UNIT VII

Respiration

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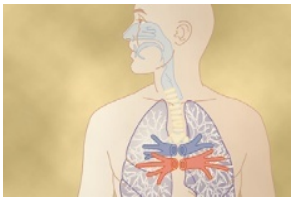
CHAPTER 37

Pulmonary Ventilation



Respiration provides oxygen to the tissues and removes carbon dioxide. The four major functions of respiration are (1) *pulmonary ventilation*, which means the inflow and outflow of air between the atmosphere and the lung alveoli; (2) *diffusion of oxygen and carbon dioxide between the alveoli and the blood*; (3) *transport of oxygen and carbon dioxide in the blood and body fluids* to and from the body's tissue cells; and (4) *regulation of ventilation* and other facets of respiration. This chapter is a discussion of pulmonary ventilation, and the subsequent five chapters cover other respiratory functions plus the physiology of special respiratory abnormalities.

Mechanics of Pulmonary Ventilation

Muscles That Cause Lung Expansion and Contraction

The lungs can be expanded and contracted in two ways: (1) by downward and upward movement of the diaphragm to lengthen or shorten the chest cavity, and (2) by elevation and depression of the ribs to increase and decrease the anteroposterior diameter of the chest cavity. Figure 37-1 shows these two methods.

Normal quiet breathing is accomplished almost entirely by the first method, that is, by movement of the diaphragm. During inspiration, contraction of the diaphragm pulls the lower surfaces of the lungs downward. Then, during expiration, the diaphragm simply relaxes, and the *elastic recoil* of the lungs, chest wall, and abdominal structures compresses the lungs and expels the air. During heavy breathing, however, the elastic forces are not powerful enough to cause the necessary rapid expiration, so extra force is achieved mainly by contraction of the *abdominal muscles*, which pushes the abdominal contents upward against the bottom of the diaphragm, thereby compressing the lungs.

The second method for expanding the lungs is to raise the rib cage. This expands the lungs because, in the natural resting position, the ribs slant downward, as shown on the left side of Figure 37-1, thus allowing the sternum to fall backward toward the vertebral column. When the rib cage is elevated, however, the ribs project almost directly forward, so the sternum also moves forward, away from the spine, making the anteroposterior thickness of the chest about 20 percent greater during maximum inspiration than during expiration. Therefore, all the muscles that elevate the chest cage are classified as muscles of inspiration, and those muscles that depress the chest cage are classified as muscles of expiration. The most important muscles that raise the rib cage are the *external intercostals*, but others that help are the (1) *sternocleidomastoid* muscles, which lift upward on the sternum; (2) *anterior serrati*, which lift many of the ribs; and (3) *scaleni*, which lift the first two ribs.

The muscles that pull the rib cage downward during expiration are mainly the (1) *abdominal recti*, which have the powerful effect of pulling downward on the lower ribs at the same time that they and other abdominal muscles also compress the abdominal contents upward against the diaphragm, and (2) *internal intercostals*.

Figure 37-1 also shows the mechanism by which the external and internal intercostals act to cause inspiration and expiration. To the left, the ribs during expiration are angled downward, and the external intercostals are elongated forward and downward. As they contract, they pull the upper ribs forward in relation to the lower ribs, and this causes leverage on the ribs to raise them upward, thereby causing inspiration. The internal intercostals function exactly in the opposite manner, functioning as expiratory muscles because they angle between the ribs in the opposite direction and cause opposite leverage.

Pressures That Cause the Movement of Air In and Out of the Lungs

The lung is an elastic structure that collapses like a balloon and expels all its air through the trachea whenever there is no force to keep it inflated. Also, there are no attachments between the lung and the walls of the chest cage, except where it is suspended at its hilum from the *mediastinum*, the middle section of the chest cavity. Instead, the lung "floats" in the thoracic cavity, surrounded by a thin layer of *pleural fluid* that lubricates movement of the lungs

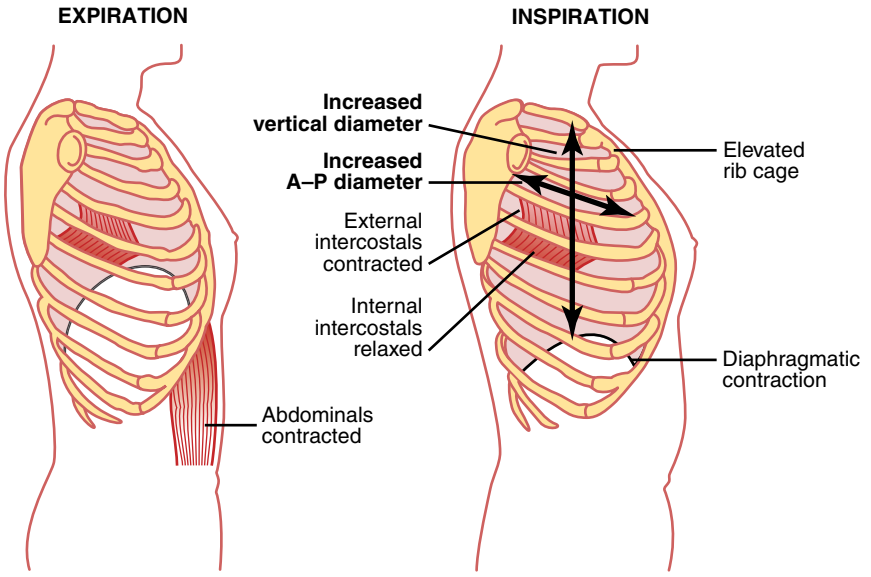


Figure 37-1 Contraction and expansion of the thoracic cage during expiration and inspiration, demonstrating diaphragmatic contraction, function of the intercostal muscles, and elevation and depression of the rib cage.

within the cavity. Further, continual suction of excess fluid into lymphatic channels maintains a slight suction between the visceral surface of the lung pleura and the parietal pleural surface of the thoracic cavity. Therefore, the lungs are held to the thoracic wall as if glued there, except that they are well lubricated and can slide freely as the chest expands and contracts.

Pleural Pressure and Its Changes During Respiration

Pleural pressure is the pressure of the fluid in the thin space between the lung pleura and the chest wall pleura. As noted earlier, this is normally a slight suction, which means a slightly *negative* pressure. The normal pleural pressure at the beginning of inspiration is about −5 centimeters of water, which is the amount of suction required to hold the lungs open to their resting level. Then, during normal inspiration, expansion of the chest cage pulls outward on the lungs with greater force and creates more negative pressure, to an average of about −7.5 centimeters of water.

These relationships between pleural pressure and changing lung volume are demonstrated in Figure 37-2, showing in the lower panel the increasing negativity of the pleural pressure from −5 to −7.5 during inspiration and in the upper panel an increase in lung volume of 0.5 liter. Then, during expiration, the events are essentially reversed.

Alveolar Pressure

Alveolar pressure is the pressure of the air inside the lung alveoli. When the glottis is open and no air is flowing into or out of the lungs, the pressures in all parts of the respiratory tree, all the way to the alveoli, are equal to atmospheric pressure, which is considered to be zero reference pressure in the airways—that is, 0 cm water pressure. To cause inward flow of air into the alveoli

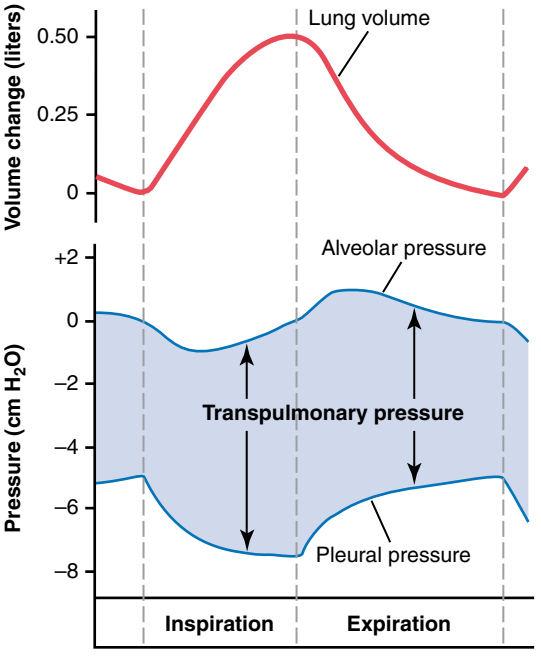


Figure 37-2 Changes in lung volume, alveolar pressure, pleural pressure, and transpulmonary pressure during normal breathing.

during inspiration, the pressure in the alveoli must fall to a value slightly below atmospheric pressure (below 0). The second curve (labeled "alveolar pressure") of Figure 37-2 demonstrates that during normal inspiration, alveolar pressure decreases to about −1 centimeters of water. This slight negative pressure is enough to pull 0.5 liter of air into the lungs in the 2 seconds required for normal quiet inspiration.

During expiration, opposite pressures occur: The alveolar pressure rises to about +1 centimeter of water, and this forces the 0.5 liter of inspired air out of the lungs during the 2 to 3 seconds of expiration.

Transpulmonary Pressure. Finally, note in Figure 37-2 the difference between the alveolar pressure and the pleural pressure. This is called the *transpulmonary pressure*. It is the pressure difference between that in the alveoli and that on the outer surfaces of the lungs, and it is a measure of the elastic forces in the lungs that tend to collapse the lungs at each instant of respiration, called the *recoil pressure*.

Compliance of the Lungs

The extent to which the lungs will expand for each unit increase in transpulmonary pressure (if enough time is allowed to reach equilibrium) is called the *lung compliance*. The total compliance of both lungs together in the normal adult human being averages about 200 milliliters of air per centimeter of water transpulmonary pressure. That is, every time the transpulmonary pressure increases 1 centimeter of water, the lung volume, after 10 to 20 seconds, will expand 200 milliliters.

Compliance Diagram of the Lungs. Figure 37-3 is a diagram relating lung volume changes to changes in transpulmonary pressure. Note that the relation is different for inspiration and expiration. Each curve is recorded by changing the transpulmonary pressure in small steps and allowing the lung volume to come to a steady level between successive steps. The two curves are called, respectively, the *inspiratory compliance curve* and the *expiratory compliance curve*, and the entire diagram is called the *compliance diagram of the lungs*.

The characteristics of the compliance diagram are determined by the elastic forces of the lungs. These can be divided into two parts: (1) *elastic forces of the lung tissue* and (2) *elastic forces caused by surface tension of the fluid that lines the inside walls of the alveoli* and other lung air spaces.

The elastic forces of the lung tissue are determined mainly by *elastin* and *collagen* fibers interwoven among the lung parenchyma. In deflated lungs, these fibers are in an elastically contracted and kinked state; then, when the lungs expand, the fibers become stretched and unkinked, thereby elongating and exerting even more elastic force.

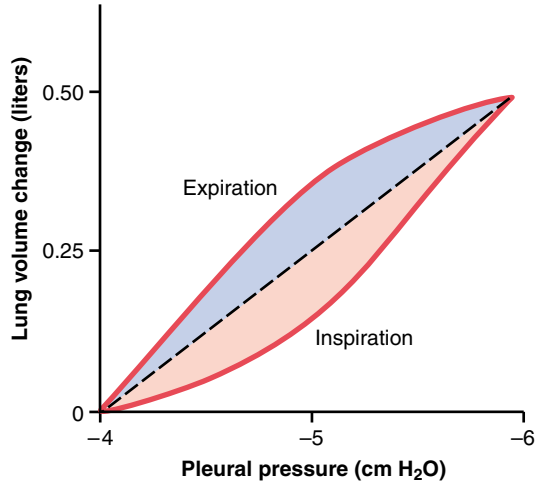


Figure 37-3 Compliance diagram in a healthy person. This diagram shows compliance of the lungs alone.

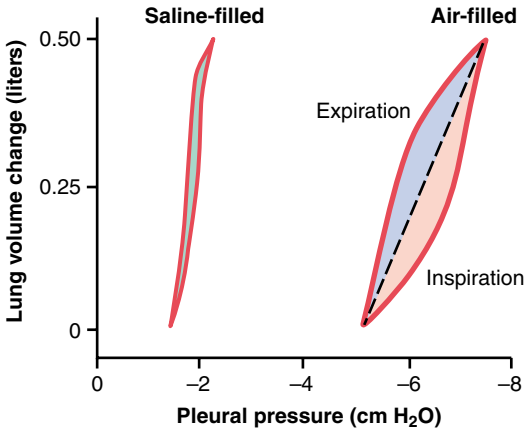


Figure 37-4 Comparison of the compliance diagrams of saline-filled and air-filled lungs when the alveolar pressure is maintained at atmospheric pressure (0 cm H_2O) and pleural pressure is changed.

The elastic forces caused by surface tension are much more complex. The significance of surface tension is shown in Figure 37-4, which compares the compliance diagram of the lungs when filled with saline solution and when filled with air. When the lungs are filled with air, there is an interface between the alveolar fluid and the air in the alveoli. In the case of the saline solution–filled lungs, there is no air-fluid interface; therefore, the surface tension effect is not present—only tissue elastic forces are operative in the saline solution–filled lung.

Note that transpleural pressures required to expand air-filled lungs are about three times as great as those required to expand saline solution–filled lungs. Thus, one can conclude that *the tissue elastic forces tending to cause collapse of the air-filled lung represent only about one third of the total lung elasticity, whereas the fluid-air surface tension forces in the alveoli represent about two thirds.*

The fluid-air surface tension elastic forces of the lungs also increase tremendously when the substance called *surfactant* is *not* present in the alveolar fluid. Let us now discuss surfactant and its relation to the surface tension forces.

Surfactant, Surface Tension, and Collapse of the Alveoli

Principle of Surface Tension. When water forms a surface with air, the water molecules on the surface of the water have an especially strong attraction for one another. As a result, the water surface is always attempting to contract. This is what holds raindrops together—a tight contractile membrane of water molecules around the entire surface of the raindrop. Now let us reverse these principles and see what happens on the inner surfaces of the alveoli. Here, the water surface is also attempting to contract. This results in an attempt to force the air out of the alveoli through the bronchi and, in doing so, causes the alveoli to try to collapse. The net effect is to cause an

elastic contractile force of the entire lungs, which is called the *surface tension elastic force*.

Surfactant and Its Effect on Surface Tension. Surfactant is a *surface active agent in water*, which means that it greatly reduces the surface tension of water. It is secreted by special surfactant-secreting epithelial cells called *type II alveolar epithelial cells*, which constitute about 10 percent of the surface area of the alveoli. These cells are granular, containing lipid inclusions that are secreted in the surfactant into the alveoli.

Surfactant is a complex mixture of several phospholipids, proteins, and ions. The most important components are the phospholipid *dipalmitoylphosphatidylcholine, surfactant apoproteins*, and *calcium ions*. The dipalmitoylphosphatidylcholine and several less important phospholipids are responsible for reducing the surface tension. They do this by not dissolving uniformly in the fluid lining the alveolar surface. Instead, part of the molecule dissolves while the remainder spreads over the surface of the water in the alveoli. This surface has from one-twelfth to one-half the surface tension of a pure water surface.

In quantitative terms, the surface tension of different water fluids is approximately the following: pure water, 72 dynes/cm; normal fluids lining the alveoli but without surfactant, 50 dynes/cm; normal fluids lining the alveoli and *with* normal amounts of surfactant included, between 5 and 30 dynes/cm.

Pressure in Occluded Alveoli Caused by Surface Tension. If the air passages leading from the alveoli of the lungs are blocked, the surface tension in the alveoli tends to collapse the alveoli. This creates positive pressure in the alveoli, attempting to push the air out. The amount of pressure generated in this way in an alveolus can be calculated from the following formula:

$$\text{Pressure} = \frac{2 \times \text{Surface tension}}{\text{Radius of alveolus}}$$

For the average-sized alveolus with a radius of about 100 micrometers and lined with *normal surfactant*, this calculates to be about 4 centimeters of water pressure (3 mm Hg). If the alveoli were lined with pure water without any surfactant, the pressure would calculate to be about 18 centimeters of water pressure, 4.5 times as great. Thus, one sees how important surfactant is in reducing alveolar surface tension and therefore also reducing the effort required by the respiratory muscles to expand the lungs.

Effect of Alveolar Radius on the Pressure Caused by Surface Tension. Note from the preceding formula that the pressure generated as a result of surface tension in the alveoli is *inversely* affected by the radius of the alveolus, which means that the smaller the alveolus, the greater the alveolar pressure caused by the surface tension. Thus, when the alveoli have half the normal radius (50 instead of 100 micrometers), the pressures noted earlier are doubled. This is especially significant in small premature babies, many of whom have alveoli with radii less than one quarter that of an adult person. Further, surfactant does not normally begin to be secreted into the alveoli until between the sixth and seventh months of gestation, and in some cases, even later than that. Therefore, many premature babies have little or no surfactant in the alveoli when they are born, and their lungs have an extreme tendency to collapse, sometimes as great as six to eight times that in a normal adult person. This causes the condition called *respiratory distress syndrome of the newborn*. It is fatal if not treated with strong measures, especially properly applied continuous positive pressure breathing.

Effect of the Thoracic Cage on Lung Expansibility

Thus far, we have discussed the expansibility of the lungs alone, without considering the thoracic cage. The thoracic cage has its own elastic and viscous characteristics, similar to those of the lungs; even if the lungs were not present in the thorax, muscular effort would still be required to expand the thoracic cage.

Compliance of the Thorax and the Lungs Together

The compliance of the entire pulmonary system (the lungs and thoracic cage together) is measured while expanding the lungs of a totally relaxed or paralyzed person. To do this, air is forced into the lungs a little at a time while recording lung pressures and volumes. To inflate this total pulmonary system, almost twice as much pressure as to inflate the same lungs after removal from the chest cage is necessary. Therefore, the compliance of the combined lung-thorax system is almost exactly one half that of the lungs alone—110 milliliters of volume per centimeter of water pressure for the combined system, compared with 200 ml/cm for the lungs alone. Furthermore, when the lungs are expanded to high volumes or compressed to low volumes, the limitations of the chest become extreme; when near these limits, the compliance of the combined lung-thorax system can be less than one fifth that of the lungs alone.

"Work" of Breathing

We have already pointed out that during normal quiet breathing, all respiratory muscle contraction occurs during inspiration; expiration is almost entirely a passive process caused by elastic recoil of the lungs and chest cage. Thus, under resting conditions, the respiratory muscles normally perform "work" to cause inspiration but not to cause expiration.

The work of inspiration can be divided into three fractions: (1) that required to expand the lungs against the lung and chest elastic forces, called *compliance work* or *elastic work*; (2) that required to overcome the viscosity of the lung and chest wall structures, called *tissue resistance work*; and (3) that required to overcome airway resistance to movement of air into the lungs, called *airway resistance work*.

Energy Required for Respiration. During normal quiet respiration, only 3 to 5 percent of the total energy expended by the body is required for pulmonary ventilation. But during heavy exercise, the amount of energy required can increase as much as 50-fold, especially if the person has any degree of increased airway resistance or decreased pulmonary compliance. Therefore, one of the major limitations on the intensity of exercise that can be performed is the person's ability to provide enough muscle energy for the respiratory process alone.

Pulmonary Volumes and Capacities

Recording Changes in Pulmonary Volume—Spirometry

Pulmonary ventilation can be studied by recording the volume movement of air into and out of the lungs, a method called *spirometry*. A typical basic spirometer is shown in Figure 37-5. It consists of a drum inverted over a chamber of water, with the drum counterbalanced by a weight. In the drum is a breathing gas, usually air or oxygen; a tube connects the mouth with the gas chamber. When one breathes into and out of the chamber, the drum rises and falls, and an appropriate recording is made on a moving sheet of paper.

Figure 37-6 shows a spirogram indicating changes in lung volume under different conditions of breathing. For ease in describing the events of pulmonary ventilation, the air in the lungs has been subdivided in this diagram into four *volumes* and four *capacities*, which are the average for a *young adult man*.

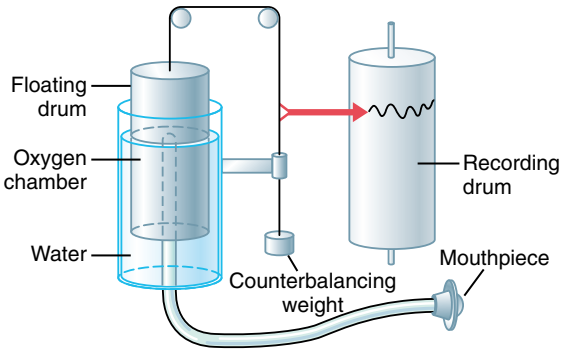


Figure 37-5 Spirometer.

