a corresponding change in lung volume because the thoracic wall and lungs are linked together by the intrapleural fluid's cohesiveness and the transmural pressure gradient.

ONSET OF INSPIRATION: CONTRACTION OF INSPIRATORY MUSCLES

Before the beginning of inspiration, the respiratory muscles are relaxed, no air is flowing, and intra-alveolar pressure is equal to atmospheric pressure. The major inspiratory muscles-the muscles that contract to accomplish an inspiration during quiet breathing-include the diaphragm and external intercostal muscles (Figure 12-10). At the onset of inspiration, these muscles are stimulated to contract, enlarging the thoracic cavity. The major inspiratory muscle is the diaphragm, a sheet of skeletal muscle that forms the floor of the thoracic cavity and is innervated by the phrenic nerve. The relaxed diaphragm has a dome

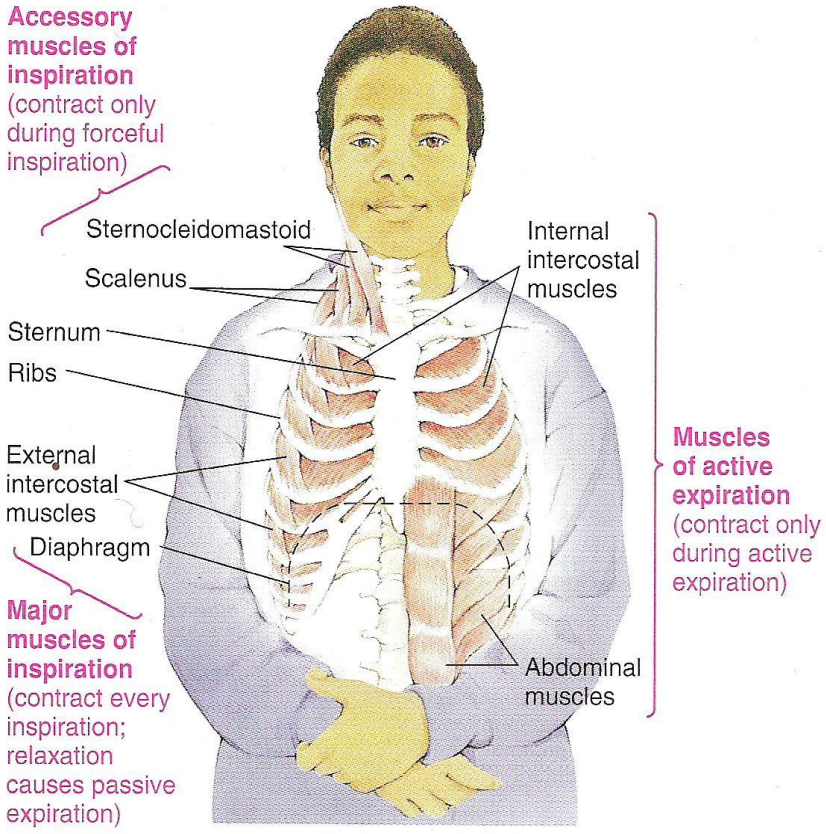


FIGURE 12-10

Anatomy of the respiratory muscles

shape that protrudes upward into the thoracic cavity When the diaphragm contracts (on stimulation by the phrenic nerve), it descends downward, enlarging the volume of the thoracic cavity by increasing its vertical (top-to-bottom) dimension (Figure 12-11a). The abdominal wall, if relaxed, bulges outward during inspiration as the descending diaphragm pushes the abdominal contents downward and forward. Seventy-five percent of the enlargement of the thoracic cavity during quiet inspiration is done by contraction of the diaphragm.

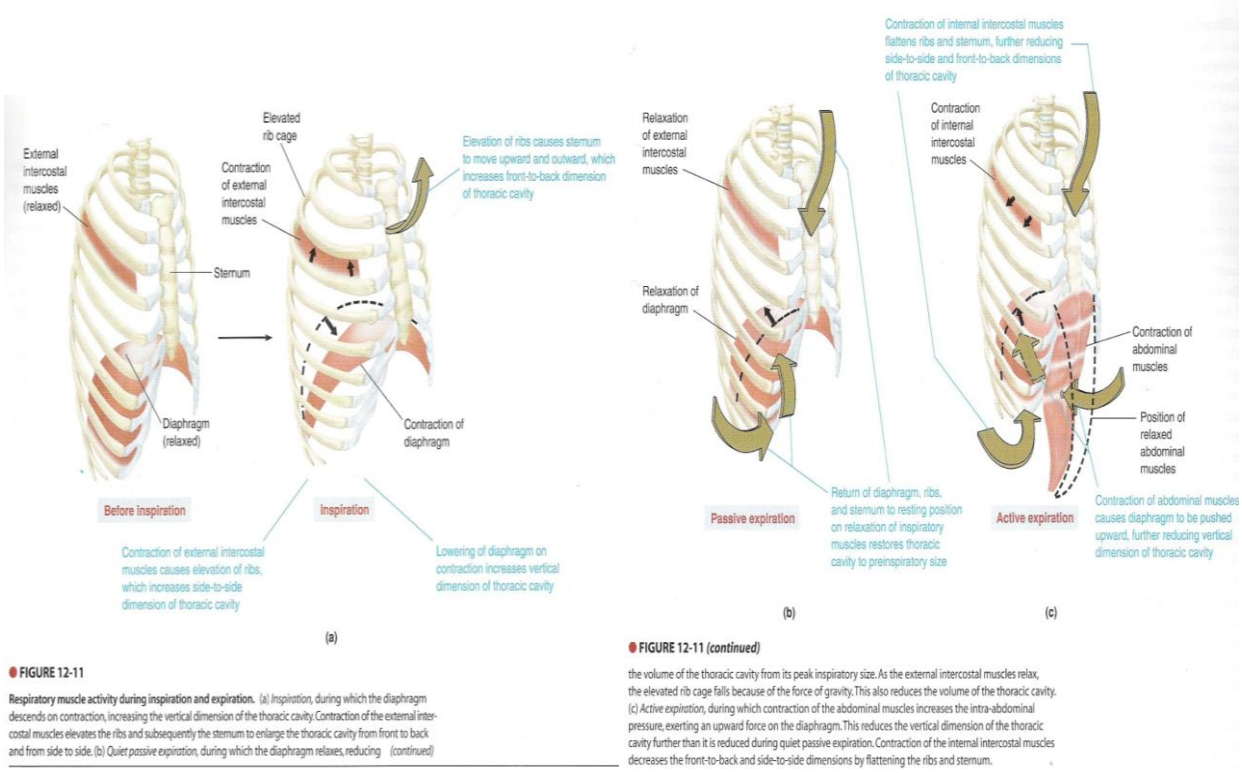


FIGURE 12-11

Respiratory muscle activity during inspiration and expiration. (a) *Inspiration*, during which the diaphragm descends on contraction, increasing the vertical dimension of the thoracic cavity. Contraction of the external intercostal muscles elevates the ribs and subsequently the sternum to enlarge the thoracic cavity from front to back and from side to side. (b) *Quiet passive expiration*, during which the diaphragm relaxes, reducing *(continued)*

FIGURE 12-11 *(continued)*

the volume of the thoracic cavity from its peak inspiratory size. As the external intercostal muscles relax, the elevated rib cage falls because of the force of gravity. This also reduces the volume of the thoracic cavity. (c) *Active expiration*, during which contraction of the abdominal muscles increases the intra-abdominal pressure, exerting an upward force on the diaphragm. This reduces the vertical dimension of the thoracic cavity further than it is reduced during quiet passive expiration. Contraction of the internal intercostal muscles decreases the front-to-back and side-to-side dimensions by flattening the ribs and sternum.

Two sets of intercostal muscles lie between the ribs (inter means "between"; costa means "rib"). The external intercostal muscles lie on top of the internal intercostal muscles. Contraction of the external intercostal muscles, whose fibers run downward and forward between adjacent ribs, enlarges the thoracic cavity in both the lateral (side-to-side) and anteroposterior (front-to-back) dimensions. When the external intercostal muscles contract, they elevate the ribs and subsequently the sternum upward and outward (Figure 12-11a).

Before inspiration, at the end of the preceding expiration, intra-alveolar pressure is equal to atmospheric pressure, so no air is flowing into or out of the lungs (Figure 12-12a). As the thoracic cavity enlarges, the lungs are also forced to expand to fill the larger thoracic cavity. As the lungs enlarge, the intra-alveolar pressure drops because the same number of air molecules now occupy a larger lung volume. In a typical inspiratory process, the intra-alveolar pressure drops 1 mm Hg to 759 mm Hg (Figure 12-12b). Because the intra--

alveolar pressure is now less than atmospheric pressure, air flows into the lungs down the pressure gradient from higher to lower pressure. Air continues to enter the lungs until no further gradient exists-that is, until intra-alveolar pressure equals atmospheric pressure. Thus lung expansion is not caused by movement of air into the lungs; instead, air flows into the lungs because of the fall in intra-alveolar pressure brought about by lung expansion.

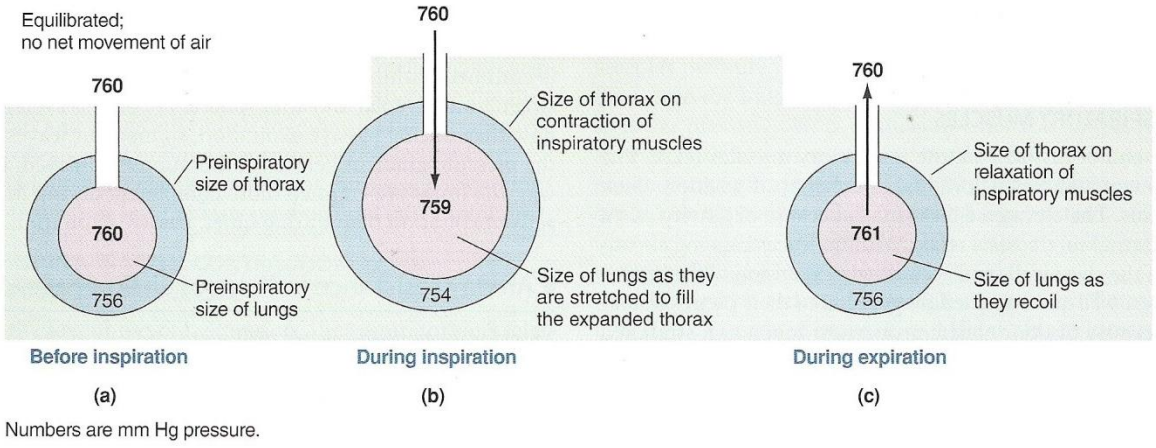


FIGURE 12-12

Changes in lung volume and intra-alveolar pressure during inspiration and expiration. (a) *Before inspiration,* at the end of the preceding expiration. Intra-alveolar pressure is equilibrated with atmospheric pressure and no air is flowing. (b) *Inspiration.* As the lungs increase in volume during inspiration, the intra-alveolar pressure decreases, establishing a pressure gradient that favors the flow of air into the alveoli from the atmosphere; that is, an inspiration occurs. (c) *Expiration.* As the lungs recoil to their preinspiratory size on relaxation of the inspiratory muscles, the intra-alveolar pressure increases, establishing a pressure gradient that favors the flow of air out of the alveoli into the atmosphere; that is, an expiration occurs.

During inspiration, the intrapleural pressure falls to 754 mm Hg as a result of expansion of the thorax. The resultant increase in the transmural pressure gradient during inspiration ensures that the lungs are stretched to fill the expanded thoracic cavity.

ROLE OF ACCESSORY INSPIRATORY MUSCLES

Deeper inspirations (more air breathed in) can be accomplished by contracting the diaphragm and external intercostal muscles more forcefully and by bringing the accessory inspiratory muscles into play to further enlarge the thoracic cavity. Contracting these accessory muscles, which are in the neck (Figure 12-10), raises the sternum and elevates the first two ribs, enlarging the upper portion of the thoracic cavity As the thoracic cavity increases even further in volume than under resting conditions, the lungs likewise expand even more, dropping the intra-alveolar pressure even further. Consequently, a larger inward flow of air occurs before equilibration with atmospheric pressure is achieved; that is, a deeper breath occurs.

At the end of inspiration, the inspiratory muscles relax. The diaphragm assumes its original

dome-shaped position when it relaxes. The elevated rib cage falls because of gravity when the external intercostals relax. With no forces causing expansion of the chest wall (and accordingly expansion of the lungs), the chest wall and stretched lungs recoil to their preinspiratory size because of their elastic properties, much as a stretched balloon would on release (Figure l2-11b). As the lungs recoil and become smaller in volume, the intra-alveolar pressure rises, because the greater number of air molecules contained within the larger lung volume at the end of inspiration are now compressed into a smaller volume. In a resting expiration, the intra-alveolar pressure increases about 1 mm Hg above atmospheric level to 761 mm Hg (Figure l2-l2c). Air now leaves the lungs down its pressure gradient from high intra-alveolar pressure to lower atmospheric pressure. Outward flow of air ceases when intra-alveolar pressure becomes equal to atmospheric pressure and a pressure gradient no longer exists. Figure 12-13 summarizes the intra-alveolar and intrapleural pressure changes that take place during one respiratory cycle.