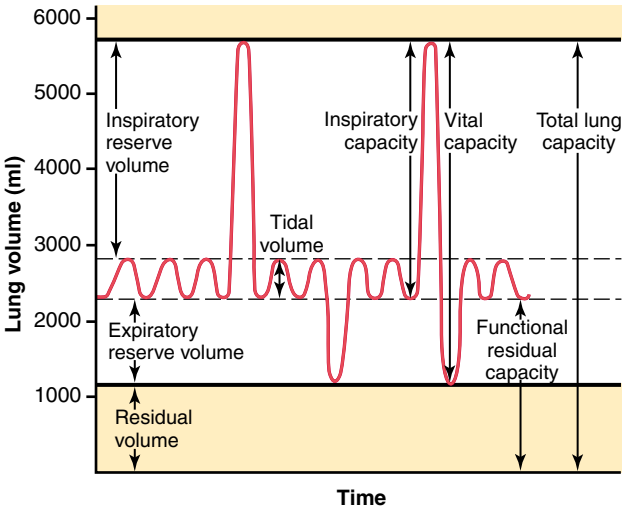


Figure 37-6 Diagram showing respiratory excursions during normal breathing and during maximal inspiration and maximal expiration.

Pulmonary Volumes

To the left in Figure 37-6 are listed four pulmonary lung volumes that, when added together, equal the maximum volume to which the lungs can be expanded. The significance of each of these volumes is the following:

1. The *tidal volume* is the volume of air inspired or expired with each normal breath; it amounts to about 500 milliliters in the adult male.
2. The *inspiratory reserve volume* is the extra volume of air that can be inspired over and above the normal tidal volume when the person inspires with full force; it is usually equal to about 3000 milliliters.
3. The *expiratory reserve volume* is the maximum extra volume of air that can be expired by forceful expiration after the end of a normal tidal expiration; this normally amounts to about 1100 milliliters.
4. The *residual volume* is the volume of air remaining in the lungs after the most forceful expiration; this volume averages about 1200 milliliters.

Pulmonary Capacities

In describing events in the pulmonary cycle, it is sometimes desirable to consider two or more of the volumes together. Such combinations are called *pulmonary capacities*. To the right in Figure 37-6 are listed the important pulmonary capacities, which can be described as follows:

1. The *inspiratory capacity* equals the *tidal volume* plus the *inspiratory reserve volume*. This is the amount of air (about 3500 milliliters) a person can breathe in, beginning at the normal expiratory level and distending the lungs to the maximum amount.
2. The *functional residual capacity* equals the *expiratory reserve volume* plus the *residual volume*. This is the amount of air that remains in the lungs at the end of normal expiration (about 2300 milliliters).
3. The *vital capacity* equals the *inspiratory reserve volume* plus the *tidal volume* plus the *expiratory reserve volume*. This is the maximum amount of air a person can expel from the lungs after first filling the lungs to their maximum extent and then expiring to the maximum extent (about 4600 milliliters).
4. The *total lung capacity* is the maximum volume to which the lungs can be expanded with the greatest possible effort (about 5800 milliliters); it is equal to the *vital capacity* plus the *residual volume*.

All pulmonary volumes and capacities are about 20 to 25 percent less in women than in men, and they are greater in large and athletic people than in small and asthenic people.

Abbreviations and Symbols Used in Pulmonary Function Studies

Spirometry is only one of many measurement procedures that the pulmonary physician uses daily. Many of these measurement procedures depend heavily on mathematical

computations. To simplify these calculations, as well as the presentation of pulmonary function data, several abbreviations and symbols have become standardized. The more important of these are given in Table 37-1. Using these symbols, we present here a few simple algebraic exercises showing some of the interrelations among the pulmonary volumes and capacities; the student should think through and verify these interrelations.

$VC = IRV + V_T + ERV$

$VC = IC + ERV$

$TLC = VC + RV$

$TLC = IC + FRC$

$FRC = ERV + RV$

Determination of Functional Residual Capacity, Residual Volume, and Total Lung Capacity—Helium Dilution Method

The functional residual capacity (FRC), which is the volume of air that remains in the lungs at the end of each normal expiration, is important to lung function. Because its value changes markedly in some types of pulmonary disease, it is often desirable to measure this capacity. The spirometer cannot be used in a direct way to measure the functional residual capacity because the air in the residual volume of the lungs cannot be expired into the spirometer, and this volume constitutes about one half of the functional residual capacity. To measure functional residual capacity, the spirometer must be used in an indirect manner, usually by means of a helium dilution method, as follows.

A spirometer of known volume is filled with air mixed with helium at a known concentration. Before breathing from the spirometer, the person expires normally. At the end of this expiration, the remaining volume in the lungs is equal to the functional residual capacity. At this point, the subject immediately begins to breathe from the spirometer, and the gases of the spirometer mix with the gases of the lungs. As a result, the helium becomes diluted by the functional residual capacity gases, and the volume of the functional residual capacity can be calculated from the degree of dilution of the helium, using the following formula:

$$FRC = \left(\frac{Ci_{He}}{Cf_{He}} - 1\right) Vi_{Spir}$$

where FRC is functional residual capacity, Ci_{He} is initial concentration of helium in the spirometer, Cf_{He} is final concentration of helium in the spirometer, and Vi_{Spir} is initial volume of the spirometer.

Table 37-1 Abbreviations and Symbols for Pulmonary Function

V_T	tidal volume	P_B	atmospheric pressure
FRC	functional residual capacity	Palv	alveolar pressure
ERV	expiratory reserve volume	Ppl	pleural pressure
RV	residual volume	P_{O_2}	partial pressure of oxygen
IC	inspiratory capacity	P_{CO_2}	partial pressure of carbon dioxide
IRV	inspiratory reserve volume	P_{N_2}	partial pressure of nitrogen
TLC	total lung capacity	Pa_{O_2}	partial pressure of oxygen in arterial blood
VC	vital capacity	Pa_{CO_2}	partial pressure of carbon dioxide in arterial blood
Raw	resistance of the airways to flow of air into the lung	P_{AO_2}	partial pressure of oxygen in alveolar gas
C	compliance	P_{ACO_2}	partial pressure of carbon dioxide in alveolar gas
V_D	volume of dead space gas	P_{AH_2O}	partial pressure of water in alveolar gas
V_A	volume of alveolar gas	R	respiratory exchange ratio
$\dot{V}_I$	inspired volume of ventilation per minute	$\dot{Q}$	cardiac output
$\dot{V}_E$	expired volume of ventilation per minute		
$\dot{V}_s$	shunt flow		
$\dot{V}_A$	alveolar ventilation per minute	Ca_{O_2}	concentration of oxygen in arterial blood
$\dot{V}O_2$	rate of oxygen uptake per minute	$C\bar{v}_{O_2}$	concentration of oxygen in mixed venous blood
$\dot{V}CO_2$	amount of carbon dioxide eliminated per minute	S_{O_2}	percentage saturation of hemoglobin with oxygen
$\dot{V}CO$	rate of carbon monoxide uptake per minute	Sa_{O_2}	percentage saturation of hemoglobin with oxygen in arterial blood
DLO_2	diffusing capacity of the lungs for oxygen		
DL_{CO}	diffusing capacity of the lungs for carbon monoxide		

Once the FRC has been determined, the residual volume (RV) can be determined by subtracting expiratory reserve volume (ERV), as measured by normal spirometry, from the FRC. Also, the total lung capacity (TLC) can be determined by adding the inspiratory capacity (IC) to the FRC. That is,

$$RV = FRC - ERV$$

and

$$TLC = FRC + IC$$

Minute Respiratory Volume Equals Respiratory Rate Times Tidal Volume

The *minute respiratory volume* is the total amount of new air moved into the respiratory passages each minute; this is equal to the *tidal volume* times the *respiratory rate per minute*. The normal tidal volume is about 500 milliliters, and the normal respiratory rate is about 12 breaths per minute. Therefore, the *minute respiratory volume averages about 6 L/min*. A person can live for a short period with a minute respiratory volume as low as 1.5 L/min and a respiratory rate of only 2 to 4 breaths per minute.

The respiratory rate occasionally rises to 40 to 50 per minute, and the tidal volume can become as great as the vital capacity, about 4600 milliliters in a young adult man. This can give a minute respiratory volume greater than 200 L/min, or more than 30 times normal. Most people cannot sustain more than one half to two thirds of these values for longer than 1 minute.

Alveolar Ventilation

The ultimate importance of pulmonary ventilation is to continually renew the air in the gas exchange areas of the lungs, where air is in proximity to the pulmonary blood. These areas include the alveoli, alveolar sacs, alveolar ducts, and respiratory bronchioles. The rate at which new air reaches these areas is called *alveolar ventilation*.

"Dead Space" and Its Effect on Alveolar Ventilation

Some of the air a person breathes never reaches the gas exchange areas but simply fills respiratory passages where gas exchange does not occur, such as the nose, pharynx, and trachea. This air is called *dead space air* because it is not useful for gas exchange.

On expiration, the air in the dead space is expired first, before any of the air from the alveoli reaches the atmosphere. Therefore, the dead space is very disadvantageous for removing the expiratory gases from the lungs.

Measurement of the Dead Space Volume. A simple method for measuring dead space volume is demonstrated by the graph in Figure 37-7. In making this measurement, the subject suddenly takes a deep breath of oxygen. This fills the entire dead space with pure oxygen. Some oxygen also mixes with the alveolar air but does not completely replace this air. Then the person expires through a rapidly recording nitrogen meter, which makes the record shown in the figure. The first portion of the expired air comes from the dead space regions of the respiratory passageways, where the air has been completely replaced by oxygen. Therefore, in the early part of the record, only oxygen appears, and the nitrogen concentration is zero. Then, when alveolar air begins to reach the nitrogen meter, the nitrogen concentration rises rapidly, because alveolar air containing large amounts of nitrogen begins to mix with the dead space air. After still more air has been expired, all the dead space air has been washed from the passages and only alveolar air remains. Therefore, the recorded nitrogen concentration reaches a plateau level equal to its concentration in the alveoli, as shown to the right in the figure. With a little thought, the student can see that the gray area represents the air that has no nitrogen in it; this area is a measure of the volume of dead space air. For exact quantification, the following equation is used:

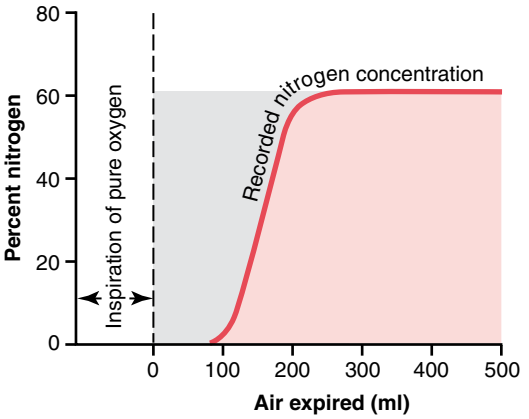


Figure 37-7 Record of the changes in nitrogen concentration in the expired air after a single previous inspiration of pure oxygen. This record can be used to calculate dead space, as discussed in the text.

$$V_D = \frac{\text{Gray area} \times V_E}{\text{Pink area} + \text{Gray area}}$$

where V_D is dead space air and V_E is the total volume of expired air.

Let us assume, for instance, that the gray area on the graph is 30 square centimeters, the pink area is 70 square centimeters, and the total volume expired is 500 milliliters. The dead space would be

$$\frac{30}{30 + 70} \times 500 = 150 \text{ ml}$$

Normal Dead Space Volume. The normal dead space air in a young adult man is about 150 milliliters. This increases slightly with age.

Anatomic Versus Physiologic Dead Space. The method just described for measuring the dead space measures the volume of all the space of the respiratory system other than the alveoli and their other closely related gas exchange areas; this space is called the *anatomic dead space*. On occasion, some of the alveoli themselves are nonfunctional or only partially functional because of absent or poor blood flow through the adjacent pulmonary capillaries. Therefore, from

a functional point of view, these alveoli must also be considered dead space. When the alveolar dead space is included in the total measurement of dead space, this is called the *physiologic dead space*, in contradistinction to the anatomic dead space. In a normal person, the anatomic and physiologic dead spaces are nearly equal because all alveoli are functional in the normal lung, but in a person with partially functional or nonfunctional alveoli in some parts of the lungs, the physiologic dead space may be as much as 10 times the volume of the anatomic dead space, or 1 to 2 liters. These problems are discussed further in Chapter 39 in relation to pulmonary gaseous exchange and in Chapter 42 in relation to certain pulmonary diseases.

Rate of Alveolar Ventilation

Alveolar ventilation per minute is the total volume of new air entering the alveoli and adjacent gas exchange areas each minute. It is equal to the respiratory rate times the amount of new air that enters these areas with each breath.

$$\dot{V}_A = Freq \times (V_T - V_D)$$

where $\dot{V}_A$ is the volume of alveolar ventilation per minute, Freq is the frequency of respiration per minute, V_T is the tidal volume, and V_D is the physiologic dead space volume.

Thus, with a normal tidal volume of 500 milliliters, a normal dead space of 150 milliliters, and a respiratory rate of 12 breaths per minute, alveolar ventilation equals $12 \times (500 - 150)$, or 4200 ml/min.

Alveolar ventilation is one of the major factors determining the concentrations of oxygen and carbon dioxide in the alveoli. Therefore, almost all discussions of gaseous exchange in the following chapters on the respiratory system emphasize alveolar ventilation.

Functions of the Respiratory Passageways

Trachea, Bronchi, and Bronchioles

Figure 37-8 shows the respiratory system, demonstrating especially the respiratory passageways. The air is distributed to the lungs by way of the trachea, bronchi, and bronchioles.

One of the most important challenges in the respiratory passageways is to keep them open and allow easy passage of air to and from the alveoli. To keep the trachea from collapsing, multiple cartilage rings extend about five sixths of the way around the trachea. In the walls of the bronchi, less extensive curved cartilage plates also maintain a reasonable amount of rigidity yet allow sufficient motion for the lungs to expand and contract. These plates become progressively less extensive in the later generations of bronchi and are gone in the bronchioles, which usually have diameters less than 1.5 millimeters. The bronchioles are not prevented from collapsing by the rigidity of their walls. Instead, they are kept expanded mainly by the same transpulmonary pressures that expand the alveoli. That is, as the alveoli enlarge, the bronchioles also enlarge, but not as much.

Muscular Wall of the Bronchi and Bronchioles and Its Control. In all areas of the *trachea* and *bronchi* not occupied by cartilage plates, the walls are composed mainly of smooth muscle. Also, the walls of the *bronchioles* are almost entirely smooth muscle, with the exception of the most terminal bronchiole, called the *respiratory bronchiole*, which is mainly pulmonary epithelium and underlying fibrous tissue plus a few smooth muscle fibers. Many obstructive diseases of the lung result from narrowing of the smaller bronchi and

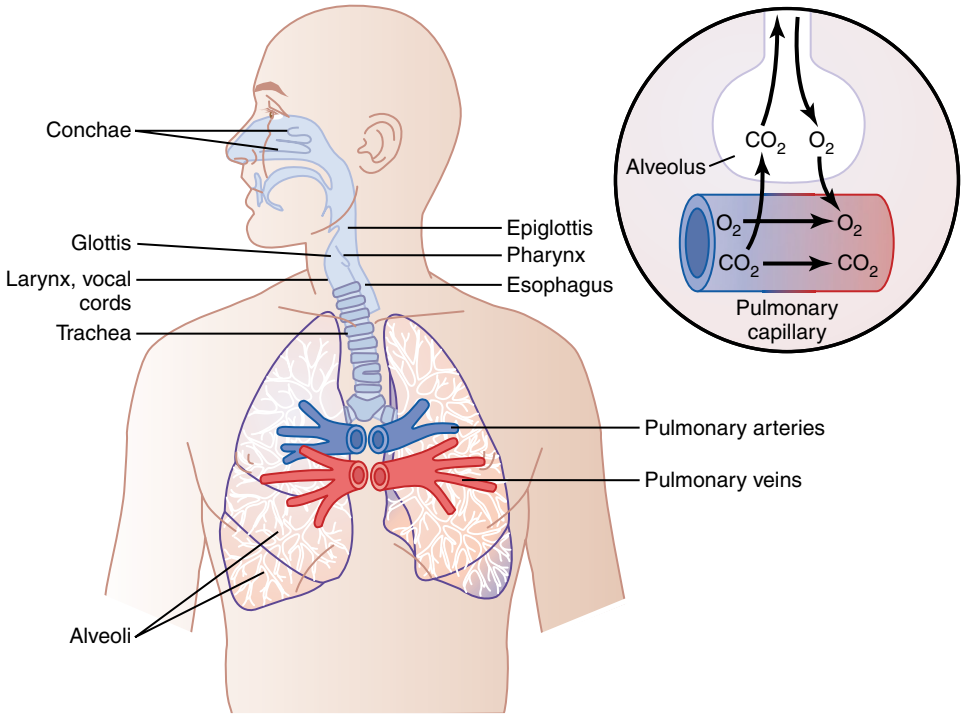


Figure 37-8 Respiratory passages.

larger bronchioles, often because of excessive contraction of the smooth muscle itself.

Resistance to Airflow in the Bronchial Tree. Under *normal respiratory conditions*, air flows through the respiratory passageways so easily that less than 1 centimeter of water pressure gradient from the alveoli to the atmosphere is sufficient to cause enough airflow for quiet breathing. The greatest amount of resistance to airflow occurs not in the minute air passages of the terminal bronchioles but in some of the larger bronchioles and bronchi near the trachea. The reason for this high resistance is that there are relatively few of these larger bronchi in comparison with the approximately 65,000 parallel terminal bronchioles, through each of which only a minute amount of air must pass.

Yet in disease conditions, the smaller bronchioles often play a far greater role in determining airflow resistance because of their small size and because they are easily occluded by (1) muscle contraction in their walls, (2) edema occurring in the walls, or (3) mucus collecting in the lumens of the bronchioles.

Nervous and Local Control of the Bronchiolar Musculature—"Sympathetic" Dilation of the Bronchioles. Direct control of the bronchioles by sympathetic nerve fibers is relatively weak because few of these fibers penetrate to the central portions of the lung. However, the bronchial tree is very much exposed to *norepinephrine* and *epinephrine* released into the blood by sympathetic stimulation of the adrenal gland medullae. Both these hormones, especially epinephrine because of its greater stimulation of *beta-adrenergic receptors*, cause dilation of the bronchial tree.

Parasympathetic Constriction of the Bronchioles. A few parasympathetic nerve fibers derived from the vagus nerves penetrate the lung parenchyma. These nerves secrete *acetylcholine* and, when activated, cause mild to moderate constriction of the bronchioles. When a disease process such as asthma has already caused some bronchiolar constriction, superimposed parasympathetic nervous stimulation often worsens the condition. When this occurs, administration of drugs that block the effects of acetylcholine, such as *atropine*, can sometimes relax the respiratory passages enough to relieve the obstruction.

Sometimes the parasympathetic nerves are also activated by reflexes that originate in the lungs. Most of these begin with irritation of the epithelial membrane of the respiratory passageways themselves, initiated by noxious gases, dust, cigarette smoke, or bronchial infection. Also, a bronchiolar constrictor reflex often occurs when microemboli occlude small pulmonary arteries.

Local Secretory Factors Often Cause Bronchiolar Constriction. Several substances formed in the lungs are often quite active in causing bronchiolar constriction. Two of the most important of these are *histamine* and *slow reactive substance of anaphylaxis*. Both of these are released in the lung tissues by *mast cells* during allergic reactions, especially those caused by pollen in the air. Therefore, they play key roles in causing the airway obstruction that occurs in allergic asthma; this is especially true of the slow reactive substance of anaphylaxis.

The same irritants that cause parasympathetic constrictor reflexes of the airways—smoke, dust, sulfur dioxide, and some of the acidic elements in smog—often act directly on the lung tissues to initiate local, non-nervous reactions that cause obstructive constriction of the airways.

Mucus Lining the Respiratory Passageways, and Action of Cilia to Clear the Passageways

All the respiratory passages, from the nose to the terminal bronchioles, are kept moist by a layer of mucus that coats the entire surface. The mucus is secreted partly by individual mucous goblet cells in the epithelial lining of the passages and partly by small submucosal glands. In addition to keeping the surfaces moist, the mucus traps small particles out of the inspired air and keeps most of these from ever reaching the alveoli. The mucus itself is removed from the passages in the following manner.

The entire surface of the respiratory passages, both in the nose and in the lower passages down as far as the terminal bronchioles, is lined with ciliated epithelium, with about 200 cilia on each epithelial cell. These cilia beat continually at a rate of 10 to 20 times per second by the mechanism explained in Chapter 2, and the direction of their "power stroke" is always toward the pharynx. That is, the cilia in the lungs beat upward, whereas those in the nose beat downward. This continual beating causes the coat of mucus to flow slowly, at a velocity of a few millimeters per minute, toward the pharynx. Then the mucus and its entrapped particles are either swallowed or coughed to the exterior.

Cough Reflex

The bronchi and trachea are so sensitive to light touch that slight amounts of foreign matter or other causes of irritation initiate the cough reflex. The larynx and carina (the point where the trachea divides into the bronchi) are especially sensitive, and the terminal bronchioles and even the alveoli are sensitive to corrosive chemical stimuli such as sulfur dioxide gas or chlorine gas. Afferent nerve impulses pass from the respiratory passages mainly through the vagus nerves to the medulla of the brain. There, an automatic sequence of events is triggered by the neuronal circuits of the medulla, causing the following effect.