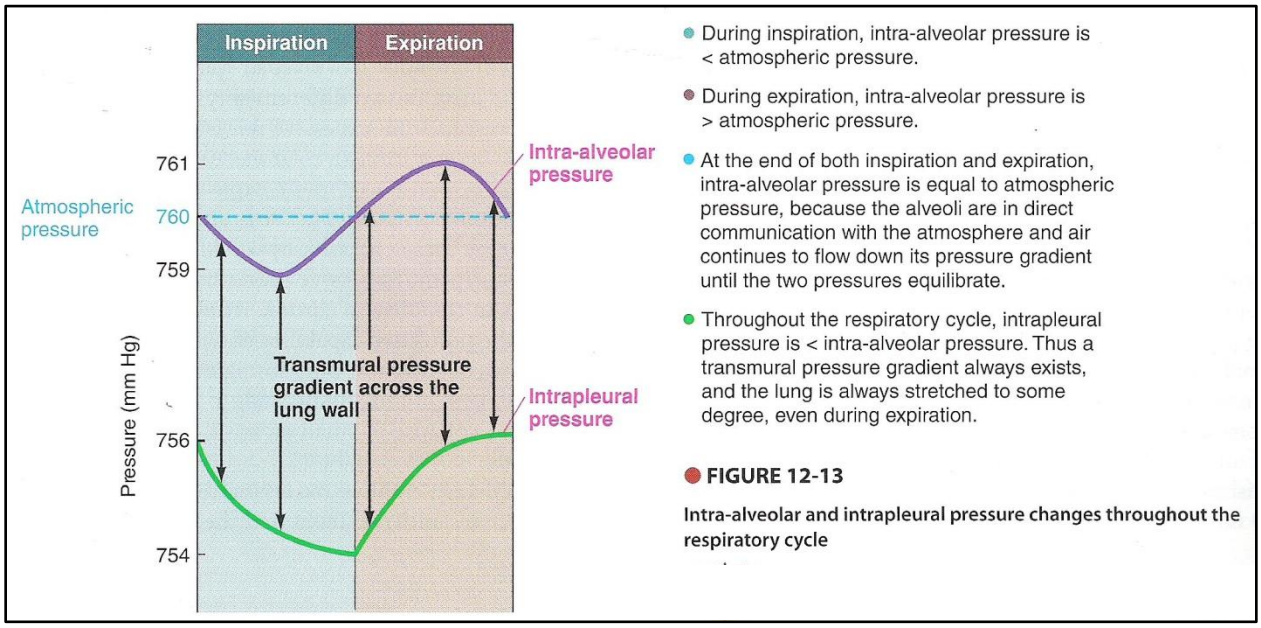


FIGURE 12-13

Intra-alveolar and intrapleural pressure changes throughout the respiratory cycle

FORCED EXPIRATION: CONTRACTION OF EXPIRATORY MUSCLES

During quiet breathing, expiration is normally a passive process, because it is accomplished by elastic recoil of the lungs on relaxation of the inspiratory muscles, with no muscular exertion or energy expenditure required. In contrast, inspiration is always active, because it is brought about only by contraction of inspiratory muscles at the expense of energy use. To empty the lungs more completely and more rapidly than is accomplished during quiet breathing, as during the deeper breaths accompanying exercise, expiration does become active. The intra-alveolar pressure must be increased even further above atmospheric pressure than can be accomplished by simple relaxation of the inspiratory muscles and elastic recoil

of the lungs. To produce such a forced, or active, expiration, expiratory muscles must contract to further reduce the volume of the thoracic cavity and lungs. The most important expiratory muscles are the muscles of the abdominal wall (Figure l2-10). As the abdominal muscles contract, the resultant increase in intra-abdominal pressure exerts an upward force on the diaphragm, pushing it further up into the thoracic cavity than its relaxed position, thus decreasing the vertical dimension of the thoracic cavity even more. The other expiratory muscles are the internal intercostal muscles, whose contraction pulls the ribs downward and inward, flattening the chest wall and further decreasing the size of the thoracic cavity; this action is just the opposite of that of the external intercostal muscles (Figure 12-11c).

Airway resistance influences airflow rates

Thus far we have discussed airflow in and out of the lungs as a function of the magnitude of the pressure gradient between the alveoli and the atmosphere. However, just as flow of blood through the blood vessels depends not only on the pressure gradient but also on the resistance to the flow offered by the vessels, so it is with airflow:

$$F = \frac{\Delta P}{R}$$

where

F = airflow rate

ΔP = difference between atmospheric and intra-alveolar pressure (pressure gradient)

R = resistance of airways, determined by their radius

The primary determinant of resistance to airflow is the radius of the conducting airways.

Normally, modest adjustments in airway size can be accomplished by autonomic nervous system regulation to suit the body's needs. Parasympathetic stimulation, which occurs in quiet, relaxed situations when the demand for airflow is low, promotes bronchiolar smooth muscle contraction, which increases airway resistance by producing **bronchoconstriction** (a reduction in bronchiolar caliber). In contrast, sympathetic stimulation and to a greater extent its associated hormone, epinephrine, bring about **bronchodilation** (an increase in bronchiolar caliber) and decreased airway resistance by promoting bronchiolar smooth-muscle relaxation. Thus during periods of sympathetic domination, when increased demands for O_2 uptake are actually or potentially placed on the body, bronchodilation ensures that the pressure gradients established by respiratory muscle activity can achieve maximum airflow rates with minimum resistance. Because of this bronchodilator action, epinephrine or similar drugs are useful therapeutic tools to counteract airway constriction in patients with bronchial spasms.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a group of lung diseases characterized by increased airway resistance resulting from narrowing of the lumen of the lower airways. When airway resistance increases, a larger pressure gradient must be established to maintain even a normal airflow rate. For example, if resistance is doubled by narrowing of airway lumens, ΔP must be doubled through increased respiratory muscle exertion to induce the same flow rate of air in and out of the lungs as a normal individual accomplishes during quiet breathing. Accordingly, patients with CODP must work harder to breathe. Chronic obstructive pulmonary disease encompasses three chronic (long-term) diseases: *chronic bronchitis, asthma,* and *emphysema.*

CHRONIC BRONCHITIS

Chronic bronchitis is a long-term inflammatory condition of the lower respiratory airways, generally triggered by frequent exposure to irritating cigarette smoke, polluted air, or allergens. In response to the chronic irritation, the airways become narrowed by prolonged edematous thickening of the airway linings, coupled with overproduction of thick mucus. Despite frequent coughing associated with the chronic irritation, the plugged mucus often cannot be satisfactorily removed. Pulmonary bacterial infections frequently occur, because the accumulated mucus serves as an excellent medium for bacterial growth.

ASTHMA

In asthma, airway obstruction is due to (1) thickening of airway walls, brought about by inflammation and histamine-induced edema; (2) plugging of the airways by excessive secretion of very thick mucus; and (3) airway hyperresponsiveness, characterized by profound constriction of the smaller airways caused by trigger-induced spasm of the smooth muscle in the walls of these airways. Triggers that lead to these inflammatory changes and the exaggerated bronchoconstrictor response include repeated exposure to allergens (such as dust mites or pollen), irritants (as in cigarette smoke), and infections. A growing number of studies suggest that long-term infections with *Chlamydia pneumaniae,* a common cause of lung infections, may underlie up to half of the adult cases of asthma. In severe asthmatic attacks, pronounced clogging and narrowing of the airways can cut off all airflow, leading to death. Asthma is the most common chronic childhood disease.

EMPHYSEMA

Emphysema is characterized by (1) collapse of the smaller airways and (2) breakdown of alveolar walls. This irreversible condition can arise in two different ways. Most commonly, emphysema results from excessive release of destructive enzymes such as

trypsin from alveolar macrophages as a defense mechanism in response to chronic exposure to inhaled cigarette smoke or other irritants. The lungs are normally protected from damage by these enzymes by α_1-antitrypsin, a protein that inhibits trypsin. Excessive secretion of these destructive enzymes in response to chronic irritation, however, can overwhelm the protective capability of α_1-antitrypsin so that these enzymes destroy not only foreign materials but lung tissue as well. Loss of lung tissue leads to breakdown of alveolar walls and collapse of small airways, the characteristics of emphysema.