First, up to 2.5 liters of air are rapidly inspired. Second, the epiglottis closes, and the vocal cords shut tightly to entrap the air within the lungs. Third, the abdominal muscles contract forcefully, pushing against the diaphragm while other expiratory muscles, such as the internal intercostals, also contract forcefully. Consequently, the pressure in the lungs rises rapidly to as much as 100 mm Hg or more. Fourth, the vocal cords and the epiglottis suddenly open widely, so that air under this high pressure in the lungs *explodes* outward. Indeed, sometimes this air is expelled at velocities ranging from 75 to 100 miles per hour. Importantly, the strong compression of the lungs collapses the bronchi and trachea by causing their noncartilaginous parts to invaginate inward, so the exploding air actually passes through *bronchial* and *tracheal slits*. The rapidly moving air usually carries with it any foreign matter that is present in the bronchi or trachea.

Sneeze Reflex

The sneeze reflex is very much like the cough reflex, except that it applies to the nasal passageways instead of the lower respiratory passages. The initiating stimulus of the sneeze reflex is irritation in the nasal passageways; the afferent impulses pass in the fifth cranial nerve to the medulla, where the reflex is triggered. A series of reactions similar to those for the cough reflex takes place; however, the uvula is depressed, so large amounts of air pass rapidly through the nose, thus helping to clear the nasal passages of foreign matter.

Normal Respiratory Functions of the Nose

As air passes through the nose, three distinct normal respiratory functions are performed by the nasal cavities: (1) the air is *warmed* by the extensive surfaces of the conchae and septum, a total area of about 160 square centimeters (see Figure 37-8); (2) the air is *almost completely humidified* even before it passes beyond the nose; and (3) the air is *partially filtered*. These functions together are called the *air conditioning function* of the upper respiratory passageways. Ordinarily, the temperature of the inspired air rises to within 1°F of body temperature and to within 2 to 3 percent of full saturation with water vapor before it reaches the trachea. When a person breathes air through a tube directly into the trachea (as through a tracheostomy), the cooling and especially the drying effect in the lower lung can lead to serious lung crusting and infection.

Filtration Function of the Nose. The hairs at the entrance to the nostrils are important for filtering out large particles. Much more important, though, is the removal of particles by *turbulent precipitation*. That is, the air passing through the nasal passageways hits many obstructing vanes: the *conchae* (also called *turbinates*, because they cause turbulence of the air); the septum; and the pharyngeal wall. Each time air hits one of these obstructions, it must change its direction of movement. The particles suspended in the air, having far more mass and momentum than air, cannot change their direction of travel as rapidly as the air can. Therefore, they continue forward, striking the surfaces of the obstructions, and are entrapped in the mucous coating and transported by the cilia to the pharynx to be swallowed.

Size of Particles Entrapped in the Respiratory Passages. The nasal turbulence mechanism for removing particles from air is so effective that almost no particles larger than 6 micrometers in diameter enter the lungs through the nose. This size is smaller than the size of red blood cells.

Of the remaining particles, many that are between 1 and 5 micrometers *settle* in the smaller bronchioles as a result of *gravitational precipitation*. For instance, terminal bronchiolar disease is common in coal miners because of settled dust particles. Some of the still smaller particles (smaller than 1 micrometer in diameter) *diffuse* against the walls of the alveoli and adhere to the alveolar fluid. But many particles smaller than 0.5 micrometer in diameter remain suspended in the alveolar air and are expelled by expiration. For instance, the particles of cigarette smoke are about 0.3 micrometer. Almost none of these particles are precipitated in the respiratory passageways before they reach the alveoli. Unfortunately, up to one third of them do precipitate in the alveoli by the diffusion process, with the balance remaining suspended and expelled in the expired air.

Many of the particles that become entrapped in the alveoli are removed by *alveolar macrophages*, as explained in Chapter 33, and others are carried away by the lung lymphatics. An excess of particles can cause growth of fibrous tissue in the alveolar septa, leading to permanent debility.

Vocalization

Speech involves not only the respiratory system but also (1) specific speech nervous control centers in the cerebral cortex, which are discussed in Chapter 57; (2) respiratory control centers of the brain; and (3) the articulation and resonance structures of the mouth and nasal cavities. Speech is composed of two mechanical functions: (1) *phonation*, which is achieved by the larynx, and (2) *articulation*, which is achieved by the structures of the mouth.

Phonation. The larynx, shown in Figure 37-9*A*, is especially adapted to act as a vibrator. The vibrating element is the *vocal folds*, commonly called the *vocal cords*. The vocal cords protrude from the lateral walls of the larynx toward the center of the glottis; they are stretched and positioned by several specific muscles of the larynx itself.

Figure 37-9*B* shows the vocal cords as they are seen when looking into the glottis with a laryngoscope. During normal breathing, the cords are wide open to allow easy passage of air. During phonation, the cords move together so that passage of air between them will cause vibration. The pitch of the vibration is determined mainly by the degree of stretch of the cords, but also by how tightly the cords are approximated to one another and by the mass of their edges.

Figure 37-9*A* shows a dissected view of the vocal folds after removal of the mucous epithelial lining. Immediately inside each cord is a strong elastic ligament called the *vocal ligament*. This is attached anteriorly to the large *thyroid cartilage*, which is the cartilage that projects forward from the anterior surface of the neck and is called the "Adam's apple." Posteriorly, the vocal ligament is attached to the *vocal processes* of two *arytenoid cartilages*. The thyroid cartilage and the arytenoid cartilages articulate from below with another cartilage not shown in Figure 37-9, the *cricoid cartilage*.

The vocal cords can be stretched by either forward rotation of the thyroid cartilage or posterior rotation of the arytenoid cartilages, activated by muscles stretching from

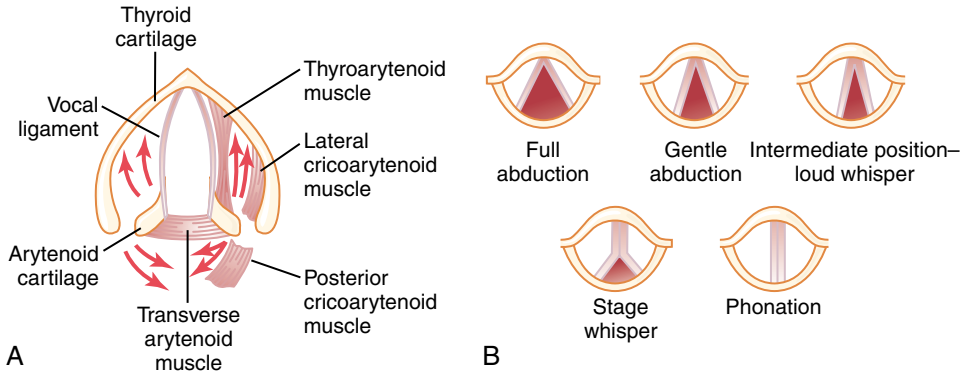


Figure 37-9 *A*, Anatomy of the larynx. *B*, Laryngeal function in phonation, showing the positions of the vocal cords during different types of phonation. (Modified from Greene MC: The Voice and Its Disorders, 4th ed. Philadelphia: JB Lippincott, 1980.)

the thyroid cartilage and arytenoid cartilages to the cricoid cartilage. Muscles located within the vocal cords lateral to the vocal ligaments, the thyroarytenoid muscles, can pull the arytenoid cartilages toward the thyroid cartilage and, therefore, loosen the vocal cords. Also, slips of these muscles *within* the vocal cords can change the *shapes and masses of the vocal cord edges*, sharpening them to emit high-pitched sounds and blunting them for the more bass sounds.

Several other sets of small laryngeal muscles lie between the arytenoid cartilages and the cricoid cartilage and can rotate these cartilages inward or outward or pull their bases together or apart to give the various configurations of the vocal cords shown in Figure 37-9*B*.

Articulation and Resonance. The three major organs of articulation are the *lips, tongue*, and *soft palate*. They need not be discussed in detail because we are all familiar with their movements during speech and other vocalizations.

The resonators include the *mouth*, the *nose* and *associated nasal sinuses*, the *pharynx*, and even the *chest cavity*. Again, we are all familiar with the resonating qualities of these structures. For instance, the function of the nasal resonators is demonstrated by the change in voice quality when a person has a severe cold that blocks the air passages to these resonators.

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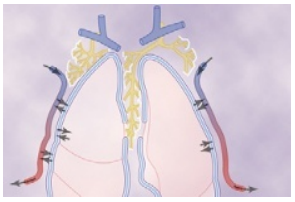
CHAPTER 38

Pulmonary Circulation, Pulmonary Edema, Pleural Fluid



The lung has two circulations: (1) *A high-pressure, low-flow circulation* supplies systemic arterial blood to the trachea, the bronchial tree including the terminal bronchioles, the supporting tissues of the lung, and the outer coats (adventia) of the pulmonary arteries and veins. The *bronchial arteries*, which are branches of the thoracic aorta, supply most of this systemic arterial blood at a pressure that is only slightly lower than the aortic pressure. (2) *A low-pressure, high-flow circulation* that supplies venous blood from all parts of the body to the alveolar capillaries where oxygen is added and carbon dioxide is removed. The *pulmonary artery*, which receives blood from the right ventricle, and its arterial branches carry blood to the alveolar capillaries for gas exchange and the pulmonary veins then return the blood to the left atrium to be pumped by the left ventricle though the systemic circulation.

In this chapter we discuss the special aspects of blood flow distribution and other hemodynamics of the pulmonary circulation that are especially important for gas exchange in the lungs.

Physiologic Anatomy of the Pulmonary Circulatory System

Pulmonary Vessels. The pulmonary artery extends only 5 centimeters beyond the apex of the right ventricle and then divides into right and left main branches that supply blood to the two respective lungs.

The pulmonary artery is thin, with a wall thickness one third that of the aorta. The pulmonary arterial branches are very short, and all the pulmonary arteries, even the smaller arteries and arterioles, have larger diameters than their counterpart systemic arteries. This, combined with the fact that the vessels are thin and distensible, gives the pulmonary arterial tree a *large compliance*, averaging almost 7 ml/mm Hg, which is similar to that of the entire systemic arterial tree. This large compliance allows the pulmonary arteries to accommodate the stroke volume output of the right ventricle.

The pulmonary veins, like the pulmonary arteries, are also short. They immediately empty their effluent blood into the left atrium.

Bronchial Vessels. Blood also flows to the lungs through small bronchial arteries that originate from the systemic circulation, amounting to about 1 to 2 percent of the total cardiac output. This bronchial arterial blood is *oxygenated* blood, in contrast to the partially deoxygenated blood in the pulmonary arteries. It supplies the supporting tissues of the lungs, including the connective tissue, septa, and large and small bronchi. After this bronchial and arterial blood has passed through the supporting tissues, it empties into the pulmonary veins and *enters the left atrium*, rather than passing back to the right atrium. Therefore, the flow into the left atrium and the left ventricular output are about 1 to 2 percent greater than that of the right ventricular output.

Lymphatics. Lymph vessels are present in all the supportive tissues of the lung, beginning in the connective tissue spaces that surround the terminal bronchioles, coursing to the hilum of the lung, and then mainly into the *right thoracic lymph duct*. Particulate matter entering the alveoli is partly removed by way of these channels, and plasma protein leaking from the lung capillaries is also removed from the lung tissues, thereby helping to prevent pulmonary edema.

Pressures in the Pulmonary System

Pressure Pulse Curve in the Right Ventricle. The pressure pulse curves of the right ventricle and pulmonary artery are shown in the lower portion of Figure 38-1. These curves are contrasted with the much higher aortic pressure curve shown in the upper portion of the figure. The systolic pressure in the right ventricle of the normal human being averages about 25 mm Hg, and the diastolic pressure averages about 0 to 1 mm Hg, values that are only one-fifth those for the left ventricle.

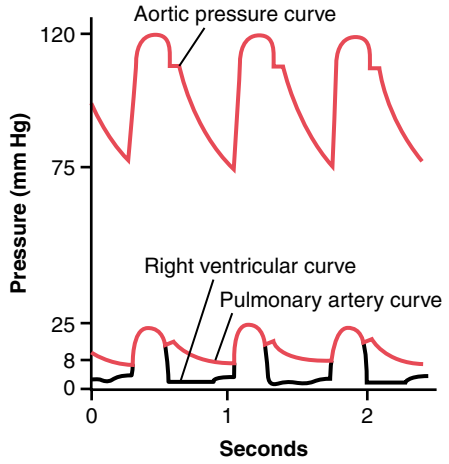


Figure 38-1 Pressure pulse contours in the right ventricle, pulmonary artery, and aorta.

Pressures in the Pulmonary Artery. During *systole*, the pressure in the pulmonary artery is essentially equal to the pressure in the right ventricle, as also shown in Figure 38-1. However, after the pulmonary valve closes at the end of systole, the ventricular pressure falls precipitously, whereas the pulmonary arterial pressure falls more slowly as blood flows through the capillaries of the lungs.

As shown in Figure 38-2, the *systolic pulmonary arterial pressure* averages about 25 mm Hg in the normal human being, the *diastolic pulmonary arterial pressure* is about 8 mm Hg, and the *mean pulmonary arterial pressure* is 15 mm Hg.

Pulmonary Capillary Pressure. The mean pulmonary capillary pressure, as diagrammed in Figure 38-2, is about 7 mm Hg. The importance of this low capillary pressure is discussed in detail later in the chapter in relation to fluid exchange functions of the pulmonary capillaries.

Left Atrial and Pulmonary Venous Pressures. The mean pressure in the left atrium and the major pulmonary veins averages about 2 mm Hg in the recumbent human being, varying from as low as 1 mm Hg to as high as 5 mm Hg. It usually is not feasible to measure a human being's left atrial pressure using a direct measuring device because it is difficult to pass a catheter through the heart chambers into the left atrium. However, the left atrial pressure can often be estimated with moderate accuracy by measuring the so-called *pulmonary wedge pressure*. This is achieved by inserting a catheter first through a peripheral vein to the right atrium, then through the right side of the heart and through the pulmonary artery into one of the small branches of the pulmonary artery, finally pushing the catheter until it *wedges tightly in the small branch*.

The pressure measured through the catheter, called the "wedge pressure," is about 5 mm Hg. Because all blood flow has been stopped in the small wedged artery, and because the blood vessels extending beyond this artery make a direct connection with the pulmonary capillaries, this wedge pressure is usually only 2 to 3 mm Hg greater than the left atrial pressure. When the left atrial pressure rises to high values, the pulmonary wedge pressure also rises. Therefore, wedge pressure measurements can be used to clinically study changes in pulmonary capillary pressure and left atrial pressure in patients with congestive heart failure.

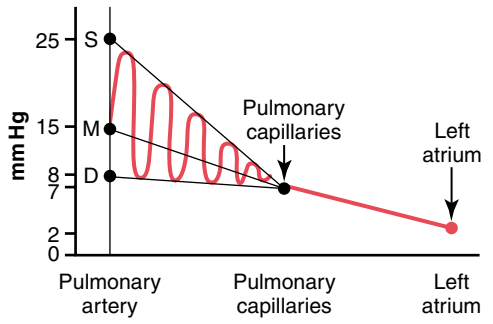


Figure 38-2 Pressures in the different vessels of the lungs. D, diastolic; M, mean; S, systolic; red curve, arterial pulsations.

Blood Volume of the Lungs

The blood volume of the lungs is about 450 milliliters, about 9 percent of the total blood volume of the entire circulatory system. Approximately 70 milliliters of this pulmonary blood volume is in the pulmonary capillaries, and the remainder is divided about equally between the pulmonary arteries and the veins.

The Lungs Serve as a Blood Reservoir. Under various physiological and pathological conditions, the quantity of blood in the lungs can vary from as little as one-half normal up to twice normal. For instance, when a person blows out air so hard that high pressure is built up in the lungs—such as when blowing a trumpet—as much as 250 milliliters of blood can be expelled from the pulmonary circulatory system into the systemic circulation. Also, loss of blood from the systemic circulation by hemorrhage can be partly compensated for by the automatic shift of blood from the lungs into the systemic vessels.

Cardiac Pathology May Shift Blood from the Systemic Circulation to the Pulmonary Circulation. Failure of the left side of the heart or increased resistance to blood flow through the mitral valve as a result of mitral stenosis or mitral regurgitation causes blood to dam up in the pulmonary circulation, sometimes increasing the pulmonary blood volume as much as 100 percent and causing large increases in the pulmonary vascular pressures. Because the volume

of the systemic circulation is about nine times that of the pulmonary system, a shift of blood from one system to the other affects the pulmonary system greatly but usually has only mild systemic circulatory effects.

Blood Flow Through the Lungs and Its Distribution

The blood flow through the lungs is essentially equal to the cardiac output. Therefore, the factors that control cardiac output—mainly peripheral factors, as discussed in Chapter 20—also control pulmonary blood flow. Under most conditions, the pulmonary vessels act as passive, distensible tubes that enlarge with increasing pressure and narrow with decreasing pressure. For adequate aeration of the blood to occur, it is important for the blood to be distributed to those segments of the lungs where the alveoli are best oxygenated. This is achieved by the following mechanism.

Decreased Alveolar Oxygen Reduces Local Alveolar Blood Flow and Regulates Pulmonary Blood Flow Distribution. When the concentration of oxygen in the air of the alveoli decreases below normal, especially when it falls below 70 percent of normal (below 73 mm Hg Po_2), the adjacent blood vessels constrict, with the vascular resistance increasing more than fivefold at extremely low oxygen levels. This is *opposite to the effect observed in systemic vessels*, which dilate rather than constrict in response to low oxygen. It is believed that the low oxygen concentration causes some yet undiscovered vasoconstrictor substance to be released from the lung tissue; this substance promotes constriction of the small arteries and arterioles. It has been suggested that this vasoconstrictor might be secreted by the alveolar epithelial cells when they become hypoxic.

This effect of low oxygen on pulmonary vascular resistance has an important function: to distribute blood flow where it is most effective. That is, if some alveoli are poorly ventilated so that their oxygen concentration becomes low, the local vessels constrict. This causes the blood to flow through other areas of the lungs that are better aerated, thus providing an automatic control system for distributing blood flow to the pulmonary areas in proportion to their alveolar oxygen pressures.

Effect of Hydrostatic Pressure Gradients in the Lungs on Regional Pulmonary Blood Flow

In Chapter 15, it was pointed out that the blood pressure in the foot of a standing person can be as much as 90 mm Hg greater than the pressure at the level of the heart. This is caused by *hydrostatic pressure*—that is, by the weight of the blood itself in the blood vessels. The same effect, but to a lesser degree, occurs in the lungs. In the normal, upright adult, the lowest point in the lungs is about 30 cm below the highest point. This represents a 23 mm Hg pressure difference, about 15 mm Hg of which is above the heart and 8 below. That is, the pulmonary arterial pressure in the uppermost portion of the lung of a standing person is about 15 mm Hg less than the pulmonary arterial pressure at the level of the heart, and the pressure in the lowest portion of the lungs is about 8 mm Hg greater. Such pressure differences have profound effects on blood flow through the different areas of the lungs. This is demonstrated by the lower curve in Figure 38-3, which depicts blood flow per unit of lung tissue at different levels of the lung in the upright person. Note that in the standing position at rest, there is little flow in the top of the lung but about five times as much flow in the bottom. To help explain these differences, one often describes the lung as being divided into three zones, as shown in Figure 38-4. In each zone, the patterns of blood flow are quite different.

Zones 1, 2, and 3 of Pulmonary Blood Flow

The capillaries in the alveolar walls are distended by the blood pressure inside them, but simultaneously they are compressed by the alveolar air pressure on their outsides. Therefore, any time the lung alveolar air pressure becomes greater than the capillary blood pressure, the capillaries close and there is no blood flow. Under different normal and pathological lung conditions, one may find any one of three possible zones (patterns) of pulmonary blood flow, as follows:

Zone 1: No blood flow during all portions of the cardiac cycle because the local alveolar capillary pressure in that area of the lung never rises higher than the alveolar air pressure during any part of the cardiac cycle

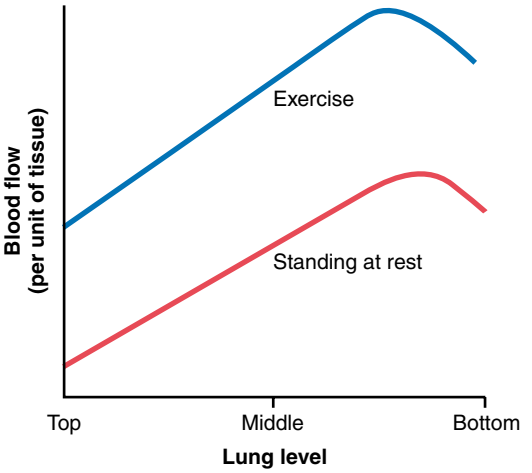


Figure 38-3 Blood flow at different levels in the lung of an upright person *at rest* and *during exercise*. Note that when the person is at rest, the blood flow is very low at the top of the lungs; most of the flow is through the bottom of the lung.