Less frequently, emphysema arises from a genetic inability to produce α1-antitrypsin so that the lung tissue has no protection from trypsin. The unprotected lung tissue gradually disintegrates under the influence of even small amounts of macrophage-released enzymes, in the absence of chronic exposure to inhaled irritants.

Elastic behavior of the lungs

During the respiratory cycle, the lungs alternately expand during inspiration and recoil during expiration. What properties of the lungs enable them to behave like balloons, being stretchable and then snapping back to their resting position when the stretching forces are removed? Two interrelated concepts are involved in pulmonary elasticity: *compliance* and *elastic recoil.*

The term compliance refers to how much effort is required to stretch or distend the lungs. A highly compliant lung stretches farther for a given increase in the pressure difference than a less compliant lung does. Stated another way, the lower the compliance of the lungs, the larger the transmural pressure gradient that must be created during inspiration to produce normal lung expansion. Therefore, the less compliant the lungs, the more work required to produce a given degree of inflation. A poorly compliant lung is referred to as a "stiff" lung, because it lacks normal stretchability.

Respiratory compliance can be decreased by a number of factors, as in *pulmonary fibrosis*, where normal lung tissue is replaced with scar-forming fibrous connective tissue as a result of chronically breathing in asbestos fibers or similar irritants.

The term elastic recoil refers to how readily the lungs rebound after having been stretched. It is responsible for the lungs returning to their preinspiratory volume when the inspiratory muscles relax at the end of inspiration.

Pulmonary elastic behavior depends mainly on two factors: *highly elastic connective tissue* in the lungs and alveolar *surface tension.*

PULMONARY ELASTIC CONNECTIVE TISSUE

Pulmonary connective tissue contains large quantities of elastin fibers. Not only do these fibers have elastic properties themselves, but they also are arranged into meshwork that amplifies their elastic behavior

ALVEOLAR SURFACE TENSION

An even more important factor influencing elastic behavior of the lungs is the alveolar surface tension displayed by the thin liquid film that lines each alveolus. At an air-water interface. the water molecules at the surface are more strongly attracted to other surrounding water molecules than to the air above the surface. This unequal attraction produces a force known as surface tension at the surface of the liquid. Surface tension has a twofold effect. First, the liquid layer resists any force that increases its surface area; that is, it opposes expansion of the alveolus, because the surface water molecules oppose being pulled apart. Accordingly, the greater the surface tension, the less compliant the lungs. Second, the liquid surface area tends to shrink as small as possible, because the surface water molecules, being preferentially attracted to each other, try to get as close together as possible. Thus the surface tension of the liquid lining an alveolus tends to reduce alveolus size, squeezing in on the air inside. This property, along with the rebound of the stretched elastin fibers, produces the lungs' elastic recoil back to their preinspiratory size when inspiration is over.

Pulmonary surfactant decreases surface tension

The cohesive forces between water molecules are so strong that if the alveoli were lined with water alone, surface tension would be so great that the lungs would collapse. The recoil force attributable to the elastin fibers and high surface tension would exceed the opposing stretching force of the transmural pressure gradient. Furthermore, the lungs would be very poorly compliant, so exhausting muscular efforts would be required to accomplish stretching and inflation of the alveoli. The tremendous surface tension of pure water is normally counteracted by pulmonary surfactant.

PULMONARY SURFACTANT

Pulmonary surfactant is a complex mixture of lipids and proteins secreted by the Type II alveolar cells **(**Figure 12-3a). It intersperses between the water molecules in the fluid lining the alveoli and lowers alveolar surface tension, because the cohesive force between a water molecule and an adjacent pulmonary surfactant molecule is very low. By lowering alveolar surface tension, pulmonary surfactant provides two important benefits:

(1) it increases pulmonary compliance, reducing the work of inflating the lungs; and (2) it reduces the lungs' tendency to recoil, so they do not collapse as readily

The opposing forces acting on the lung (that is, the forces keeping the alveoli open and the countering forces that promote alveolar collapse) are summarized in Table 12-1.

TABLE 12-1

Opposing Forces Acting on the Lung

FORCES KEEPING THE ALVEOLI OPEN	FORCES PROMOTING ALVEOLAR COLLAPSE
Transmural pressure gradient	Elasticity of stretched pulmonary connective tissue fibers
Pulmonary surfactant (which opposes alveolar surface tension)	Alveolar surface tension

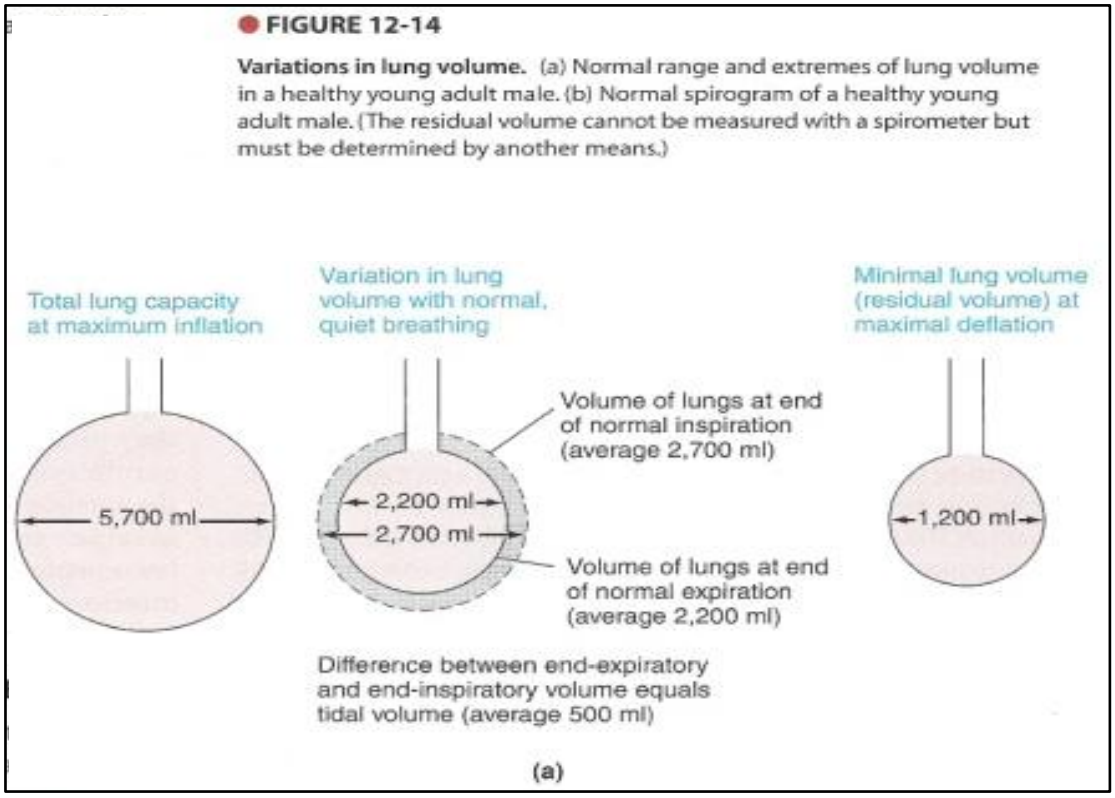
NEW BORN RESPIRATORY DISTRESS SYNDROME

Developing fetal lungs normally cannot synthesize pulmonary surfactant until late in pregnancy especially in an infant born prematurely, not enough pulmonary surfactant may be produced to reduce the alveolar surface tension to manageable levels. The resulting collection of symptoms is termed **newborn respiratory distress syndrome**. The infant must make very strenuous inspiratory efforts to overcome the high surface tension in an attempt to inflate the poorly compliant lungs. Moreover, the work of breathing is further increased because the alveoli, in the absence of surfactant, tend to collapse almost completely during each expiration. Lung expansion may require transmural pressure gradients of 20 to 30 mm Hg (compared to the normal 4 to 6 mm Hg) to overcome the tendency of surfactant-deprived alveoli to collapse.

The lungs normally operate at about "half full"

On average, in healthy young adults, the maximum air that the lungs can hold is about 5.7 liters in males (4.2 liters in females). Anatomic build, age, the distensibility of the lungs, and the presence or absence of respiratory disease affect this total lung capacity. Normally, during quiet breathing the lungs are nowhere near maximally inflated nor are

they deflated to their minimum volume. Thus the lungs normally remain moderately inflated throughout the respiratory cycle. At the end of a normal quiet expiration, the lungs still contain about 2200 ml of air. During each typical breath under resting conditions, about 500 ml of air are inspired and the same quantity is expired, so during quiet breathing the lung volume varies between 2200 ml at the end of expiration to 2700 ml at the end of inspiration (Figure 12-14a). During maximal expiration, lung volume can decrease to 1200 ml in males (1000 ml in females).



An important outcome of not being able to empty the lungs completely is that even during maximal expiratory efforts, gas exchange can still continue between blood flowing through the lungs and the remaining alveolar air. Another advantage of the lungs not completely emptying with each breath is a reduction in the work of breathing.

LUNG VOLUMES AND CAPACITIES

Basically, a spirometer consists of an air-filled drum floating in a water-filled chamber. As the person, breathes air in and out of the drum through a tube connecting the mouth to the air chamber, the drum rises and falls in the water chamber (Figure 12-15). This rise and fall can be recorded as a spirogram, which is calibrated to volume changes. The pen records inspiration as an upward deflection and expiration as a downward deflection.

FIGURE 12-15

A spirometer. A spirometer is a device that measures the volume of air breathed in and out; it consists of an air-filled drum floating in a water-filled chamber. As a person breathes air in and out of the drum through a connecting tube, the resultant rise and fall of the drum are recorded as a spirogram, which is calibrated to the magnitude of the volume change.

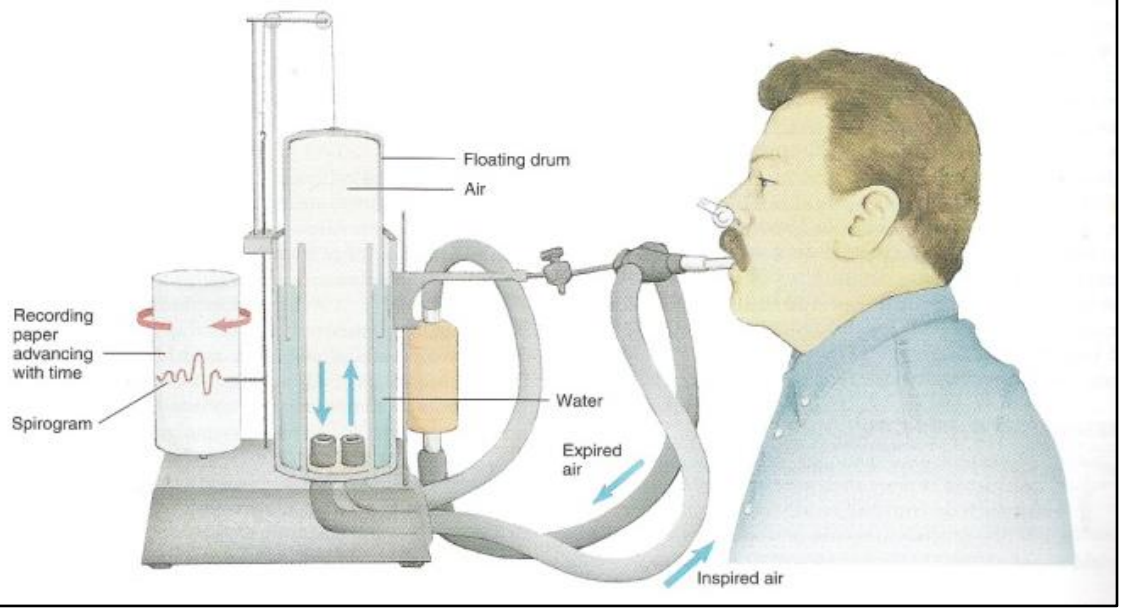


Figure 12-14b is a hypothetical example of a spirogram in a healthy young adult male. Generally, the values are lower for females. The following lung volumes and lung capacities can be determined.