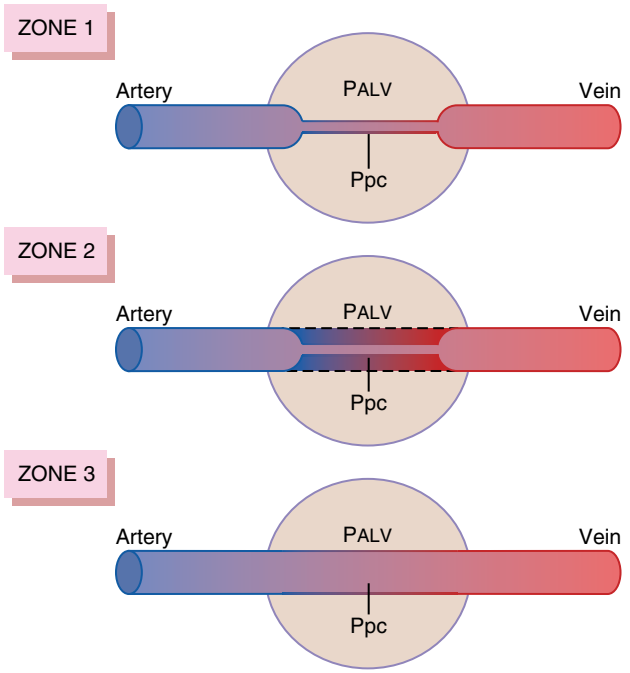


Figure 38-4 Mechanics of blood flow in the three blood flow zones of the lung: *zone 1, no flow*—alveolar air pressure (PALV) is greater than arterial pressure; *zone 2, intermittent flow*—systolic arterial pressure rises higher than alveolar air pressure, but diastolic arterial pressure falls below alveolar air pressure; and *zone 3, continuous flow*—arterial pressure and pulmonary capillary pressure (Ppc) remain greater than alveolar air pressure at all times.

Zone 2: Intermittent blood flow only during the peaks of pulmonary arterial pressure because the systolic pressure is then greater than the alveolar air pressure, but the diastolic pressure is less than the alveolar air pressure

Zone 3: Continuous blood flow because the alveolar capillary pressure remains greater than alveolar air pressure during the entire cardiac cycle

Normally, the lungs have only zones 2 and 3 blood flow—zone 2 (intermittent flow) in the apices and zone 3 (continuous flow) in all the lower areas. For example, when a person is in the upright position, the pulmonary arterial pressure at the lung apex is about 15 mm Hg less than the pressure at the level of the heart. Therefore, the apical systolic pressure is only 10 mm Hg (25 mm Hg at heart level minus 15 mm Hg hydrostatic pressure difference). This 10 mm Hg apical blood pressure is greater than the zero alveolar air pressure, so blood flows through the pulmonary apical capillaries during cardiac systole. Conversely, during diastole, the 8 mm Hg diastolic pressure at the level of the heart is not sufficient to push the blood up the 15 mm Hg hydrostatic pressure gradient required to cause diastolic capillary flow. Therefore, blood flow through the apical part of the lung is intermittent, with flow during systole but cessation of flow during diastole; this is called *zone 2 blood flow*. Zone 2 blood flow begins in the normal lungs about 10 cm above the midlevel of the heart and extends from there to the top of the lungs.

In the lower regions of the lungs, from about 10 cm above the level of the heart all the way to the bottom of the lungs, the pulmonary arterial pressure during both systole and diastole remains greater than the zero alveolar air pressure. Therefore, there is continuous flow through the alveolar capillaries, or zone 3 blood flow. Also, when a person is lying down, no part of the lung is more than a few centimeters above the level of the heart. In this case, blood flow in a normal person is entirely zone 3 blood flow, including the lung apices.

Zone 1 Blood Flow Occurs Only Under Abnormal Conditions. Zone 1 blood flow, which means no blood flow at any time during the cardiac cycle, occurs when either the pulmonary systolic arterial pressure is too low or the alveolar pressure is too high to allow flow. For instance, if an upright person is breathing against a positive air pressure so that the intra-alveolar air pressure is at least 10 mm Hg greater than normal but the pulmonary systolic blood pressure is normal, one would expect zone 1 blood flow—no blood flow—in the lung apices. Another instance in which zone 1 blood flow occurs is in an upright person whose pulmonary systolic arterial pressure is exceedingly low, as might occur after severe blood loss.

Effect of Exercise on Blood Flow Through the Different Parts of the Lungs. Referring again to Figure 38-3, one sees that the blood flow in all parts of the lung increases during exercise. The increase in flow in the top of the lung may be 700 to 800 percent, whereas the increase in the lower part of the lung may be no more than 200 to 300 percent. The reason for these differences is that the pulmonary vascular pressures rise enough during exercise to convert the lung apices from a zone 2 pattern into a zone 3 pattern of flow.

Increased Cardiac Output During Heavy Exercise Is Normally Accommodated by the Pulmonary Circulation Without Large Increases in Pulmonary Artery Pressure

During heavy exercise, blood flow through the lungs increases fourfold to sevenfold. This extra flow is accommodated in the lungs in three ways: (1) by increasing the number of open capillaries, sometimes as much as threefold; (2) by distending all the capillaries and increasing the rate of flow through each capillary more than twofold; and (3) by increasing the pulmonary arterial pressure. In the normal person, the first two changes decrease pulmonary vascular resistance so much that the pulmonary arterial pressure rises very little, even during maximum exercise; this effect is shown in Figure 38-5.

The ability of the lungs to accommodate greatly increased blood flow during exercise without increasing the pulmonary arterial pressure conserves the energy of the right side of the heart. This ability also prevents a significant rise in pulmonary capillary pressure, thus also preventing the development of pulmonary edema.

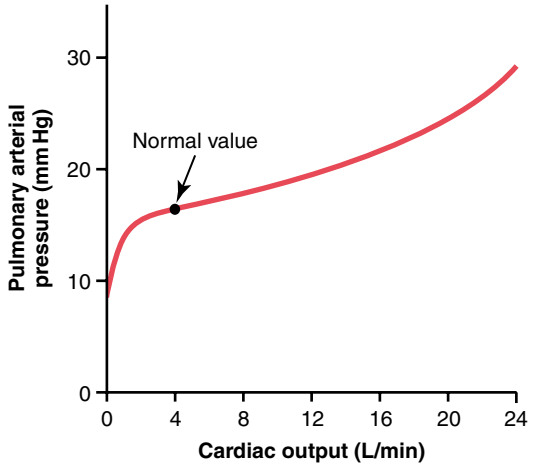


Figure 38-5 Effect on mean pulmonary arterial pressure caused by increasing the cardiac output during exercise.

Function of the Pulmonary Circulation When the Left Atrial Pressure Rises as a Result of Left-Sided Heart Failure

The left atrial pressure in a healthy person almost never rises above +6 mm Hg, even during the most strenuous exercise. These small changes in left atrial pressure have virtually no effect on pulmonary circulatory function because this merely expands the pulmonary venules and opens up more capillaries so that blood continues to flow with almost equal ease from the pulmonary arteries.

When the left side of the heart fails, however, blood begins to dam up in the left atrium. As a result, the left atrial pressure can rise on occasion from its normal value of 1 to 5 mm Hg all the way up to 40 to 50 mm Hg. The initial rise in atrial pressure, up to about 7 mm Hg, has very little effect on pulmonary circulatory function. But when the left atrial pressure rises to greater than 7 or 8 mm Hg, further increases in left atrial pressure above these levels cause almost equally great increases in pulmonary arterial pressure, thus causing a concomitant increased load on the right heart. Any increase in left atrial pressure above 7 or 8 mm Hg increases the capillary pressure almost equally as much. When the left atrial pressure has risen above 30 mm Hg, causing similar increases in capillary pressure, pulmonary edema is likely to develop, as we discuss later in the chapter.

Pulmonary Capillary Dynamics

Exchange of gases between the alveolar air and the pulmonary capillary blood is discussed in the next chapter. However, it is important for us to note here that the alveolar walls are lined with so many capillaries that, in most places, the capillaries almost touch one another side by side. Therefore, it is often said that the capillary blood flows in the alveolar walls as a "sheet of flow," rather than in individual capillaries.

Pulmonary Capillary Pressure. No direct measurements of pulmonary capillary pressure have ever been made. However, "isogravimetric" measurement of pulmonary capillary pressure, using a technique described in Chapter 16, has given a value of 7 mm Hg. This is probably nearly correct because the mean left atrial pressure is about 2 mm Hg and the mean pulmonary arterial pressure is only 15 mm Hg, so the mean pulmonary capillary pressure must lie somewhere between these two values.

Length of Time Blood Stays in the Pulmonary Capillaries. From histological study of the total cross-sectional area of all the pulmonary capillaries, it can be calculated that when the cardiac output is normal, blood passes through the pulmonary capillaries in about 0.8 second. When the cardiac output increases, this can shorten to as little as 0.3 second. The shortening would be much greater were it not for the fact that additional capillaries, which normally are collapsed, open up to accommodate the increased blood flow. Thus, in only a fraction of a second, blood passing through the alveolar capillaries becomes oxygenated and loses its excess carbon dioxide.

Capillary Exchange of Fluid in the Lungs and Pulmonary Interstitial Fluid Dynamics

The dynamics of fluid exchange across the lung capillary membranes are *qualitatively* the same as for peripheral tissues. However, *quantitatively*, there are important differences, as follows:

1. The pulmonary capillary pressure is low, about 7 mm Hg, in comparison with a considerably higher functional capillary pressure in the peripheral tissues of about 17 mm Hg.
2. The interstitial fluid pressure in the lung is slightly more negative than that in the peripheral subcutaneous tissue. (This has been measured in two ways: by a micropipette inserted into the pulmonary interstitium, giving a value of about −5 mm Hg, and by measuring the absorption pressure of fluid from the alveoli, giving a value of about −8 mm Hg.)
3. The pulmonary capillaries are relatively leaky to protein molecules, so the colloid osmotic pressure of the pulmonary interstitial fluid is about 14 mm Hg, in comparison with less than half this value in the peripheral tissues.
4. The alveolar walls are extremely thin, and the alveolar epithelium covering the alveolar surfaces is so weak that it can be ruptured by any positive pressure in the interstitial spaces greater than alveolar air pressure (>0 mm Hg), which allows dumping of fluid from the interstitial spaces into the alveoli.

Now let us see how these quantitative differences affect pulmonary fluid dynamics.

Interrelations Between Interstitial Fluid Pressure and Other Pressures in the Lung. Figure 38-6 shows a pulmonary capillary, a pulmonary alveolus, and a lymphatic capillary draining the interstitial space between the blood capillary and the alveolus. Note the balance of forces at the blood capillary membrane, as follows:

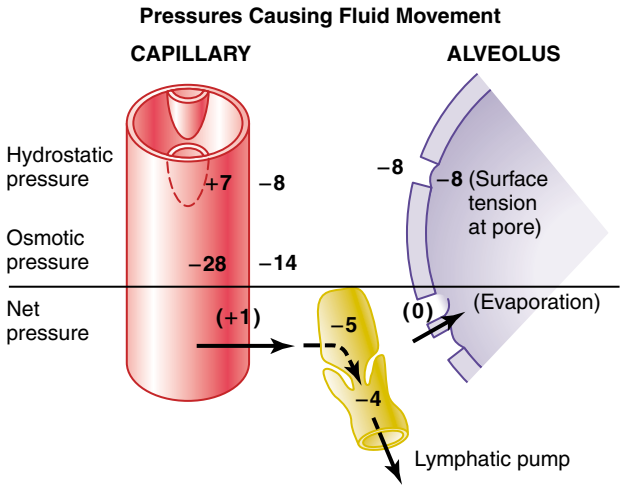


Figure 38-6 Hydrostatic and osmotic forces in mm Hg at the capillary (*left*) and alveolar membrane (*right*) of the lungs. Also shown is the tip end of a lymphatic vessel (*center*) that pumps fluid from the pulmonary interstitial spaces. (Modified from Guyton AC, Taylor AE, Granger HJ: Circulatory Physiology II: Dynamics and Control of the Body Fluids. Philadelphia: WB Saunders, 1975.)

	mm Hg
Forces tending to cause movement of fluid outward from the capillaries and into the pulmonary interstitium:	
Capillary pressure	7
Interstitial fluid colloid osmotic pressure	14
Negative interstitial fluid pressure	8
TOTAL OUTWARD FORCE	29
Forces tending to cause absorption of fluid into the capillaries:	
Plasma colloid osmotic pressure	28
TOTAL INWARD FORCE	28

Thus, the normal outward forces are slightly greater than the inward forces, providing a *mean filtration pressure* at the pulmonary capillary membrane; this can be calculated as follows:

	mm Hg
Total outward force	+29
Total inward force	−28
MEAN FILTRATION PRESSURE	+1

This filtration pressure causes a slight continual flow of fluid from the pulmonary capillaries into the interstitial spaces, and except for a small amount that evaporates in the alveoli, this fluid is pumped back to the circulation through the pulmonary lymphatic system.

Negative Pulmonary Interstitial Pressure and the Mechanism for Keeping the Alveoli "Dry." What keeps the alveoli from filling with fluid under normal conditions? One's first inclination is to think that the alveolar epithelium is strong enough and continuous enough to keep fluid from leaking out of the interstitial spaces into the alveoli. This is not true because experiments have shown that there are always openings between the alveolar epithelial cells through which even large protein molecules, as well as water and electrolytes, can pass.

However, if one remembers that the pulmonary capillaries and the pulmonary lymphatic system normally maintain a slight *negative pressure* in the interstitial spaces, it is clear that whenever extra fluid appears in the alveoli, it will simply be sucked mechanically into the lung interstitium through the small openings between the alveolar epithelial cells. Then the excess fluid is either carried away through the pulmonary lymphatics or absorbed into the pulmonary capillaries. Thus, under normal conditions, the alveoli are kept "dry," except for a small amount of fluid that seeps from the epithelium onto the lining surfaces of the alveoli to keep them moist.

Pulmonary Edema

Pulmonary edema occurs in the same way that edema occurs elsewhere in the body. Any factor that increases fluid filtration out of the pulmonary capillaries or that impedes pulmonary lymphatic function and causes the pulmonary interstitial fluid pressure to rise from the negative range into the positive range will cause rapid filling of the pulmonary interstitial spaces and alveoli with large amounts of free fluid.

The most common causes of pulmonary edema are as follows:

1. Left-sided heart failure or mitral valve disease, with consequent great increases in pulmonary venous pressure and pulmonary capillary pressure and flooding of the interstitial spaces and alveoli.
2. Damage to the pulmonary blood capillary membranes caused by infections such as pneumonia or by breathing noxious substances such as chlorine gas or sulfur dioxide gas. Each of these causes rapid leakage of both plasma proteins and fluid out of the capillaries and into both the lung interstitial spaces and the alveoli.

"Pulmonary Edema Safety Factor." Experiments in animals have shown that the pulmonary capillary pressure normally must rise to a value at least equal to the colloid osmotic pressure of the plasma inside the capillaries before significant pulmonary edema will occur. To give an example, Figure 38-7 shows how different levels of left atrial

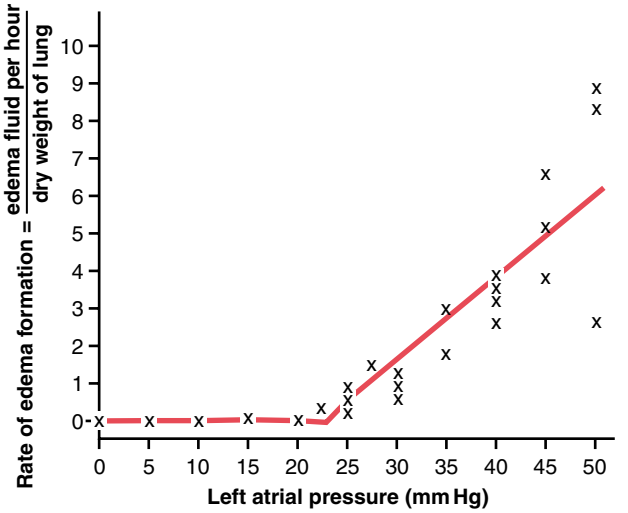


Figure 38-7 Rate of fluid loss into the lung tissues when the left atrial pressure (and pulmonary capillary pressure) is increased. (From Guyton AC, Lindsey AW: Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. Circ Res 7:649, 1959.)

pressure increase the rate of pulmonary edema formation in dogs. Remember that every time the left atrial pressure rises to high values, the pulmonary capillary pressure rises to a level 1 to 2 mm Hg greater than the left atrial pressure. In these experiments, as soon as the left atrial pressure rose above 23 mm Hg (causing the pulmonary capillary pressure to rise above 25 mm Hg), fluid began to accumulate in the lungs. This fluid accumulation increased even more rapidly with further increases in capillary pressure. The plasma colloid osmotic pressure during these experiments was equal to this 25 mm Hg critical pressure level. Therefore, in the human being, whose normal plasma colloid osmotic pressure is 28 mm Hg, one can predict that the pulmonary capillary pressure must rise from the normal level of 7 mm Hg to more than 28 mm Hg to cause pulmonary edema, giving an *acute safety factor against pulmonary edema* of 21 mm Hg.

Safety Factor in Chronic Conditions. When the pulmonary capillary pressure remains elevated chronically (for at least 2 weeks), the lungs become even more resistant to pulmonary edema because the lymph vessels expand greatly, increasing their capability of carrying fluid away from the interstitial spaces perhaps as much as 10-fold. Therefore, in patients with chronic mitral stenosis, pulmonary capillary pressures of 40 to 45 mm Hg have been measured without the development of lethal pulmonary edema.

Rapidity of Death in Acute Pulmonary Edema. When the pulmonary capillary pressure rises even slightly above the safety factor level, lethal pulmonary edema can occur within hours, or even within 20 to 30 minutes if the capillary pressure rises 25 to 30 mm Hg above the safety factor level. Thus, in acute left-sided heart failure, in which the pulmonary capillary pressure occasionally does rise to 50 mm Hg, death frequently ensues in less than 30 minutes from acute pulmonary edema.

Fluid in the Pleural Cavity

When the lungs expand and contract during normal breathing, they slide back and forth within the pleural cavity. To facilitate this, a thin layer of mucoid fluid lies between the parietal and visceral pleurae.

Figure 38-8 shows the dynamics of fluid exchange in the pleural space. The pleural membrane is a porous, mesenchymal, serous membrane through which small amounts of interstitial fluid transude continually into the pleural space. These fluids carry with them tissue proteins, giving the pleural fluid a mucoid characteristic, which is what allows extremely easy slippage of the moving lungs.

The total amount of fluid in each pleural cavity is normally slight, only a few milliliters. Whenever the quantity becomes more than barely enough to begin flowing in the pleural cavity, the excess fluid is pumped away by lymphatic vessels opening directly from the pleural cavity into (1) the mediastinum, (2) the superior surface of the diaphragm, and (3) the lateral surfaces of the parietal pleura. Therefore, the *pleural space*—the space between the parietal and visceral pleurae—is called a *potential space* because it normally is so narrow that it is not obviously a physical space.

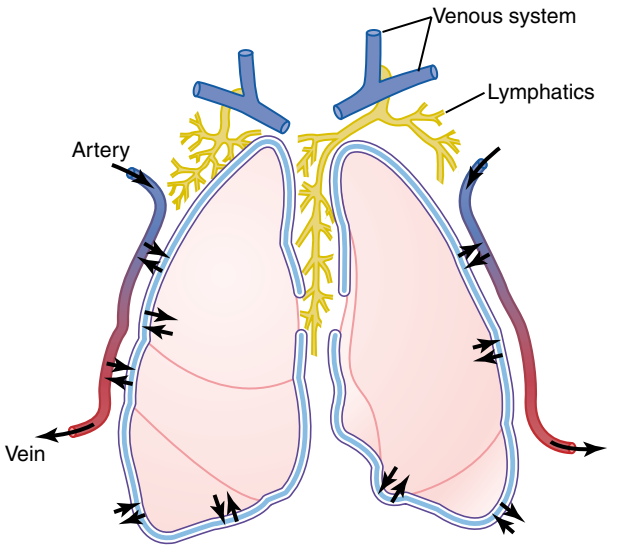


Figure 38-8 Dynamics of fluid exchange in the intrapleural space.

"Negative Pressure" in Pleural Fluid. A negative force is always required on the outside of the lungs to keep the lungs expanded. This is provided by negative pressure in the normal pleural space. The basic cause of this negative pressure is pumping of fluid from the space by the lymphatics (which is also the basis of the negative pressure found in most tissue spaces of the body). Because the normal collapse tendency of the lungs is about −4 mm Hg, the pleural fluid pressure must always be at least as negative as −4 mm Hg to keep the lungs expanded. Actual measurements have shown that the pressure is usually about −7 mm Hg, which is a few millimeters of mercury more negative than the collapse pressure of the lungs. Thus, the negativity of the pleural fluid keeps the normal lungs pulled against the parietal pleura of the chest cavity, except for an extremely thin layer of mucoid fluid that acts as a lubricant.

Pleural Effusion—Collection of Large Amounts of Free Fluid in the Pleural Space. Pleural effusion is analogous to edema fluid in the tissues and can be called "edema of the pleural cavity." The causes of the effusion are the same as the causes of edema in other tissues (discussed in Chapter 25), including (1) blockage of lymphatic drainage from the pleural cavity; (2) cardiac failure, which causes excessively high peripheral and pulmonary capillary pressures, leading to excessive transudation of fluid into the pleural cavity; (3) greatly reduced plasma colloid osmotic pressure, thus allowing excessive transudation of fluid; and (4) infection or any other cause of inflammation of the surfaces of the pleural cavity, which breaks down the capillary membranes and allows rapid dumping of both plasma proteins and fluid into the cavity.

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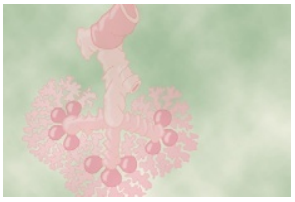
CHAPTER 39

Physical Principles of Gas Exchange; Diffusion of Oxygen and Carbon Dioxide Through the Respiratory Membrane



After the alveoli are ventilated with fresh air, the next step in the respiratory process is *diffusion* of oxygen from the alveoli into the pulmonary blood and diffusion of carbon dioxide in the opposite direction, out of the blood. The process of diffusion is simply the random motion of molecules in all directions through the respiratory membrane and adjacent fluids. However, in respiratory physiology, one is concerned not only with the basic mechanism by which diffusion occurs but also with the *rate* at which it occurs; this is a much more complex problem, requiring a deeper understanding of the physics of diffusion and gas exchange.

Physics of Gas Diffusion and Gas Partial Pressures

Molecular Basis of Gas Diffusion

All the gases of concern in respiratory physiology are simple molecules that are free to move among one another, a process called "diffusion." This is also true of gases dissolved in the fluids and tissues of the body.

For diffusion to occur there must be a source of energy. This is provided by the kinetic motion of the molecules themselves. Except at absolute zero temperature, all molecules of all matter are continually undergoing motion. For free molecules that are not physically attached to others, this means linear movement at high velocity until they strike other molecules. Then they bounce away in new directions and continue until striking other molecules again. In this way, the molecules move rapidly and randomly among one another.

Net Diffusion of a Gas in One Direction—Effect of a Concentration Gradient. If a gas chamber or a solution has a high concentration of a particular gas at one end of the chamber and a low concentration at the other end, as shown in Figure 39-1, net diffusion of the gas will occur from the high-concentration area toward the low-concentration area. The reason is obvious: There are far more molecules at end A of the chamber to diffuse toward end B than there are molecules to diffuse in the opposite direction. Therefore, the rates of diffusion in each of the two directions are proportionately different, as demonstrated by the lengths of the arrows in the figure.

Gas Pressures in a Mixture of Gases—"Partial Pressures" of Individual Gases

Pressure is caused by multiple impacts of moving molecules against a surface. Therefore, the pressure of a gas acting on the surfaces of the respiratory passages and alveoli is proportional to the summated force of impact of all the molecules of that gas striking the surface at any given instant. This means that *the pressure is directly proportional to the concentration of the gas molecules*.

In respiratory physiology, one deals with mixtures of gases, mainly of *oxygen, nitrogen*, and *carbon dioxide*. The rate of diffusion of each of these gases is directly proportional to the pressure caused by that gas alone, which is called the *partial pressure* of that gas. The concept of partial pressure can be explained as follows.

Consider air, which has an approximate composition of 79 percent nitrogen and 21 percent oxygen. The total pressure of this mixture at sea level averages 760 mm Hg. It is clear from the preceding description of the molecular basis of pressure that each gas contributes to the total pressure in direct proportion to its concentration. Therefore, 79 percent of the 760 mm Hg is caused by nitrogen (600 mm Hg) and 21 percent by oxygen (160 mm Hg). Thus, the "partial pressure" of nitrogen in the mixture is 600 mm Hg, and the "partial pressure" of oxygen is 160 mm Hg; the total pressure is 760 mm Hg, the sum of the individual partial pressures. The partial pressures of individual gases in a mixture are designated by the symbols P_{O_2}, P_{CO_2}, P_{N_2}, P_{He}, and so forth.

Pressures of Gases Dissolved in Water and Tissues

Gases dissolved in water or in body tissues also exert pressure because the dissolved gas molecules are moving randomly and have kinetic energy. Further, when the gas dissolved in fluid encounters a surface, such as the membrane of a cell, it exerts its own partial pressure in the same way that a gas in the gas phase does. The partial pressures of the separate dissolved gases are designated the same as the partial pressures in the gas state, that is, P_{O_2}, P_{CO_2}, P_{N_2}, P_{He}, and so forth.

Factors That Determine the Partial Pressure of a Gas Dissolved in a Fluid. The partial pressure of a gas in a solution is determined not only by its concentration but also by the *solubility coefficient* of the gas. That is, some types of molecules, especially carbon dioxide, are physically or chemically attracted to water molecules, whereas others are repelled. When molecules are attracted, far more of them can be dissolved without building up excess partial pressure

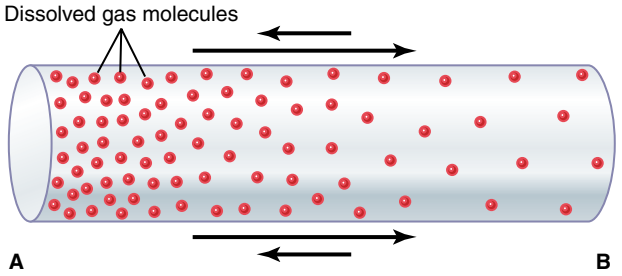


Figure 39-1 Diffusion of oxygen from one end of a chamber (*A*) to the other (*B*). The difference between the lengths of the arrows represents *net diffusion*.

within the solution. Conversely, in the case of those that are repelled, high partial pressure will develop with fewer dissolved molecules. These relations are expressed by the following formula, which is *Henry's law:*

$$\text{Partial pressure} = \frac{\text{Concentration of dissolved gas}}{\text{Solubility coefficient}}$$

When partial pressure is expressed in atmospheres (1 atmosphere pressure equals 760 mm Hg) and concentration is expressed in volume of gas dissolved in each volume of water, the solubility coefficients for important respiratory gases at body temperature are the following:

Oxygen	0.024
Carbon dioxide	0.57
Carbon monoxide	0.018
Nitrogen	0.012
Helium	0.008

From this table, one can see that carbon dioxide is more than 20 times as soluble as oxygen. Therefore, the partial pressure of carbon dioxide (for a given concentration) is less than one-twentieth that exerted by oxygen.

Diffusion of Gases Between the Gas Phase in the Alveoli and the Dissolved Phase in the Pulmonary Blood. The partial pressure of each gas in the alveolar respiratory gas mixture tends to force molecules of that gas into solution in the blood of the alveolar capillaries. Conversely, the molecules of the same gas that are already dissolved in the blood are bouncing randomly in the fluid of the blood, and some of these bouncing molecules escape back into the alveoli. The rate at which they escape is directly proportional to their partial pressure in the blood.

But in which direction will *net diffusion* of the gas occur? The answer is that net diffusion is determined by the difference between the two partial pressures. If the partial pressure is greater in the gas phase in the alveoli, as is normally true for oxygen, then more molecules will diffuse into the blood than in the other direction. Alternatively, if the partial pressure of the gas is greater in the dissolved state in the blood, which is normally true for carbon dioxide, then net diffusion will occur toward the gas phase in the alveoli.

Vapor Pressure of Water

When nonhumidified air is breathed into the respiratory passageways, water immediately evaporates from the surfaces of these passages and humidifies the air. This results from the fact that water molecules, like the different dissolved gas molecules, are continually escaping from the water surface into the gas phase. The partial pressure that the water molecules exert to escape through the surface is called the *vapor pressure* of the water. At normal body temperature, 37°C, this vapor pressure is 47 mm Hg. Therefore, once the gas mixture has become fully humidified—that is, once it is in "equilibrium" with the water—the partial pressure of the water vapor in the gas mixture is 47 mm Hg. This partial pressure, like the other partial pressures, is designated P_{H_2O}.

The vapor pressure of water depends entirely on the temperature of the water. The greater the temperature, the greater the kinetic activity of the molecules and, therefore, the greater the likelihood that the water molecules will escape from the surface of the water into the gas phase. For instance, the water vapor pressure at 0°C is 5 mm Hg, and at 100°C it is 760 mm Hg. But the most important value to remember is the *vapor pressure at body temperature, 47 mm Hg*; this value appears in many of our subsequent discussions.

Diffusion of Gases Through Fluids—Pressure Difference Causes Net Diffusion

From the preceding discussion, it is clear that when the partial pressure of a gas is greater in one area than in another area, there will be net diffusion from the high-pressure area toward the low-pressure area. For instance, returning to Figure 39-1, one can readily see that the molecules in the area of high pressure, because of their greater number, have a greater chance of moving randomly into the area of low pressure than do molecules attempting to go in the other direction. However, some molecules do bounce randomly from the area of low pressure toward the area of high pressure. Therefore, the *net diffusion* of gas from the area of high pressure to the area of low pressure is equal to the number of molecules bouncing in this forward direction *minus* the number bouncing in the opposite direction; this is proportional to the gas partial pressure difference between the two areas, called simply the *pressure difference for causing diffusion*.

Quantifying the Net Rate of Diffusion in Fluids. In addition to the pressure difference, several other factors affect the rate of gas diffusion in a fluid. They are (1) the solubility of the gas in the fluid, (2) the cross-sectional area of the fluid, (3) the distance through which the gas must diffuse, (4) the molecular weight of the gas, and (5) the temperature of the fluid. In the body, the last of these factors, the temperature, remains reasonably constant and usually need not be considered.

The greater the solubility of the gas, the greater the number of molecules available to diffuse for any given partial pressure difference. The greater the cross-sectional area of the diffusion pathway, the greater the total number of molecules that diffuse. Conversely, the greater the distance the molecules must diffuse, the longer it will take the molecules to diffuse the entire distance. Finally, the greater the velocity of kinetic movement of the molecules, which is inversely proportional to the square root of the molecular weight, the greater the rate of diffusion of the gas. All these factors can be expressed in a single formula, as follows:

$$D \propto \frac{\Delta P \times A \times S}{d \times \sqrt{MW}},$$

in which D is the diffusion rate, ΔP is the partial pressure difference between the two ends of the diffusion pathway, A is the cross-sectional area of the pathway, S is the solubility of the gas, d is the distance of diffusion, and MW is the molecular weight of the gas.

It is obvious from this formula that the characteristics of the gas itself determine two factors of the formula: solubility and molecular weight. Together, these two factors determine the *diffusion coefficient of the gas*, which is proportional to $S/\sqrt{MW}$ that is, the relative rates at which different gases at the same partial pressure levels will diffuse are proportional to their diffusion coefficients. Assuming that the diffusion coefficient for oxygen is 1, the *relative* diffusion coefficients for different gases of respiratory importance in the body fluids are as follows:

Oxygen	1.0
Carbon dioxide	20.3
Carbon monoxide	0.81
Nitrogen	0.53
Helium	0.95

Diffusion of Gases Through Tissues

The gases that are of respiratory importance are all highly soluble in lipids and, consequently, are highly soluble in cell membranes. Because of this, the major limitation to the movement of gases in tissues is the rate at which the gases can diffuse through the tissue water instead of through the cell membranes. Therefore, diffusion of gases through the tissues, including through the respiratory membrane, is almost equal to the diffusion of gases in water, as given in the preceding list.

Compositions of Alveolar Air and Atmospheric Air Are Different

Alveolar air does not have the same concentrations of gases as atmospheric air by any means, which can readily be seen by comparing the alveolar air composition in Table 39-1 with that of atmospheric air. There are several reasons for the differences. First, the alveolar air is only partially replaced by atmospheric air with each breath. Second, oxygen is constantly being absorbed into the pulmonary blood from the alveolar air. Third, carbon dioxide is constantly diffusing from the pulmonary blood into the alveoli. And fourth, dry atmospheric air that enters the respiratory passages is humidified even before it reaches the alveoli.

Humidification of the Air in the Respiratory Passages. Table 39-1 shows that atmospheric air is composed almost entirely of nitrogen and oxygen; it normally contains almost no carbon dioxide and little water vapor. However, as soon as the atmospheric air enters the respiratory passages, it is exposed to the fluids that cover the respiratory surfaces. Even before the air enters the alveoli, it becomes (for all practical purposes) totally humidified.

The partial pressure of water vapor at a normal body temperature of 37°C is 47 mm Hg, which is therefore the partial pressure of water vapor in the alveolar air. Because the total pressure in the alveoli cannot rise to more than the atmospheric pressure (760 mm Hg at sea level), this water vapor simply *dilutes* all the other gases in the inspired air. Table 39-1 also shows that humidification of the air dilutes the oxygen partial pressure at sea level from an average of 159 mm Hg in atmospheric air to 149 mm Hg in the humidified air, and it dilutes the nitrogen partial pressure from 597 to 563 mm Hg.

Rate at Which Alveolar Air Is Renewed by Atmospheric Air

In Chapter 37, it was pointed out that the average male *functional residual capacity* of the lungs (the volume of air remaining in the lungs at the end of normal expiration) measures about 2300 milliliters. Yet only 350 milliliters of new air is brought into the alveoli with each normal inspiration, and this same amount of old alveolar air is expired. Therefore, the volume of alveolar air replaced by new atmospheric air with each breath is only one seventh of the total, so multiple breaths are required to exchange most of the alveolar air. Figure 39-2 shows this slow rate of renewal of the alveolar air. In the first alveolus of the figure, excess gas is present in the alveoli, but note that even at the end of 16 breaths, the excess gas still has not been completely removed from the alveoli.

Figure 39-3 demonstrates graphically the rate at which excess gas in the alveoli is normally removed, showing that with normal alveolar ventilation, about one-half the gas is

Table 39-1 Partial Pressures of Respiratory Gases as They Enter and Leave the Lungs (at Sea Level)

	Atmospheric Air* (mm Hg)		Humidified Air (mm Hg)		Alveolar Air (mm Hg)		Expired Air (mm Hg)	
N_2	597.0	(78.62%)	563.4	(74.09%)	569.0	(74.9%)	566.0	(74.5%)
O_2	159.0	(20.84%)	149.3	(19.67%)	104.0	(13.6%)	120.0	(15.7%)
CO_2	0.3	(0.04%)	0.3	(0.04%)	40.0	(5.3%)	27.0	(3.6%)
H_2O	3.7	(0.50%)	47.0	(6.20%)	47.0	(6.2%)	47.0	(6.2%)
TOTAL	760.0	(100.0%)	760.0	(100.0%)	760.0	(100.0%)	760.0	(100.0%)

*On an average cool, clear day.

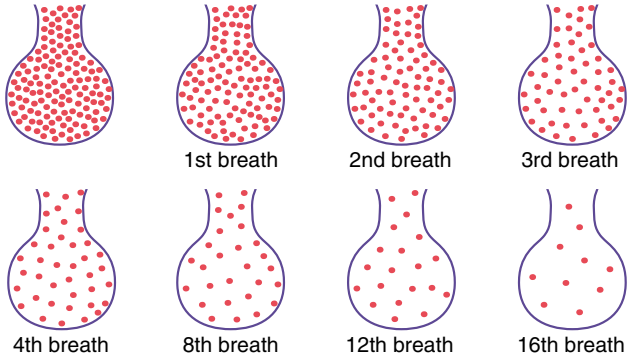


Figure 39-2 Expiration of a gas from an alveolus with successive breaths.

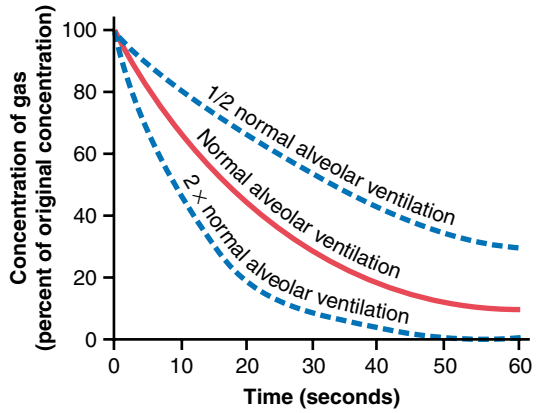


Figure 39-3 Rate of removal of excess gas from alveoli.

removed in 17 seconds. When a person's rate of alveolar ventilation is only one-half normal, one-half the gas is removed in 34 seconds, and when the rate of ventilation is twice normal, one half is removed in about 8 seconds.

Importance of the Slow Replacement of Alveolar Air. The slow replacement of alveolar air is of particular importance in preventing sudden changes in gas concentrations in the blood. This makes the respiratory control mechanism much more stable than it would be otherwise, and it helps prevent excessive increases and decreases in tissue oxygenation, tissue carbon dioxide concentration, and tissue pH when respiration is temporarily interrupted.

Oxygen Concentration and Partial Pressure in the Alveoli

Oxygen is continually being absorbed from the alveoli into the blood of the lungs, and new oxygen is continually being breathed into the alveoli from the atmosphere. The more rapidly oxygen is absorbed, the lower its concentration in the alveoli becomes; conversely, the more rapidly new oxygen is breathed into the alveoli from the atmosphere, the higher its concentration becomes. Therefore, oxygen concentration in the alveoli, as well as its partial pressure, is controlled by (1) the rate of absorption of oxygen into the blood and (2) the rate of entry of new oxygen into the lungs by the ventilatory process.

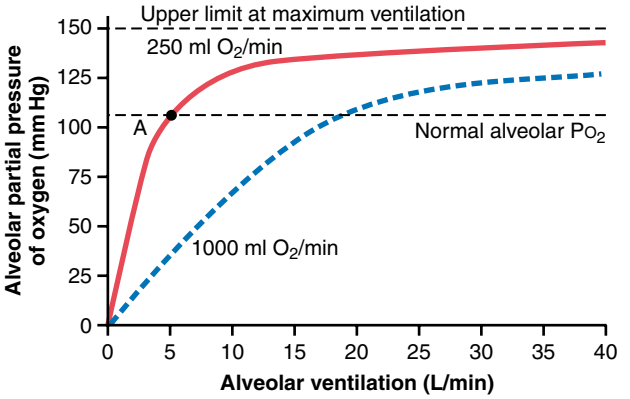


Figure 39-4 Effect of alveolar ventilation on the alveolar P_{O_2} at two rates of oxygen absorption from the alveoli—250 ml/min and 1000 ml/min. *Point A* is the normal operating point.

Figure 39-4 shows the effect of both alveolar ventilation and rate of oxygen absorption into the blood on the alveolar partial pressure of oxygen (P_{O_2}). One curve represents oxygen absorption at a rate of 250 ml/min, and the other curve represents a rate of 1000 ml/min. At a normal ventilatory rate of 4.2 L/min and an oxygen consumption of 250 ml/min, the normal operating point in Figure 39-4 is point A. The figure also shows that when 1000 milliliters of oxygen is being absorbed each minute, as occurs during moderate exercise, the rate of alveolar ventilation must increase fourfold to maintain the alveolar P_{O_2} at the normal value of 104 mm Hg.

Another effect shown in Figure 39-4 is that an extremely marked increase in alveolar ventilation can never increase the alveolar P_{O_2} above 149 mm Hg as long as the person is breathing normal atmospheric air at sea level pressure, because this is the maximum P_{O_2} in humidified air at this pressure. If the person breathes gases that contain partial pressures of oxygen higher than 149 mm Hg, the alveolar P_{O_2} can approach these higher pressures at high rates of ventilation.

CO_2 Concentration and Partial Pressure in the Alveoli

Carbon dioxide is continually being formed in the body and then carried in the blood to the alveoli; it is continually being removed from the alveoli by ventilation. Figure 39-5 shows the effects on the alveolar partial pressure of carbon dioxide (P_{CO_2}) of both alveolar ventilation and two rates of carbon dioxide excretion, 200 and 800 ml/min. One curve represents a normal rate of carbon dioxide excretion of 200 ml/min. At the normal rate of alveolar ventilation of 4.2 L/min, the operating point for alveolar P_{CO_2} is at point A in Figure 39-5 (i.e., 40 mm Hg).