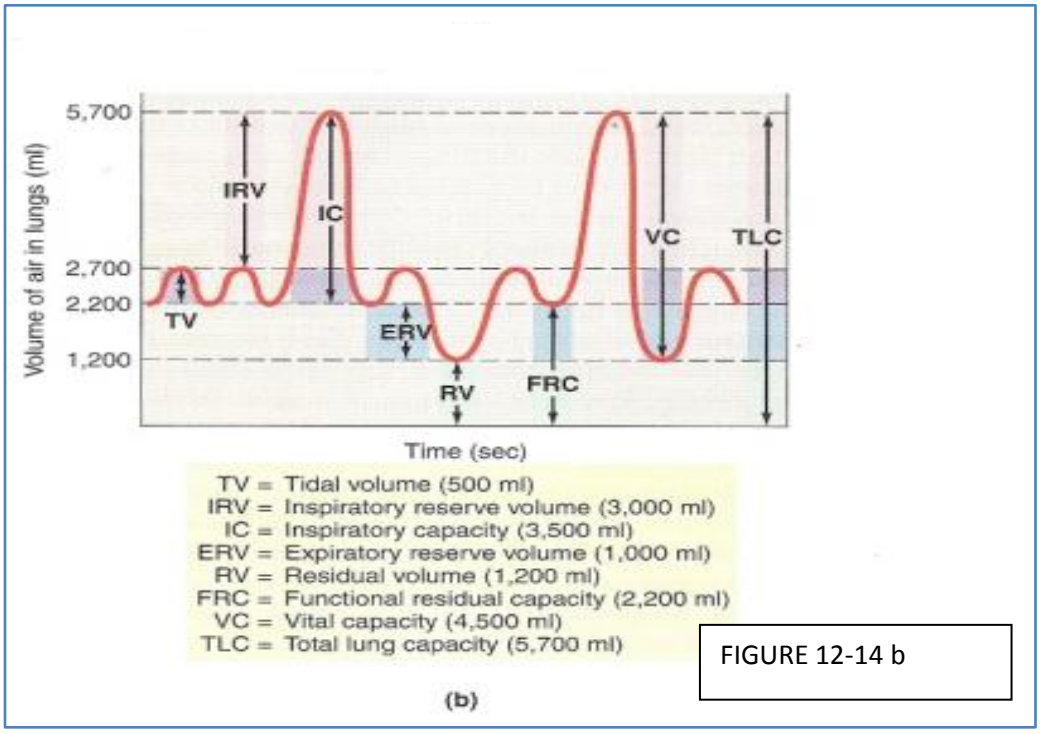


FIGURE 12-14 b

- **Tidal volume (TV).** The volume of air entering or leaving the lungs during a single breath. Average value under resting conditions = 500 ml.
- **Inspiratory reserve volume (IRV).** The extra volume of air that can be maximally inspired over and above the typical resting tidal volume. The IRV is accomplished by maximal contraction of the diaphragm, external intercostal muscles, and accessory inspiratory muscles. Average value = 3000 ml.
- **Inspiratory capacity (IC).** The maximum volume of air that can be inspired at the end of a normal quiet expiration (IC = IRV + TV). Average value = 3500 ml.
- **Expiratory reserve volume (ERV).** The extra volume of air that can be actively expired by maximally contracting the expiratory muscles beyond that normally passively expired at the end of a typical resting tidal volume. Average value = 1000 ml.
- **Residual volume (RV).** The minimum volume of air remaining in the lungs even after a maximal expiration. Average value = 1200 ml. The residual volume cannot be measured directly with a spirometer, because this volume of air does not move in and out of the lungs. It can be determined indirectly, however, through gas dilution techniques involving inspiration of a known quantity of a harmless tracer gas such as helium.
- **Functional residual capacity (FRC).** The volume of air in the lungs at the end of a normal passive expiration (FRC = ERV + RV). Average value = 2200 ml.
- **Vital capacity (VC).** The maximum volume of air that can be moved out during a single breath following a maximal inspiration. Average value = 4500 ml.
- **Total lung capacity (TLC).** The maximum volume of air that the lungs can hold (TLC = VC + RV). Average value = 5700 ml.

GAS EXCHANGE

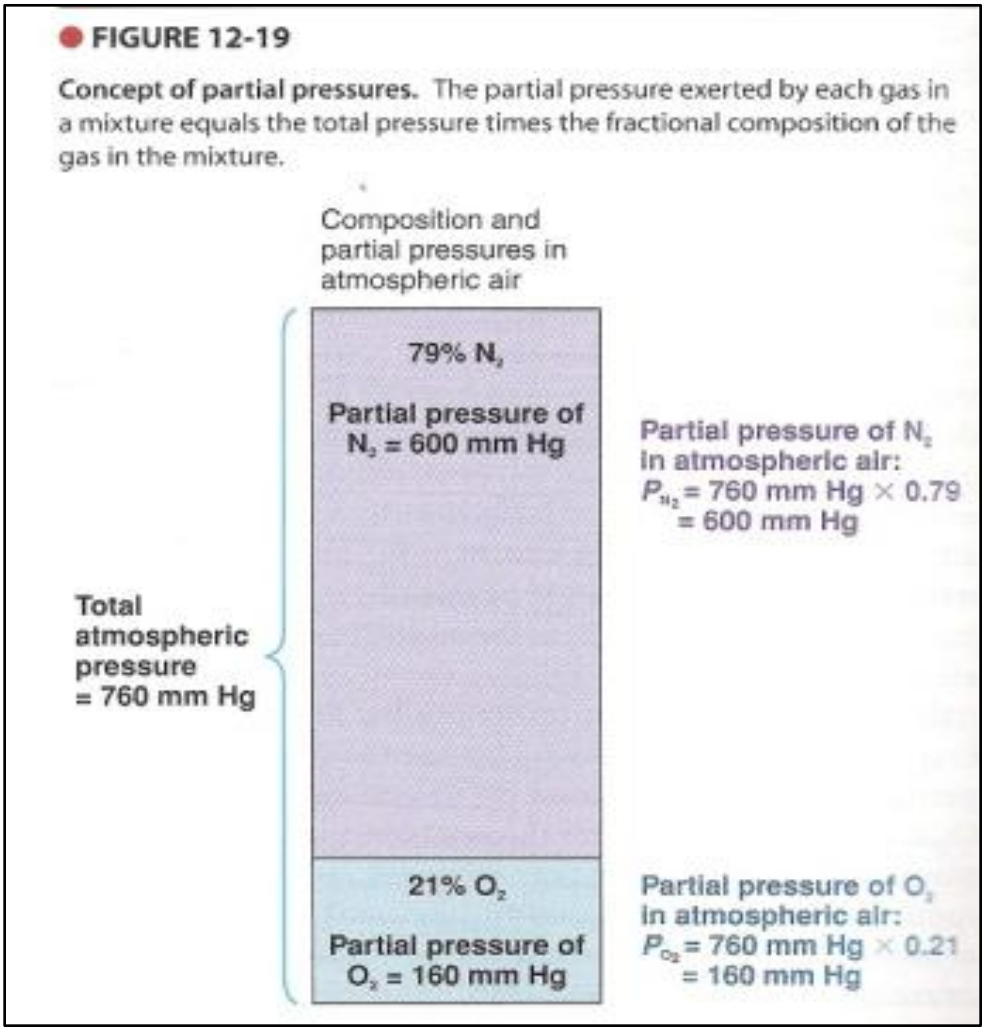
The ultimate purpose of breathing is to provide a continual supply of fresh O_2 for pickup by the blood and to constantly remove CO_2 unloaded from the blood. Blood acts as a transport system for O_2 and CO_2 between the lungs and tissues, with the tissue cells extracting O_2 from the blood and eliminating CO_2 into it.

Gases move down partial pressure gradients.

Gas exchange at both the pulmonary capillary and the tissue capillary levels involves simple passive diffusion of O_2 and CO_2 down *partial pressure gradients.* No active transport mechanisms exist for these gases.

PARTIAL PRESSURES

Atmospheric air is a mixture of gases; typical dry air contains about 79% nitrogen (N_2) and 21% O_2 with almost negligible percentages of CO_2, H_2O vapor, other gases, and pollutants. Altogether, these gases exert a total atmospheric pressure of 760 mm Hg at sea level. This total pressure is equal to the sum of the pressures that each gas in the mixture partially contributes. The pressure exerted by a particular gas is directly proportional to the percentage of that gas in the total air mixture. Because 79% of the air consists of N_2 molecules, 79% of the 760 mm Hg atmospheric pressure, or 600 mm Hg, is exerted by the N_2 molecules. Similarly, because O_2 represents 21 % of the atmosphere, 21% of the 760 mm Hg atmospheric pressure, or 160 mm Hg, is exerted by O_2 (Figure 12-19). The individual pressure exerted independently by a particular gas within a mixture of gases is known as its partial pressure, designated by P_{gas}. Thus the partial pressure of O_2 in atmospheric air, P_{O_2} is normally 160 mm Hg. The atmospheric partial pressure of CO_2, P_{CO_2} is negligible at 0.23 mm Hg.



Gases dissolved in a liquid such as blood or another body fluid also exert a partial pressure. The greater the partial pressure of a gas in a liquid, the more of that gas dissolved.