Two other facts are also evident from Figure 39-5: First, *the alveolar P_{CO_2} increases directly in proportion to the rate of carbon dioxide excretion*, as represented by the fourfold elevation of the curve (when 800 milliliters of CO_2 are excreted per minute). Second, *the alveolar P_{CO_2} decreases in inverse proportion to alveolar ventilation.*

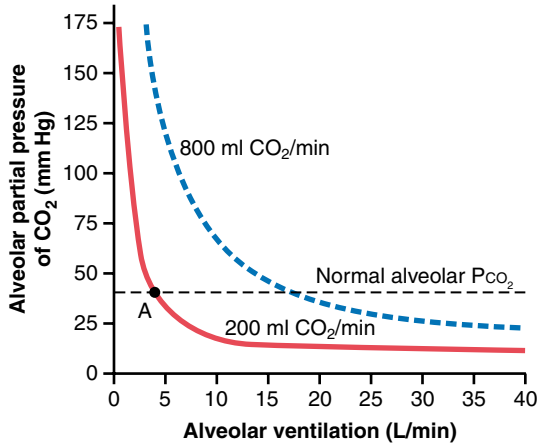


Figure 39-5 Effect of alveolar ventilation on the alveolar P_{CO_2} at two rates of carbon dioxide excretion from the blood—800 ml/min and 200 ml/min. *Point A* is the normal operating point.

Therefore, the concentrations and partial pressures of both oxygen and carbon dioxide in the alveoli are determined by the rates of absorption or excretion of the two gases and by the amount of alveolar ventilation.

Expired Air Is a Combination of Dead Space Air and Alveolar Air

The overall composition of expired air is determined by (1) the amount of the expired air that is dead space air and (2) the amount that is alveolar air. Figure 39-6 shows the progressive changes in oxygen and carbon dioxide partial pressures in the expired air during the course of expiration. The first portion of this air, the dead space air from the respiratory passageways, is typical humidified air, as shown in Table 39-1. Then, progressively more and more alveolar air becomes mixed with the dead space air until all the dead space air has finally been washed out and nothing but alveolar air is expired at the end of expiration. Therefore, the method of collecting alveolar air for study is simply to collect a sample of the last portion of the expired air after forceful expiration has removed all the dead space air.

Normal expired air, containing both dead space air and alveolar air, has gas concentrations and partial pressures approximately as shown in Table 39-1 (i.e., concentrations between those of alveolar air and humidified atmospheric air).

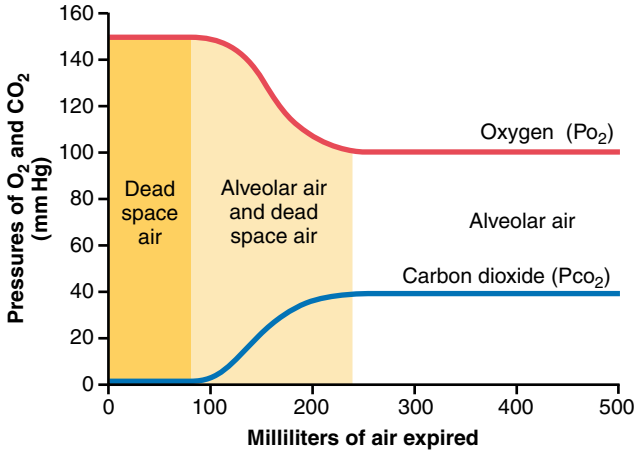


Figure 39-6 Oxygen and carbon dioxide partial pressures in the various portions of normal expired air.

Diffusion of Gases Through the Respiratory Membrane

Respiratory Unit. Figure 39-7 shows the *respiratory unit* (also called "respiratory lobule"), which is composed of a *respiratory bronchiole, alveolar ducts, atria*, and *alveoli*. There are about 300 million alveoli in the two lungs, and each alveolus has an average diameter of about 0.2 millimeter. The alveolar walls are extremely thin, and between the alveoli is an almost solid network of interconnecting capillaries, shown in Figure 39-8. Indeed, because of the extensiveness of the capillary plexus, the flow of blood in the alveolar wall has been described as a "sheet" of flowing blood. Thus, it is obvious that the alveolar gases are in very close proximity to the blood of the pulmonary capillaries. Further, gas exchange between the alveolar air and the pulmonary blood occurs through the membranes of all the terminal portions of the lungs, not merely in the alveoli themselves. All these membranes are collectively known as the *respiratory membrane*, also called the *pulmonary membrane*.

Respiratory Membrane. Figure 39-9 shows the ultrastructure of the respiratory membrane drawn in cross section on the left and a red blood cell on the right. It also shows the diffusion of oxygen from the alveolus into the red blood cell and diffusion of carbon dioxide in

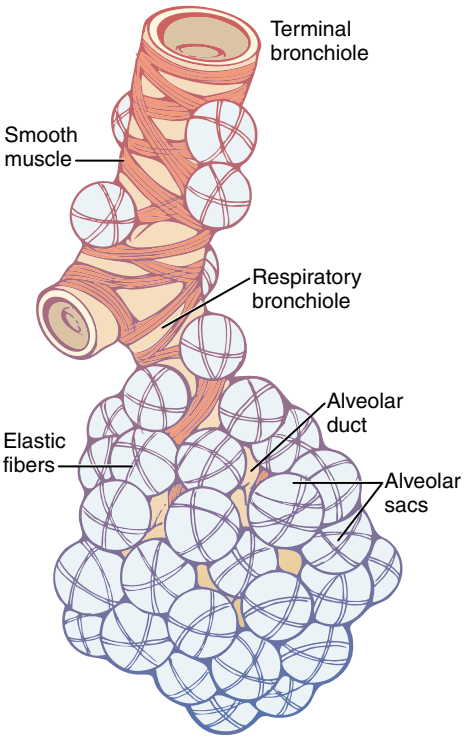


Figure 39-7 Respiratory unit.

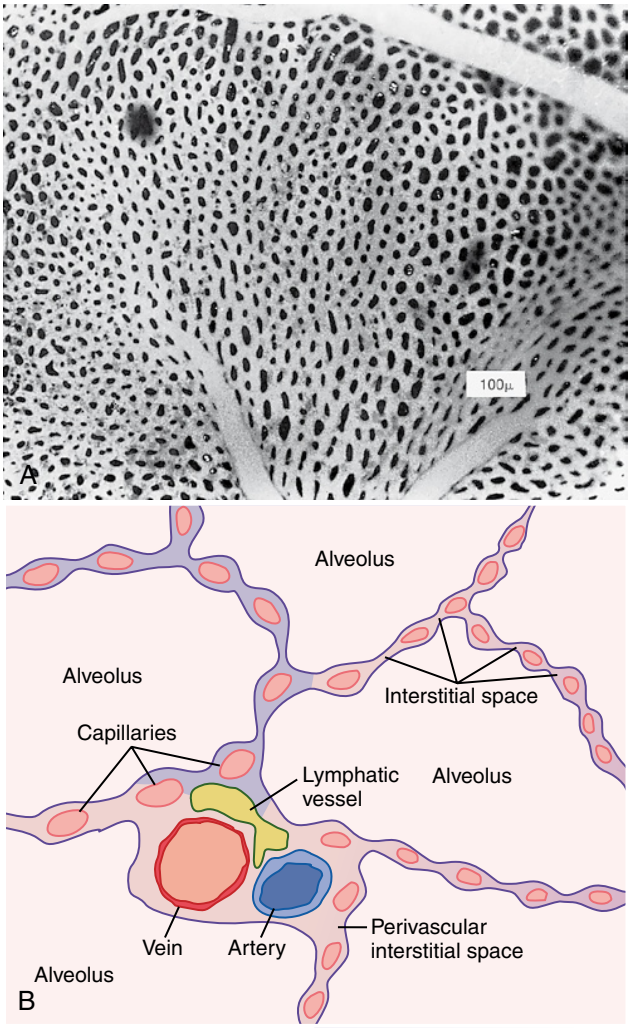


Figure 39-8 *A*, Surface view of capillaries in an alveolar wall. *B*, Cross-sectional view of alveolar walls and their vascular supply. (*A*, From Maloney JE, Castle BL: Pressure-diameter relations of capillaries and small blood vessels in frog lung. Respir Physiol 7:150, 1969. Reproduced by permission of ASP Biological and Medical Press, North-Holland Division.)

the opposite direction. Note the following different layers of the respiratory membrane:

1. A layer of fluid lining the alveolus and containing surfactant that reduces the surface tension of the alveolar fluid
2. The alveolar epithelium composed of thin epithelial cells
3. An epithelial basement membrane
4. A thin interstitial space between the alveolar epithelium and the capillary membrane
5. A capillary basement membrane that in many places fuses with the alveolar epithelial basement membrane
6. The capillary endothelial membrane

Despite the large number of layers, the overall thickness of the respiratory membrane in some areas is as little as 0.2 micrometer, and it averages about 0.6 micrometer, except where there are cell nuclei. From histological

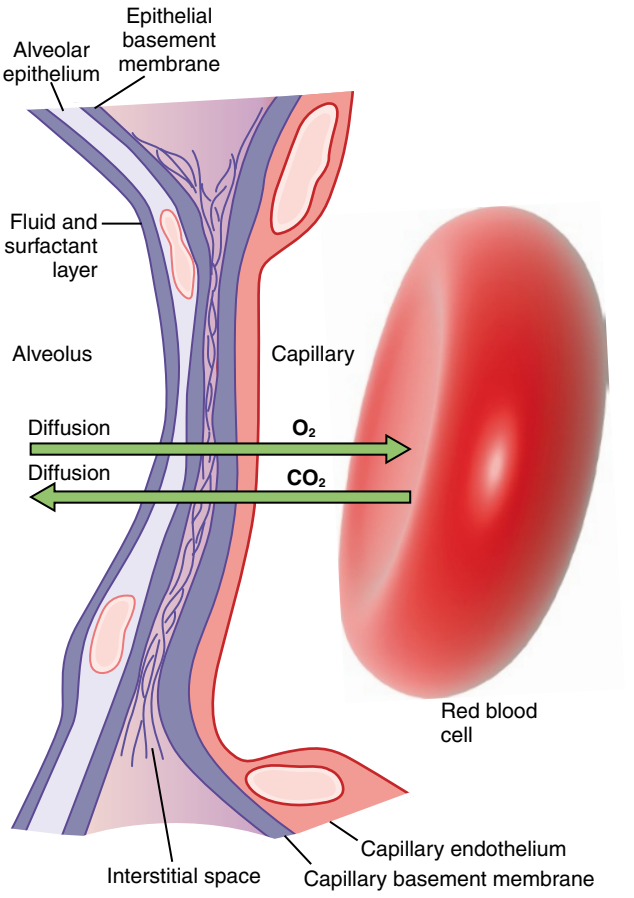


Figure 39-9 Ultrastructure of the alveolar respiratory membrane, shown in cross section.

studies, it has been estimated that the total surface area of the respiratory membrane is about 70 square meters in the normal adult human male. This is equivalent to the floor area of a 25-by-30-foot room. The total quantity of blood in the capillaries of the lungs at any given instant is 60 to 140 milliliters. Now imagine this small amount of blood spread over the entire surface of a 25-by-30-foot floor, and it is easy to understand the rapidity of the respiratory exchange of oxygen and carbon dioxide.

The average diameter of the pulmonary capillaries is only about 5 micrometers, which means that red blood cells must squeeze through them. The red blood cell membrane usually touches the capillary wall, so oxygen and carbon dioxide need not pass through significant amounts of plasma as they diffuse between the alveolus and the red cell. This, too, increases the rapidity of diffusion.

Factors That Affect the Rate of Gas Diffusion Through the Respiratory Membrane

Referring to the earlier discussion of diffusion of gases in water, one can apply the same principles and mathematical formulas to diffusion of gases through the respiratory membrane. Thus, the factors that determine how rapidly a gas will pass through the membrane are (1) the *thickness of the membrane*, (2) the *surface area of the membrane*,

(3) the *diffusion coefficient* of the gas in the substance of the membrane, and (4) the *partial pressure difference* of the gas between the two sides of the membrane.

The *thickness of the respiratory membrane* occasionally increases—for instance, as a result of edema fluid in the interstitial space of the membrane and in the alveoli—so the respiratory gases must then diffuse not only through the membrane but also through this fluid. Also, some pulmonary diseases cause fibrosis of the lungs, which can increase the thickness of some portions of the respiratory membrane. Because the rate of diffusion through the membrane is inversely proportional to the thickness of the membrane, any factor that increases the thickness to more than two to three times normal can interfere significantly with normal respiratory exchange of gases.

The *surface area of the respiratory membrane* can be greatly decreased by many conditions. For instance, removal of an entire lung decreases the total surface area to one half normal. Also, in *emphysema*, many of the alveoli coalesce, with dissolution of many alveolar walls. Therefore, the new alveolar chambers are much larger than the original alveoli, but the total surface area of the respiratory membrane is often decreased as much as fivefold because of loss of the alveolar walls. When the total surface area is decreased to about one-third to one-fourth normal, exchange of gases through the membrane is impeded to a significant degree, *even under resting conditions*, and during competitive sports and other strenuous exercise even the slightest decrease in surface area of the lungs can be a serious detriment to respiratory exchange of gases.

The *diffusion coefficient* for transfer of each gas through the respiratory membrane depends on the gas's *solubility* in the membrane and, inversely, on the *square root* of the gas's *molecular weight*. The rate of diffusion in the respiratory membrane is almost exactly the same as that in water, for reasons explained earlier. Therefore, for a given pressure difference, carbon dioxide diffuses about 20 times as rapidly as oxygen. Oxygen diffuses about twice as rapidly as nitrogen.

The *pressure difference* across the respiratory membrane is the difference between the partial pressure of the gas in the alveoli and the partial pressure of the gas in the pulmonary capillary blood. The partial pressure represents a measure of the total number of molecules of a particular gas striking a unit area of the alveolar surface of the membrane in unit time, and the pressure of the gas in the blood represents the number of molecules that attempt to escape from the blood in the opposite direction. Therefore, the difference between these two pressures is a measure of the *net tendency* for the gas molecules to move through the membrane.

When the partial pressure of a gas in the alveoli is greater than the pressure of the gas in the blood, as is true for oxygen, net diffusion from the alveoli into the blood occurs; when the pressure of the gas in the blood is greater than the partial pressure in the alveoli, as is true for carbon dioxide, net diffusion from the blood into the alveoli occurs.

Diffusing Capacity of the Respiratory Membrane

The ability of the respiratory membrane to exchange a gas between the alveoli and the pulmonary blood is expressed in quantitative terms by the *respiratory membrane's diffusing capacity*, which is defined as the *volume of a gas that will diffuse through the membrane each minute for a partial pressure difference of 1 mm Hg*. All the factors discussed earlier that affect diffusion through the respiratory membrane can affect this diffusing capacity.

Diffusing Capacity for Oxygen. In the average young man, the *diffusing capacity for oxygen* under resting conditions averages *21 ml/min/mm Hg*. In functional terms, what does this mean? The mean oxygen pressure difference across the respiratory membrane during normal, quiet breathing is about 11 mm Hg. Multiplication of this pressure by the diffusing capacity (11 × 21) gives a total of about 230 milliliters of oxygen diffusing through the respiratory membrane each minute; this is equal to the rate at which the resting body uses oxygen.

Increased Oxygen Diffusing Capacity During Exercise. During strenuous exercise or other conditions that greatly increase pulmonary blood flow and alveolar ventilation, the diffusing capacity for oxygen increases in young men to a maximum of about 65 ml/min/mm Hg, which is three times the diffusing capacity under resting conditions. This increase is caused by several factors, among which are (1) opening up of many previously dormant pulmonary capillaries or extra dilation of already open capillaries, thereby increasing the surface area of the blood into which the oxygen can diffuse; and (2) a better match between the ventilation of the alveoli and the perfusion of the alveolar capillaries with blood, called the *ventilation-perfusion ratio*, which is explained in detail later in this chapter. Therefore, during exercise, oxygenation of the blood is increased not only by increased alveolar ventilation but also by greater diffusing capacity of the respiratory membrane for transporting oxygen into the blood.

Diffusing Capacity for Carbon Dioxide. The diffusing capacity for carbon dioxide has never been measured because of the following technical difficulty: Carbon dioxide diffuses through the respiratory membrane so rapidly that the average P_{CO_2} in the pulmonary blood is not far different from the P_{CO_2} in the alveoli—the average difference is less than 1 mm Hg—and with the available techniques, this difference is too small to be measured.

Nevertheless, measurements of diffusion of other gases have shown that the diffusing capacity varies directly with the diffusion coefficient of the particular gas. Because the diffusion coefficient of carbon dioxide is slightly more than 20 times that of oxygen, one would expect a diffusing capacity for carbon dioxide under resting conditions of about 400 to 450 ml/min/mm Hg and during exercise of about 1200 to 1300 ml/min/mm Hg. Figure 39-10

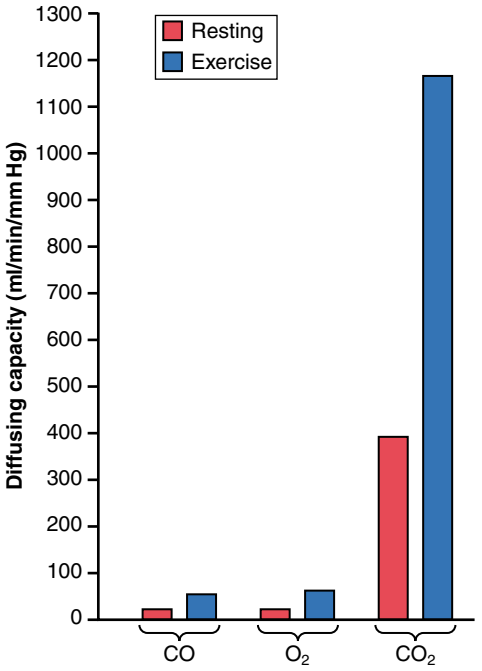


Figure 39-10 *Diffusing capacities* for carbon monoxide, oxygen, and carbon dioxide in the normal lungs under resting conditions and during exercise.

compares the measured or calculated diffusing capacities of carbon monoxide, oxygen, and carbon dioxide at rest and during exercise, showing the extreme diffusing capacity of carbon dioxide and the effect of exercise on the diffusing capacity of each of these gases.

Measurement of Diffusing Capacity—the Carbon Monoxide Method. The oxygen diffusing capacity can be calculated from measurements of (1) alveolar P_{O_2}, (2) P_{O_2} in the pulmonary capillary blood, and (3) the rate of oxygen uptake by the blood. However, measuring the P_{O_2} in the pulmonary capillary blood is so difficult and so imprecise that it is not practical to measure oxygen diffusing capacity by such a direct procedure, except on an experimental basis.

To obviate the difficulties encountered in measuring oxygen diffusing capacity directly, physiologists usually measure carbon monoxide diffusing capacity instead and then calculate the oxygen diffusing capacity from this. The principle of the carbon monoxide method is the following: A small amount of carbon monoxide is breathed into the alveoli, and the partial pressure of the carbon monoxide in the alveoli is measured from appropriate alveolar air samples. The carbon monoxide pressure in the blood is essentially zero because hemoglobin combines with this gas so rapidly that its pressure never has time to build up. Therefore, the pressure difference of carbon monoxide across the respiratory membrane is equal to its partial pressure in the alveolar air sample. Then, by measuring the volume of carbon monoxide absorbed in a short period and dividing this by the alveolar carbon monoxide partial pressure, one can determine accurately the carbon monoxide diffusing capacity.

To convert carbon monoxide diffusing capacity to oxygen diffusing capacity, the value is multiplied by a factor of 1.23 because the diffusion coefficient for oxygen is 1.23 times that for carbon monoxide. Thus, the average diffusing capacity for carbon monoxide in young men at rest is 17 ml/min/mm Hg, and the diffusing capacity for oxygen is 1.23 times this, or 21 ml/min/mm Hg.

Effect of the Ventilation-Perfusion Ratio on Alveolar Gas Concentration

In the early part of this chapter, we learned that two factors determine the P_{O_2} and the P_{CO_2} in the alveoli: (1) the rate of alveolar ventilation and (2) the rate of transfer of oxygen and carbon dioxide through the respiratory membrane. These earlier discussions made the assumption that all the alveoli are ventilated equally and that blood flow through the alveolar capillaries is the same for each alveolus. However, even normally to some extent, and especially in many lung diseases, some areas of the lungs are well ventilated but have almost no blood flow, whereas other areas may have excellent blood flow but little or no ventilation. In either of these conditions, gas exchange through the respiratory membrane is seriously impaired, and the person may suffer severe respiratory distress despite both normal *total* ventilation and normal *total* pulmonary blood flow, but with the ventilation and blood flow going to different parts of the lungs. Therefore, a highly quantitative concept has been developed to help us understand respiratory exchange when there is imbalance between alveolar ventilation and alveolar blood flow. This concept is called the *ventilation-perfusion ratio*.