PARTIAL PRESSURE GRADIENTS

A difference in partial pressure between capillary blood and surrounding structures is known as a partial pressure gradient. Partial pressure gradients exist between the alveolar air and pulmonary capillary blood. Similarly, partial pressure gradients exist between systemic capillary blood and surrounding tissues. A gas always diffuses down its partial pressure gradient from the area of higher partial pressure to the area of lower partial pressure, similar to diffusion down a concentration gradient.

Oxygen enters and CO_2 leaves the blood in the lungs passively down partial pressure gradients

ALVEOLAR P_{O_2} AND P_{CO_2}

Alveolar air is not of the same composition as inspired atmospheric air, for two reasons. First, as soon as atmospheric air enters the respiratory passages, exposure to the moist airways saturates it with H_2O. Like any other gas, water vapor exerts a partial pressure. Humidification of inspired air in effect "dilutes" the partial pressure of the inspired gases, because the sum of the partial pressures must total the atmospheric pressure. Second, alveolar P_{O_2} is also lower than atmospheric P_{O_2}because fresh inspired air is mixed with the large volume of old air that remained in the lungs and dead space at the end of the preceding expiration (the functional residual capacity). At the end of inspiration, less than 15% of the air in the alveoli is fresh air. As a result of humidification and the small turnover of alveolar air, the average alveolar P_{O_2} is 100 mm Hg, compared to the atmospheric P_{O_2} of 160 mm Hg.

It is logical to think that alveolar P_{O_2} would increase during inspiration with the arrival of fresh air and would decrease during expiration. Only small fluctuations of a few mm Hg occur, however, for two reasons. First, only a small proportion of the total alveolar air is exchanged with each breath. The relatively small volume of inspired, high-P_{O_2} air is quickly mixed with the much larger volume of retained alveolar air, which has a lower P_{O_2} Thus the O_2 in the inspired air can only slightly elevate the level of the total alveolar P_{O_2}. Even this potentially small elevation of P_{O_2} is diminished for another reason. Oxygen is continually moving by passive diffusion down its partial pressure gradient from the alveoli into the blood. The O_2 arriving in the alveoli in the newly inspired air simply replaces the O_2 diffusing out of the alveoli into the pulmonary capillaries. Therefore, alveolar P_{O_2}remains relatively constant at about 100 mm Hg throughout the respiratory cycle. Because pulmonary blood P_{O_2} equilibrates with alveolar P_{O_2}, the P_{O_2} of the blood leaving the lungs likewise remains fairly constant at this same value.

Accordingly, the amount of O_2 in the blood available to the tissues varies only slightly during the respiratory cycle.

A similar situation exists in reverse for CO_2, Carbon dioxide, which is continually produced by the body tissues as a metabolic waste product, is constantly added to the blood at the level of the systemic capillaries. In the pulmonary capillaries, CO_2 diffuses down its partial pressure gradient from the blood into the alveoli and is subsequently removed from the body during expiration. As with O_2, alveolar P_{CO_2} remains fairly constant throughout the respiratory cycle but at a lower value of 40 mm Hg.

P_{O_2} AND P_{CO_2} GRADIENTS ACROSS THE PULMONARY CAPILLARIES

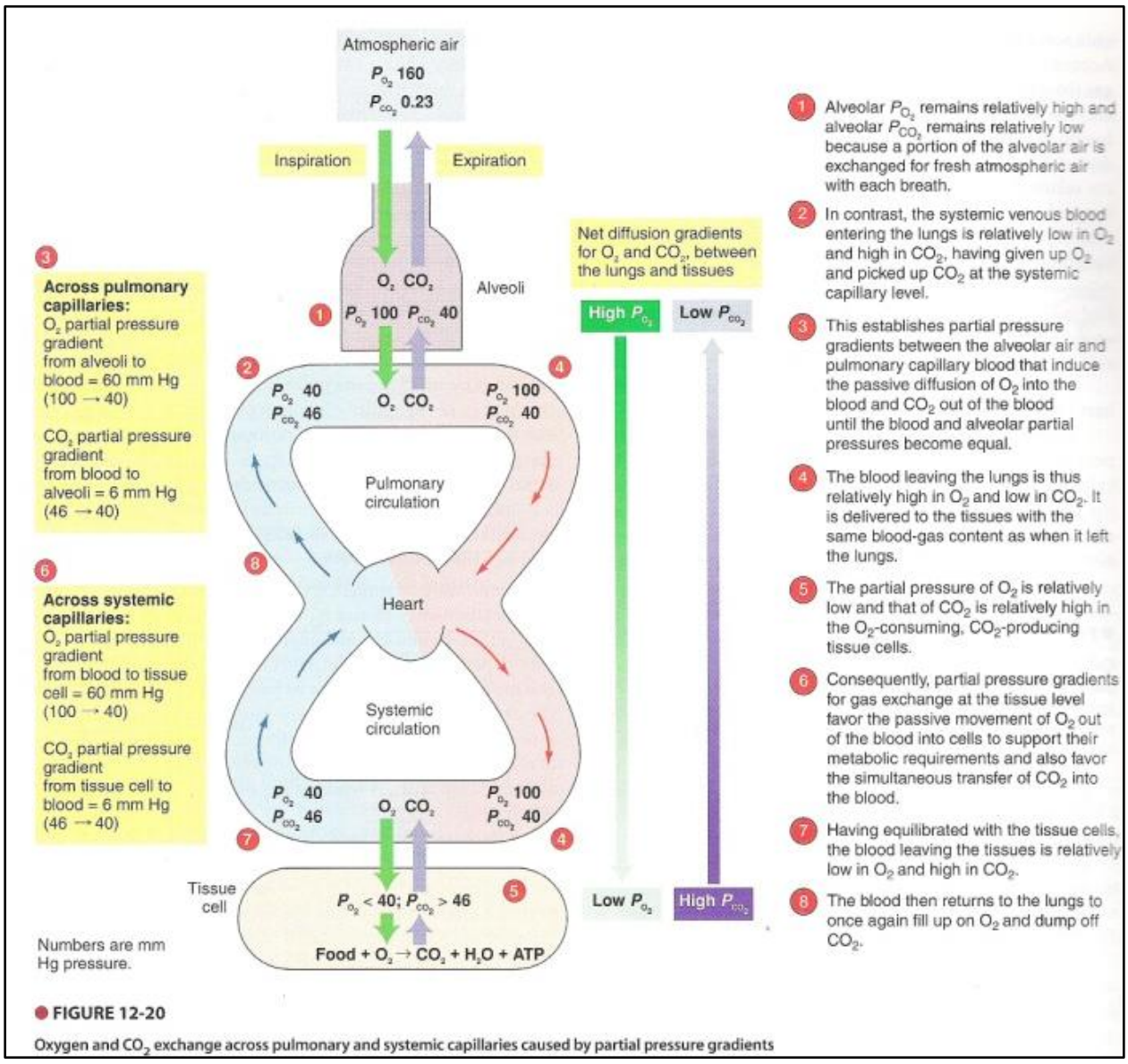


FIGURE 12-20

Oxygen and CO_2 exchange across pulmonary and systemic capillaries caused by partial pressure gradients

As blood passes through the lungs, it picks up O_2 and gives up CO_2 simply by diffusion down partial pressure gradients that exist between the blood and alveoli. Ventilation constantly replenishes alveolar O_2 and removes CO_2, thus maintaining the appropriate partial pressure gradients between the blood and alveoli. The blood entering the pulmonary capillaries is systemic venous blood pumped to the lungs through the pulmonary arteries. This blood, having just returned from the body tissues, is relatively low in O_2 with a P_{O_2} of 40 mm Hg, and is relatively high in CO_2, with a P_{CO_2} of 46 mm Hg. As this blood flows through the pulmonary capillaries, it is exposed to alveolar air (Figure 12-20). Because the alveolar P_{O_2} at 100 mm Hg is higher than the P_{O_2} of 40 mm Hg in the blood entering the lungs, O_2 diffuses down its partial pressure gradient from the alveoli into the blood until no further gradient exists. As the blood leaves the pulmonary capillaries, it has a P_{O_2} equal to alveolar P_{O_2} at 100 mm Hg.