In quantitative terms, the ventilation-perfusion ratio is expressed as $\dot{V}_A/\dot{Q}$. When $\dot{V}_A$ (alveolar ventilation) is normal for a given alveolus and $\dot{Q}$ (blood flow) is also normal for the same alveolus, the ventilation-perfusion ratio ($\dot{V}_A/\dot{Q}$) is also said to be normal. When the ventilation ($\dot{V}_A$) is zero, yet there is still perfusion ($\dot{Q}$) of the alveolus, the $\dot{V}_A/\dot{Q}$ is zero. Or, at the other extreme, when there is adequate ventilation ($\dot{V}_A$) but zero perfusion ($\dot{Q}$), the ratio $\dot{V}_A/\dot{Q}$ is infinity. At a ratio of either zero or infinity, there is no exchange of gases through the respiratory membrane of the affected alveoli, which explains the importance of this concept. Therefore, let us explain the respiratory consequences of these two extremes.

Alveolar Oxygen and Carbon Dioxide Partial Pressures When $\dot{V}_A/\dot{Q}$ Equals Zero. When $\dot{V}_A/\dot{Q}$ is equal to zero—that is, without any alveolar ventilation—the air in the alveolus comes to equilibrium with the blood oxygen and carbon dioxide because these gases diffuse between the blood and the alveolar air. Because the blood that perfuses the capillaries is venous blood returning to the lungs from the systemic circulation, it is the gases in this blood with which the alveolar gases equilibrate. In Chapter 40, we describe how the normal venous blood ($\bar{v}$) has a P_{O_2} of 40 mm Hg and a P_{CO_2} of 45 mm Hg. Therefore, these are also the normal partial pressures of these two gases in alveoli that have blood flow but no ventilation.

Alveolar Oxygen and Carbon Dioxide Partial Pressures When $\dot{V}_A/\dot{Q}$ Equals Infinity. The effect on the alveolar gas partial pressures when $\dot{V}_A/\dot{Q}$ equals infinity is entirely different from the effect when $\dot{V}_A/\dot{Q}$ equals zero because now there is no capillary blood flow to carry oxygen away or to bring carbon dioxide to the alveoli. Therefore, instead of the alveolar gases coming to equilibrium with the venous blood, the alveolar air becomes equal to the humidified inspired air.

That is, the air that is inspired loses no oxygen to the blood and gains no carbon dioxide from the blood. And because normal inspired and humidified air has a P_{O_2} of 149 mm Hg and a P_{CO_2} of 0 mm Hg, these will be the partial pressures of these two gases in the alveoli.

Gas Exchange and Alveolar Partial Pressures When $\dot{V}_A/\dot{Q}$ Is Normal. When there is both normal alveolar ventilation and normal alveolar capillary blood flow (normal alveolar perfusion), exchange of oxygen and carbon dioxide through the respiratory membrane is nearly optimal, and alveolar P_{O_2} is normally at a level of 104 mm Hg, which lies between that of the inspired air (149 mm Hg) and that of venous blood (40 mm Hg). Likewise, alveolar P_{CO_2} lies between two extremes; it is normally 40 mm Hg, in contrast to 45 mm Hg in venous blood and 0 mm Hg in inspired air. Thus, under normal conditions, the alveolar air P_{O_2} averages 104 mm Hg and the P_{CO_2} averages 40 mm Hg.

P_{O_2}-P_{CO_2}, $\dot{V}_A/\dot{Q}$ Diagram

The concepts presented in the preceding sections can be shown in graphical form, as demonstrated in Figure 39-11, called the P_{O_2}-P_{CO_2}, $\dot{V}_A/\dot{Q}$ diagram. The curve in the diagram represents all possible P_{O_2} and P_{CO_2} combinations between the limits of $\dot{V}_A/\dot{Q}$ equals zero and $\dot{V}_A/\dot{Q}$ equals infinity when the gas pressures in the venous blood are normal and the person is breathing air at sea-level pressure. Thus, point $\bar{v}$ is the plot of P_{O_2} and P_{CO_2} when $\dot{V}_A/\dot{Q}$ equals zero. At this point, the P_{O_2} is 40 mm Hg and the P_{CO_2} is 45 mm Hg, which are the values in normal venous blood.

At the other end of the curve, when $\dot{V}_A/\dot{Q}$ equals infinity, point I represents inspired air, showing P_{O_2} to be 149 mm Hg while P_{CO_2} is zero. Also plotted on the curve is the point that represents normal alveolar air when $\dot{V}_A/\dot{Q}$ is normal. At this point, P_{O_2} is 104 mm Hg and P_{CO_2} is 40 mm Hg.

Concept of "Physiologic Shunt" (When $\dot{V}_A/\dot{Q}$ Is Below Normal)

Whenever $\dot{V}_A/\dot{Q}$ is below normal, there is inadequate ventilation to provide the oxygen needed to fully oxygenate the blood flowing through the alveolar capillaries. Therefore, a certain fraction of the venous blood passing through the pulmonary capillaries does not become oxygenated. This fraction is called *shunted blood*. Also, some additional blood flows through bronchial vessels rather than through alveolar capillaries, normally about 2 percent of the cardiac output; this, too, is unoxygenated, shunted blood.

The total quantitative amount of shunted blood per minute is called the *physiologic shunt*. This physiologic shunt is measured in clinical pulmonary function laboratories by analyzing the concentration of oxygen in both mixed venous blood and arterial blood, along with simultaneous measurement of cardiac output. From these values, the physiologic shunt can be calculated by the following equation:

$$\frac{\dot{Q}_{PS}}{\dot{Q}_T} = \frac{Ci_{O_2} - Ca_{O_2}}{Ci_{O_2} - C\bar{v}_{O_2}}.$$

in which $\dot{Q}_{PS}$ is the physiologic shunt blood flow per minute, $\dot{Q}_T$ is cardiac output per minute, Ci_{O_2} is the concentration of oxygen in the arterial blood if there is an "ideal" ventilation-perfusion ratio, Ca_{O_2} is the measured concentration of oxygen in the arterial blood, and $C\bar{v}_{O_2}$ is the measured concentration of oxygen in the mixed venous blood.

The greater the physiologic shunt, the greater the *amount of blood that fails to be oxygenated* as it passes through the lungs.

Concept of the "Physiologic Dead Space" (When $\dot{V}_A/\dot{Q}$ Is Greater Than Normal)

When ventilation of some of the alveoli is great but alveolar blood flow is low, there is far more available oxygen in the alveoli than can be transported away from the alveoli by the flowing blood. Thus, the ventilation of these alveoli is said to be *wasted*. The ventilation of the anatomical dead space areas of the respiratory passageways is also wasted. The sum of these two types of wasted ventilation is called the *physiologic dead space*. This is measured in the clinical pulmonary function laboratory by making appropriate blood and expiratory gas measurements and using the following equation, called the Bohr equation:

$$\frac{\dot{V}_{D_{phys}}}{\dot{V}_T} = \frac{Pa_{CO_2} - P\bar{e}_{CO_2}}{Pa_{CO_2}},$$

in which $\dot{V}_{D_{phys}}$ is the physiologic dead space, $\dot{V}_T$ is the tidal volume, Pa_{CO_2} is the partial pressure of carbon dioxide in the arterial blood, and $P\bar{e}_{CO_2}$ is the average partial pressure of carbon dioxide in the entire expired air.

When the physiologic dead space is great, much of the *work of ventilation* is wasted effort because so much of the ventilating air never reaches the blood.

Abnormalities of Ventilation-Perfusion Ratio

Abnormal $\dot{V}_A/\dot{Q}$ in the Upper and Lower Normal Lung. In a normal person in the upright position, both pulmonary capillary blood flow and alveolar ventilation are considerably less in the upper part of the lung than in the lower part; however, blood flow is decreased considerably more than ventilation is. Therefore, at the top of the lung, $\dot{V}_A/\dot{Q}$ is as much as 2.5 times as great as the ideal value, which causes a moderate degree of *physiologic dead space* in this area of the lung.

At the other extreme, in the bottom of the lung, there is slightly too little ventilation in relation to blood flow, with $\dot{V}_A/\dot{Q}$ as low as 0.6 times the ideal value. In this area, a small fraction of the blood fails to become normally oxygenated, and this represents a *physiologic shunt*.

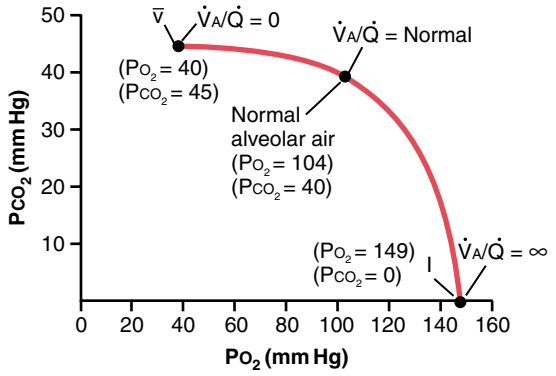


Figure 39-11 Normal P_{O_2}-P_{CO_2}, $\dot{V}_A/\dot{Q}$ diagram.

In both extremes, inequalities of ventilation and perfusion decrease slightly the lung's effectiveness for exchanging oxygen and carbon dioxide. However, during exercise, blood flow to the upper part of the lung increases markedly, so far less physiologic dead space occurs, and the effectiveness of gas exchange now approaches optimum.

Abnormal $\dot{V}_A/\dot{Q}$ in Chronic Obstructive Lung Disease. Most people who smoke for many years develop various degrees of bronchial obstruction; in a large share of these persons, this condition eventually becomes so severe that they develop serious alveolar air trapping and resultant *emphysema.* The emphysema in turn causes many of the alveolar walls to be destroyed. Thus, two abnormalities occur in smokers to cause abnormal $\dot{V}_A/\dot{Q}$. First, because many of the small bronchioles are obstructed, the alveoli beyond the obstructions are unventilated, causing a $\dot{V}_A/\dot{Q}$ that approaches zero. Second, in those areas of the lung where the alveolar walls have been mainly destroyed but there is still alveolar ventilation, most of the ventilation is wasted because of inadequate blood flow to transport the blood gases.

Thus, in chronic obstructive lung disease, some areas of the lung exhibit *serious physiologic shunt*, and other areas exhibit *serious physiologic dead space.* Both conditions tremendously decrease the effectiveness of the lungs as gas exchange organs, sometimes reducing their effectiveness to as little as one-tenth normal. In fact, this is the most prevalent cause of pulmonary disability today.

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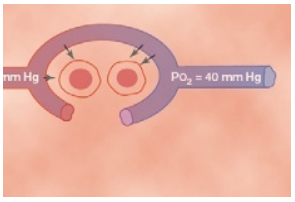
CHAPTER 40

Transport of Oxygen and Carbon Dioxide in Blood and Tissue Fluids



Once *oxygen* has diffused from the alveoli into the pulmonary blood, it is transported to the peripheral tissue capillaries almost entirely in combination with hemoglobin. The presence of hemoglobin in the red blood cells allows the blood to transport 30 to 100 times as much oxygen as could be transported in the form of dissolved oxygen in the water of the blood. In the body's tissue cells, oxygen reacts with various foodstuffs to form large quantities of *carbon dioxide*. This carbon dioxide enters the tissue capillaries and is transported back to the lungs. Carbon dioxide, like oxygen, also combines with chemical substances in the blood that increase carbon dioxide transport 15- to 20-fold. The purpose of this chapter is to present both qualitatively and quantitatively the physical and chemical principles of oxygen and carbon dioxide transport in the blood and tissue fluids. Transport of Oxygen from the Lungs to the Body Tissues In Chapter 39, we pointed out that gases can move from one point to another by diffusion and that the cause of this movement is always a partial pressure difference from the first point to the next. Thus, oxygen diffuses from the alveoli into the pulmonary capillary blood because the oxygen partial pressure (P_{O_2}) in the alveoli is greater than the P_{O_2} in the pulmonary capillary blood. In the other tissues of the body, a higher P_{O_2} in the capillary blood than in the tissues causes oxygen to diffuse into the surrounding cells. Conversely, when oxygen is metabolized in the cells to form carbon dioxide, the intracellular carbon dioxide pressure (P_{CO_2}) rises to a high value, which causes carbon dioxide to diffuse into the tissue capillaries. After blood flows to the lungs, the carbon dioxide diffuses out of the blood into the alveoli, because the P_{CO_2} in the pulmonary capillary blood is greater than that in the alveoli. Thus, the transport of oxygen and carbon dioxide by the blood depends on both diffusion and the flow of blood. We now consider quantitatively the factors responsible for these effects. Diffusion of Oxygen from the Alveoli to the Pulmonary Capillary Blood The top part of Figure 40-1 shows a pulmonary alveolus adjacent to a pulmonary capillary, demonstrating diffusion of oxygen molecules between the alveolar air and the pulmonary blood. The P_{O_2} of the gaseous oxygen in the alveolus averages 104 mm Hg, whereas the P_{O_2} of the venous blood entering the pulmonary capillary at its arterial end averages only 40 mm Hg because a large amount of oxygen was removed from this blood as it passed through the peripheral tissues. Therefore, the *initial* pressure difference that causes oxygen to diffuse into the pulmonary capillary is 104 – 40, or 64 mm Hg. In the graph at the bottom of the figure, the curve shows the rapid rise in blood P_{O_2} as the blood passes through the capillary; the blood P_{O_2} rises almost to that of the alveolar air by the time the blood has moved a third of the distance through the capillary, becoming almost 104 mm Hg. Uptake of Oxygen by the Pulmonary Blood During Exercise. During strenuous exercise, a person's body may require as much as 20 times the normal amount of oxygen. Also, because of increased cardiac output during exercise, the time that the blood remains in the pulmonary capillary may be reduced to less than one-half normal. Yet because of the great *safety factor* for diffusion of oxygen through the pulmonary membrane, the blood still becomes *almost saturated* with oxygen by the time it leaves the pulmonary capillaries. This can be explained as follows. First, it was pointed out in Chapter 39 that the diffusing capacity for oxygen increases almost threefold during exercise; this results mainly from increased surface area of capillaries participating in the diffusion and also from a more nearly ideal ventilation-perfusion ratio in the upper part of the lungs. Second, note in the curve of Figure 40-1 that under nonexercising conditions, the blood becomes almost saturated with oxygen by the time it has passed through one third of the pulmonary capillary, and little additional oxygen normally enters the blood during the latter two thirds of its transit. That is, the blood normally stays in the lung capillaries about three times as long as needed to cause full oxygenation. Therefore, during exercise, even with a shortened time of exposure in the capillaries, the blood can still become fully oxygenated, or nearly so. Transport of Oxygen in the Arterial Blood About 98 percent of the blood that enters the left atrium from the lungs has just passed through the alveolar capillaries and has become oxy-

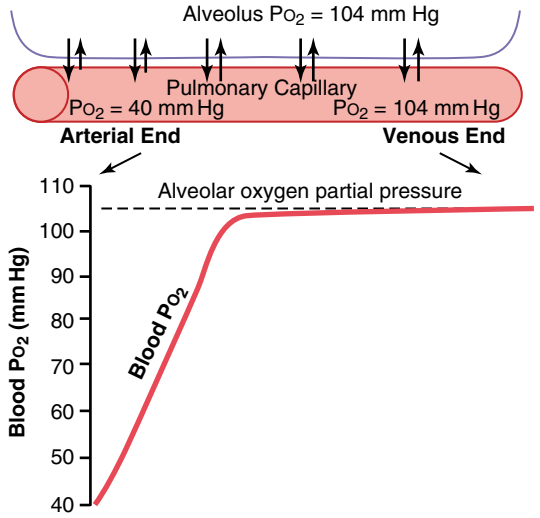


Figure 40-1 Uptake of oxygen by the pulmonary capillary blood. (The curve in this figure was constructed from data in Milhorn HT Jr, Pulley PE Jr: A theoretical study of pulmonary capillary gas exchange and venous admixture. Biophys J 8:337, 1968.)

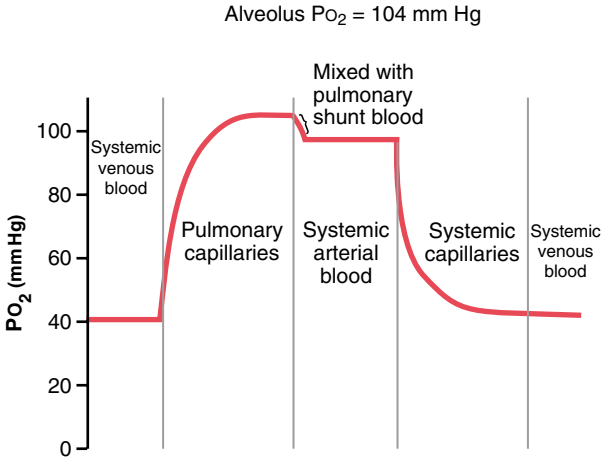


Figure 40-2 Changes in P_{O_2} in the pulmonary capillary blood, systemic arterial blood, and systemic capillary blood, demonstrating the effect of "venous admixture."

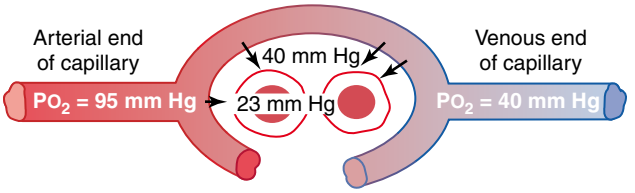


Figure 40-3 Diffusion of oxygen from a peripheral tissue capillary to the cells. (P_{O_2} in interstitial fluid = 40 mm Hg, and in tissue cells = 23 mm Hg.)

genated up to a P_{O_2} of about 104 mm Hg. Another 2 percent of the blood has passed from the aorta through the bronchial circulation, which supplies mainly the deep tissues of the lungs and is not exposed to lung air. This blood flow is called "shunt flow," meaning that blood is shunted past the gas exchange areas. On leaving the lungs, the P_{O_2} of the shunt blood is about that of normal systemic venous blood, about 40 mm Hg. When this blood combines in the pulmonary veins with the oxygenated blood from the alveolar capillaries, this so-called *venous admixture of blood* causes the P_{O_2} of the blood entering the left heart and pumped into the aorta to fall to about 95 mm Hg. These changes in blood P_{O_2} at different points in the circulatory system are shown in Figure 40-2. Diffusion of Oxygen from the Peripheral Capillaries into the Tissue Fluid When the arterial blood reaches the peripheral tissues, its P_{O_2} in the capillaries is still 95 mm Hg. Yet, as shown in Figure 40-3, the P_{O_2} in the *interstitial fluid* that surrounds the tissue cells averages only 40 mm Hg. Thus, there is a tremendous initial pressure difference that causes oxygen to diffuse rapidly from the capillary blood into the tissues—so rapidly that the capillary P_{O_2} falls almost to equal the 40 mm Hg pressure in the interstitium. Therefore, the P_{O_2} of the blood leaving the tissue capillaries and entering the systemic veins is also about 40 mm Hg. Effect of Rate of Blood Flow on Interstitial Fluid P_{O_2}. If the blood flow through a particular tissue is increased, greater quantities of oxygen are transported into the tissue and the tissue P_{O_2} becomes correspondingly higher. This is shown in Figure 40-4. Note that an increase in flow to 400 percent of normal increases the P_{O_2} from 40 mm Hg (at point A in the figure) to 66 mm Hg (at point B). However, the upper limit to which the P_{O_2} can rise, even with maximal blood flow, is 95 mm Hg because this is the oxygen pressure in the arterial blood. Conversely, if blood flow through the tissue decreases, the tissue P_{O_2} also decreases, as shown at point C. Effect of Rate of Tissue Metabolism on Interstitial Fluid P_{O_2}. If the cells use more oxygen for metabolism than normally, this reduces the interstitial fluid P_{O_2}. Figure 40-4 also demonstrates this effect, showing reduced interstitial fluid P_{O_2} when the cellular oxygen consumption is increased and increased P_{O_2} when consumption is decreased. In summary, tissue P_{O_2} is determined by a balance between (1) the rate of oxygen transport to the tissues in the blood and (2) the rate at which the oxygen is used by the tissues. Diffusion of Oxygen from the Peripheral Capillaries to the Tissue Cells Oxygen is always being used by the cells. Therefore, the intracellular P_{O_2} in the peripheral tissue cells remains lower than the P_{O_2} in the peripheral capillar-

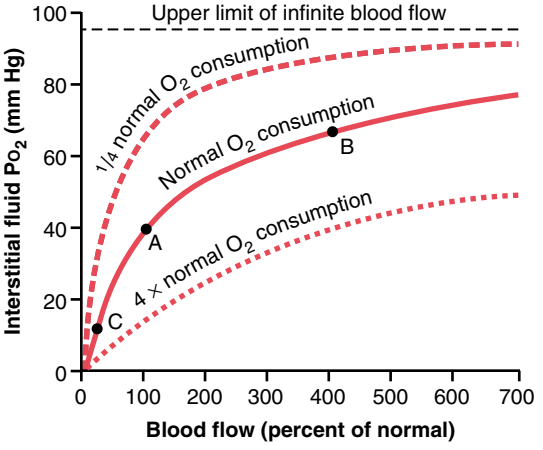


Figure 40-4 Effect of blood flow and rate of oxygen consumption on tissue P_{O_2}.