The partial pressure gradient for CO_2 is in the opposite direction. Blood entering the pulmonary capillaries has a P_{CO_2} of 46 mm Hg, whereas alveolar P_{CO_2} is only 40 mm Hg. Carbon dioxide diffuses from the blood into the alveoli until blood P_{CO_2} equilibrates with alveolar P_{CO_2}.Thus the blood leaving the pulmonary capillaries has a P_{CO_2} of 40 mm Hg. After leaving the lungs, the blood, which now has a P_{O_2} of 100 mm Hg and a P_{CO_2} of 40 mm Hg, is returned to the heart, then pumped out to the body tissues as systemic arterial blood.

The CO_2 remaining in the blood even after passage through the lungs plays an important role in the acid-base balance of the body, because CO_2 generates carbonic acid. Furthermore, arterial P_{CO_2} is important in driving respiration. This mechanism will be described later.

The amount of O_2 picked up in the lungs matches the amount extracted and used by the tissues. When the tissues metabolize more actively (for example, during exercise), they extract more O_2 from the blood, reducing the systemic venous P_{O_2} even lower than 40 mm Hg-for example, to a P_{O_2} of 30 mm Hg. This additional transfer of O_2 into the blood replaces the increased amount of O_2 consumed, so O_2 uptake matches O_2 use even when O_2 consumption increases. At the same time that more O_2 is diffusing from the alveoli into the blood because of the increased partial pressure gradient, ventilation is stimulated so that O_2, enters the alveoli more rapidly from the atmosphere to replace the O_2 diffusing into the blood. Similarly, the amount of CO_2 given up to the alveoli from the blood matches the amount of CO_2 picked up at the tissues.

Factors other than the partial pressure gradient influence the rate of gas transfer.

Several pathologic conditions can markedly reduce pulmonary surface area and, in turn, decrease

the rate of gas exchange. Most notably, in *emphysema* surface area is reduced. Inadequate gas exchange can also occur when the thickness of the barrier separating the air and blood is pathologically increased, because a gas takes longer to diffuse through the greater thickness. Thickness increases in (1) *pulmonary edema*, an excess accumulation of interstitial fluid between the alveoli and pulmonary capillaries caused by pulmonary inflammation or left-sided congestive heart failure; *(2) pulmonary fibrosis* involving replacement of delicate lung tissue with thick fibrous tissue in response to certain chronic irritants; and (3) *pneumonia*, which is characterized by inflammatory fluid accumulation within or around the alveoli.

Gas exchange across the systemic capillaries

Just as they do at the pulmonary capillaries, O_2 and CO_2 move between the systemic capillary blood and the tissue cells by simple passive diffusion down partial pressure gradients. Refer again to Figure 12-20. The arterial blood that reaches the systemic capillaries is essentially the same blood that left the lungs by means of the pulmonary veins, because the only two places in the entire circulatory system at which gas exchange can take place are the pulmonary capillaries and the systemic capillaries. The arterial P_{O_2} is 100 mm Hg, and the arterial P_{CO_2} is 40 mm Hg, the same as alveolar P_{O_2} and P_{CO_2}.

P_{O_2} AND P_{CO_2} GRADIENTS ACROSS THE SYSTEMIC CAPILLARIES

Cells constantly consume O_2 and produce CO_2 through oxidative metabolism. Cellular P_{O_2} averages about 40 mm Hg and P_{CO_2} about 46 mm Hg, although these values are highly variable, depending on the level of cellular metabolic activity. Oxygen moves by diffusion down its partial pressure gradient from the entering systemic capillary blood (P_{O_2} = 100 mm Hg) into the adjacent cells (P_{O_2} = 40 mm Hg) until equilibrium is reached. Therefore, the P_{O_2} of venous blood leaving the systemic capillaries is equal to the tissue P_{O_2} at an average of 40 mm Hg.

The reverse situation exists for CO_2, Carbon dioxide rapidly diffuses out of the cells (P_{CO_2} = 46 mm Hg) into the entering capillary blood (P_{CO_2} = 40 mm Hg) down the partial pressure gradient created by the ongoing production of CO_2, Transfer of CO_2 continues until blood P_{CO_2} equilibrates with tissue P_{CO_2}. Accordingly, blood leaving the systemic capillaries has an average P_{CO_2} of 46 mm Hg. This systemic venous blood, which is relatively low in O_2 (P_{O_2} = 40 mm Hg) and relatively high in CO_2 (P_{CO_2} = 46 mm Hg), returns to the heart and is subsequently pumped to the lungs as the cycle repeats itself.

The more actively a tissue is metabolizing, the lower the cellular P_{O_2} falls and the higher the cellular P_{CO_2} rises. As a consequence of the larger blood-to-cell partial pressure gradients, more

O_2 diffuses from the blood into the cells, and more CO_2 moves in the opposite direction before blood P_{O_2} and P_{CO_2} achieve equilibrium with the surrounding cells. Thus the amount of O_2 transferred to the cells and the amount of CO_2 carried away from the cells both depend on the rate of cellular metabolism.

GAS TRANSPORT

Oxygen picked up by the blood at the lungs must be transported to the tissues for cell use. Conversely, CO_2 produced at the cell level must be transported to the lungs for elimination.

Most O_2 in the blood is transported bound to hemoglobin

Oxygen is present in the blood in two forms: physically dissolved and chemically bound to hemoglobin (Table 12-3).

TABLE 12-3
Methods of Gas Transport in the Blood

GAS	METHOD OF TRANSPORT IN BLOOD	PERCENTAGE CARRIED IN THIS FORM
O_2	Physically dissolved	1.5
	Bound to hemoglobin	98.5
CO_2	Physically dissolved	10
	Bound to hemoglobin	30
	As bicarbonate (HCO_3^-)	60

PHYSIALLY DISSOLVED O_2

Very little O_2 physically dissolves in plasma water, because O_2 is poorly soluble in body fluids. The amount dissolved is directly proportional to the P_{O_2} of the blood; the higher the P_{O_2} the more O_2 dissolved. At a normal arterial P_{O_2} of 100 mm Hg, only 3 ml of O_2 can dissolve in 1 liter of blood. Only 1.5% of the O_2 in the blood is dissolved; the remaining 98.5% is transported in combination with Hb. *The* O_2 *bound to* Hb *does not contribute to the* P_{O_2} *of the blood;* thus blood P_{O_2} is not a *mea*sure of the total O_2 content of the blood but only of the dissolved portion of O_2.