ies. Also, in many instances, there is considerable physical distance between the capillaries and the cells. Therefore, the normal intracellular P_{O_2} ranges from as low as 5 mm Hg to as high as 40 mm Hg, averaging (by direct measurement in lower animals) 23 mm Hg. Because only 1 to 3 mm Hg of oxygen pressure is normally required for full support of the chemical processes that use oxygen in the cell, one can see that even this low intracellular P_{O_2} of 23 mm Hg is more than adequate and provides a large safety factor. Diffusion of Carbon Dioxide from the Peripheral Tissue Cells into the Capillaries and from the Pulmonary Capillaries into the Alveoli When oxygen is used by the cells, virtually all of it becomes carbon dioxide, and this increases the intracellular P_{CO_2}; because of this high tissue cell P_{CO_2}, carbon dioxide diffuses from the cells into the tissue capillaries and is then carried by the blood to the lungs. In the lungs, it diffuses from the pulmonary capillaries into the alveoli and is expired. Thus, at each point in the gas transport chain, carbon dioxide diffuses in the direction exactly opposite to the diffusion of oxygen. Yet there is one major difference between diffusion of carbon dioxide and of oxygen: *carbon dioxide can diffuse about 20 times as rapidly as oxygen*. Therefore, the pressure differences required to cause carbon dioxide diffusion are, in each instance, far less than the pressure differences required to cause oxygen diffusion. The CO_2 pressures are approximately the following: 1.Intracellular P_{CO_2}, 46 mm Hg; interstitial P_{CO_2}, 45 mm Hg. Thus, there is only a 1 mm Hg pressure differential, as shown in Figure 40-5. 2.P_{CO_2} of the arterial blood entering the tissues, 40 mm Hg; P_{CO_2} of the venous blood leaving the tissues, 45 mm Hg. Thus, as shown in Figure 40-5, the tissue capillary blood comes almost exactly to equilibrium with the interstitial P_{CO_2} of 45 mm Hg. 3.P_{CO_2} of the blood entering the pulmonary capillaries at the arterial end, 45 mm Hg; P_{CO_2} of the alveolar air, 40 mm Hg. Thus, only a 5 mm Hg pressure difference causes all the required carbon dioxide diffusion out of the pulmonary capillaries into the alveoli. Furthermore, as shown in Figure 40-6, the P_{CO_2} of the pulmonary capillary blood falls to almost exactly equal the alveolar P_{CO_2} of 40 mm Hg before it has passed more than about one third the distance through the capillaries. This is the same effect that was observed earlier for oxygen diffusion, except that it is in the opposite direction. Effect of Rate of Tissue Metabolism and Tissue Blood Flow on Interstitial P_{CO_2}. Tissue capillary blood flow and tissue metabolism affect the P_{CO_2} in ways exactly opposite to their effect on tissue P_{O_2}. Figure 40-7 shows these effects, as follows: 1.A decrease in blood flow from normal (point A) to one quarter-normal (point B) increases peripheral tissue P_{CO_2} from the normal value of 45 mm Hg to an elevated level of 60 mm Hg. Conversely, increasing the blood flow to six times normal (point C) decreases the interstitial P_{CO_2} from the normal value of 45 mm Hg to 41 mm Hg, down to a level almost equal to the P_{CO_2} in the arterial blood (40 mm Hg) entering the tissue capillaries. 2.Note also that a 10-fold increase in tissue metabolic rate greatly elevates the interstitial fluid P_{CO_2} at all rates of

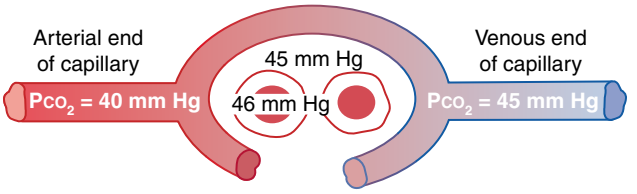


Figure 40-5 Uptake of carbon dioxide by the blood in the tissue capillaries. (P_{CO_2} in tissue cells = 46 mm Hg, and in interstitial fluid = 45 mm Hg.)

blood flow, whereas decreasing the metabolism to one-quarter normal causes the interstitial fluid P_{CO_2} to fall to about 41 mm Hg, closely approaching that of the arterial blood, 40 mm Hg. Role of Hemoglobin in Oxygen Transport Normally, about 97 percent of the oxygen transported from the lungs to the tissues is carried in chemical combination with hemoglobin in the red blood cells. The remaining 3 percent is transported in the dissolved state in the water of the plasma and blood cells. Thus, *under normal conditions*, oxygen is carried to the tissues almost entirely by hemoglobin. Reversible Combination of Oxygen with Hemoglobin The chemistry of hemoglobin is presented in Chapter 32, where it was pointed out that the oxygen molecule combines loosely and reversibly with the heme portion of hemoglobin. When P_{O_2} is high, as in the pulmonary capillaries, oxygen binds with the hemoglobin, but when P_{O_2} is low, as in the tissue capillaries, oxygen is released from the hemoglobin. This is the basis for almost all oxygen transport from the lungs to the tissues. Oxygen-Hemoglobin Dissociation Curve. Figure 40-8 shows the oxygen-hemoglobin dissociation curve, which demonstrates a progressive increase in the percentage of hemoglobin bound with oxygen as blood P_{O_2} increases, which is called the *percent saturation of hemoglobin*. Because the blood leaving the lungs and entering the systemic arteries usually has a P_{O_2} of about 95 mm Hg, one can see from the dissociation curve that the *usual*

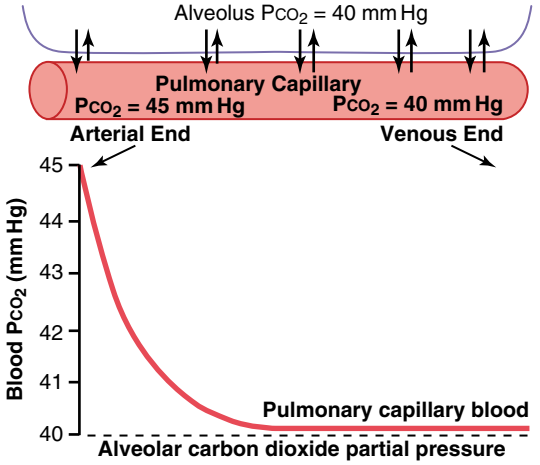


Figure 40-6 Diffusion of carbon dioxide from the pulmonary blood into the alveolus. (This curve was constructed from data in Milhorn HT Jr, Pulley PE Jr: A theoretical study of pulmonary capillary gas exchange and venous admixture. Biophys J 8:337, 1968.)

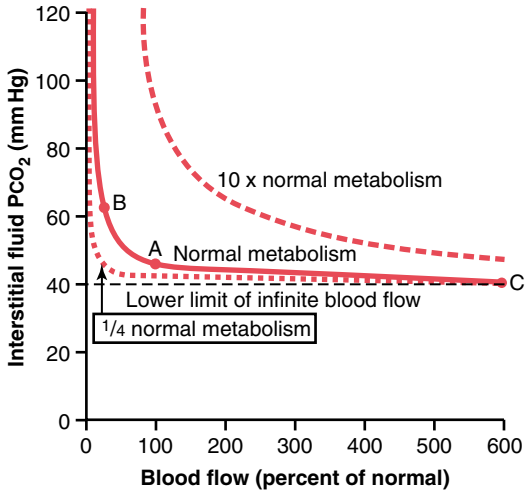


Figure 40-7 Effect of blood flow and metabolic rate on peripheral tissue P_{CO_2}.

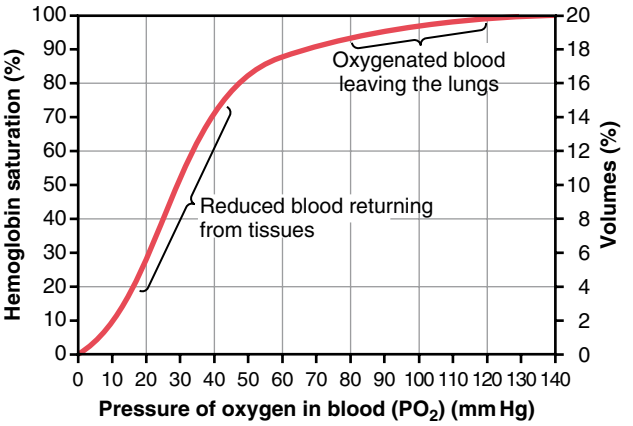


Figure 40-8 Oxygen-hemoglobin dissociation curve.

oxygen saturation of systemic arterial blood averages 97 percent. Conversely, in normal venous blood returning from the peripheral tissues, the P_{O_2} is about 40 mm Hg, and *the saturation of hemoglobin averages 75 percent*. Maximum Amount of Oxygen That Can Combine with the Hemoglobin of the Blood. The blood of a normal person contains about 15 grams of hemoglobin in each 100 milliliters of blood, and each gram of hemoglobin can bind with a maximum of 1.34 milliliters of oxygen (1.39 milliliters when the hemoglobin is chemically pure, but impurities such as methemoglobin reduce this). Therefore, 15 times 1.34 equals 20.1, which means that, on average, the 15 grams of hemoglobin in 100 milliliter of blood can combine with a total of about 20 milliliters of oxygen if the hemoglobin is 100 percent saturated. This is usually expressed as *20 volumes percent*. The oxygen-hemoglobin dissociation curve for the normal person can also be expressed in terms of volume percent of oxygen, as shown by the far right scale in Figure 40-8, instead of percent saturation of hemoglobin. Amount of Oxygen Released from the Hemoglobin When Systemic Arterial Blood Flows Through the Tissues. The total quantity of oxygen *bound with hemoglobin* in normal systemic arterial blood, which is 97 percent saturated, is about 19.4 milliliters per 100 milliliters of blood. This is shown in Figure 40-9. On passing through the tissue capillaries, this amount is reduced, on average, to 14.4 milliliters (P_{O_2} of 40 mm Hg, 75 percent saturated hemoglobin). Thus, *under normal conditions, about 5 milliliters of oxygen are transported from the lungs to the tissues by each 100 milliliters of blood flow*. Transport of Oxygen During Strenuous Exercise. During heavy exercise, the muscle cells use oxygen at a rapid rate, which, in extreme cases, can cause the muscle interstitial fluid P_{O_2} to fall from the normal 40 mm Hg to as low as 15 mm Hg. At this low pressure, only 4.4 milliliters of oxygen remain bound with the hemoglobin in each 100 milliliters of blood, as shown in Figure 40-9. Thus, 19.4 – 4.4, or 15 milliliters, is the quantity of oxygen actually delivered to the tissues by each 100 milliliters of blood flow. Thus, three times as much oxygen as normal is delivered in each volume of blood that passes through the tissues. And keep in mind that the cardiac output can increase to six to seven times normal in well-trained marathon runners. Thus, multiplying the increase in cardiac output (6- to 7-fold) by the increase in oxygen transport in each volume of blood (3-fold) gives a 20-fold increase in oxygen transport to the tissues. We see later in the chapter that several other factors facilitate delivery of oxygen into muscles during exercise, so muscle tissue P_{O_2} often falls on slightly below normal even during very strenuous exercise. Utilization Coefficient. The percentage of the blood that gives up its oxygen as it passes through the tissue capillaries is called the *utilization coefficient*. The normal value for this is about 25 percent, as is evident from the preceding discussion—that is, 25 percent of the oxygenated hemoglobin gives its oxygen to the tissues. During strenuous exercise, the utilization coefficient in the entire body can increase to 75 to 85 percent. And in local tissue areas where blood flow is extremely slow or the metabolic rate is very high, utilization coefficients approaching 100 percent have been recorded—that is, essentially all the oxygen is given to the tissues. Effect of Hemoglobin to "Buffer" the Tissue P_{O_2} Although hemoglobin is necessary for the transport of oxygen to the tissues, it performs another function essential to life. This is its function as a "tissue oxygen buffer" system. That is, the hemoglobin in the blood is mainly responsible for stabilizing the oxygen pressure in the tissues. This can be explained as follows. Role of Hemoglobin in Maintaining Nearly Constant P_{O_2} in the Tissues. Under basal conditions, the tissues require about 5 milliliters of oxygen from each 100 milliliters of blood passing through the tissue capillaries. Referring to the oxygen-hemoglobin dissociation curve in Figure 40-9, one can see that for the normal 5 milliliters of oxygen to be released per 100 milliliters of blood flow, the P_{O_2} must fall to about 40 mm Hg. Therefore, the tissue P_{O_2} normally cannot rise above this 40 mm Hg level because, if it did, the amount of oxygen needed by the tissues would not be released from the hemoglobin. In this way, the hemoglobin normally sets an upper limit on the oxygen pressure in the tissues at about 40 mm Hg. Conversely,

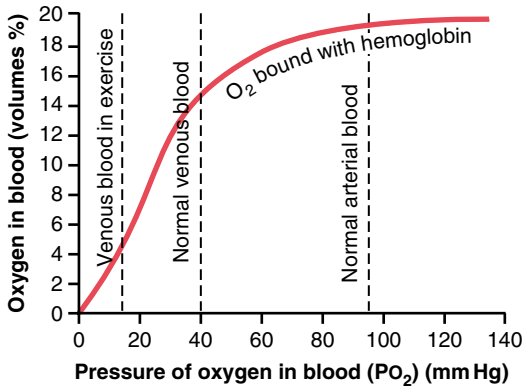


Figure 40-9 Effect of blood PO_2 on the quantity of oxygen bound with hemoglobin in each 100 milliliters of blood.

during heavy exercise, extra amounts of oxygen (as much as 20 times normal) must be delivered from the hemoglobin to the tissues. But this can be achieved with little further decrease in tissue P_{O_2} because of (1) the steep slope of the dissociation curve and (2) the increase in tissue blood flow caused by the decreased P_{O_2}; that is, a very small fall in P_{O_2} causes large amounts of extra oxygen to be released from the hemoglobin. It can be seen, then, that the hemoglobin in the blood automatically delivers oxygen to the tissues at a pressure that is held rather tightly between about 15 and 40 mm Hg. When Atmospheric Oxygen Concentration Changes Markedly, the Buffer Effect of Hemoglobin Still Maintains Almost Constant Tissue P_{O_2}. The normal P_{O_2} in the alveoli is about 104 mm Hg, but as one ascends a mountain or ascends in an airplane, the P_{O_2} can easily fall to less than half this amount. Alternatively, when one enters areas of compressed air, such as deep in the sea or in pressurized chambers, the P_{O_2} may rise to 10 times this level. Even so, the tissue P_{O_2} changes little. It can be seen from the oxygen-hemoglobin dissociation curve in Figure 40-8 that when the alveolar P_{O_2} is decreased to as low as 60 mm Hg, the arterial hemoglobin is still 89 percent saturated with oxygen—only 8 percent below the normal saturation of 97 percent. Further, the tissues still remove about 5 milliliters of oxygen from each 100 milliliter of blood passing through the tissues; to remove this oxygen, the P_{O_2} of the venous blood falls to 35 mm Hg—only 5 mm Hg below the normal value of 40 mm Hg. Thus, the tissue P_{O_2} hardly changes, despite the marked fall in alveolar P_{O_2} from 104 to 60 mm Hg. Conversely, when the alveolar P_{O_2} rises as high as 500 mm Hg, the maximum oxygen saturation of hemoglobin can never rise above 100 percent, which is only 3 percent above the normal level of 97 percent. Only a small amount of additional oxygen dissolves in the fluid of the blood, as will be discussed subsequently. Then, when the blood passes through the tissue capillaries and loses several milliliters of oxygen to the tissues, this reduces the P_{O_2} of the capillary blood to a value only a few milliliters greater than the normal 40 mm Hg. Consequently, the level of alveolar oxygen may vary greatly—from 60 to more than 500 mm Hg P_{O_2}—and still the P_{O_2} in the peripheral tissues does not vary more than a few milliliters from normal, *demonstrating beautifully the tissue "oxygen buffer" function of the blood hemoglobin system.* Factors That Shift the Oxygen-Hemoglobin Dissociation Curve—Their Importance for Oxygen Transport The oxygen-hemoglobin dissociation curves of Figures 40-8 and 40-9 are for normal, average blood. However, a number of factors can displace the dissociation curve in one direction or the other in the manner shown in Figure 40-10. This figure shows that when the blood becomes slightly acidic, with the pH decreasing from the normal value of 7.4 to 7.2, the oxygen-hemoglobin dissociation curve shifts, on average, about 15 percent to the right. Conversely, an increase in pH from the normal 7.4 to 7.6 shifts the curve a similar amount to the left. In addition to pH changes, several other factors are known to shift the curve. Three of these, all of which shift the curve to the *right*, are (1) increased carbon dioxide concentration, (2) increased blood temperature, and (3) increased 2,3-biphosphoglycerate (BPG), a metabolically important phosphate compound present in the blood in different concentrations under different metabolic conditions. Increased Delivery of Oxygen to the Tissues When Carbon Dioxide and Hydrogen Ions Shift the Oxygen-Hemoglobin Dissociation Curve—The Bohr Effect. A shift of the oxygen-hemoglobin dissociation curve to the right in response to increases in blood carbon dioxide and hydrogen ions has a significant effect by enhancing the release of oxygen from the blood in the tissues and enhancing oxygenation of the blood in the lungs. This is called the *Bohr effect,* which can be explained as follows: As the blood passes through the tissues, carbon dioxide diffuses from the tissue cells into the blood. This increases the blood P_{CO_2}, which in turn raises the blood H_2CO_3 (carbonic acid) and the hydrogen ion concentration. These effects shift the oxygen-hemoglobin dissociation curve to the right and downward, as shown in Figure 40-10, forcing oxygen away from the hemoglobin and therefore delivering increased amounts of oxygen to the tissues. Exactly the opposite effects occur in the lungs, where carbon dioxide diffuses from the blood into the alveoli. This reduces the blood P_{CO_2} and decreases the hydrogen ion concentration, shifting the oxygen-hemoglobin dissociation curve to the left and upward. Therefore, the quantity of oxygen that binds with the hemoglobin at any given alveolar P_{O_2} becomes considerably increased, thus allowing greater oxygen transport to the tissues. Effect of BPG to Cause Rightward Shift of the Oxygen-Hemoglobin Dissociation Curve. The normal BPG in the blood keeps the oxygen-hemoglobin dissociation curve shifted slightly to the right all the time. In hypoxic conditions that last longer than a few hours, the quantity of BPG in the blood increases considerably, thus shifting the oxygen-hemoglobin dissociation curve even farther to the right. This causes oxygen to be released to the tissues at as much as 10 mm Hg higher tissue oxygen pressure than would be the case without this increased BPG. Therefore, under some conditions, the BPG mecha-

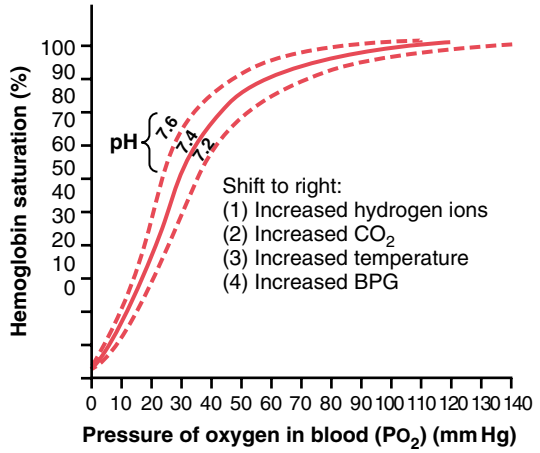


Figure 40-10 Shift of the oxygen-hemoglobin dissociation curve to the right caused by an increase in hydrogen ion concentration (decrease in pH). BPG, 2,3-biphosphoglycerate.

nism can be important for adaptation to hypoxia, especially to hypoxia caused by poor tissue blood flow. Rightward Shift of the Oxygen-Hemoglobin Dissociation Curve During Exercise. During exercise, several factors shift the dissociation curve considerably to the right, thus delivering extra amounts of oxygen to the active, exercising muscle fibers. The exercising muscles, in turn, release large quantities of carbon dioxide; this and several other acids released by the muscles increase the hydrogen ion concentration in the muscle capillary blood. In addition, the temperature of the muscle often rises 2° to 3°C, which can increase oxygen delivery to the muscle fibers even more. All these factors act together to shift the oxygen-hemoglobin dissociation curve *of the muscle capillary blood* considerably to the right. This rightward shift of the curve forces oxygen to be released from the blood hemoglobin to the muscle at P_{O_2} levels as great as 40 mm Hg, even when 70 percent of the oxygen has already been removed from the hemoglobin. Then, in the lungs, the shift occurs in the opposite direction, allowing the pickup of extra amounts of oxygen from the alveoli. Metabolic Use of Oxygen by the Cells Effect of Intracellular P_{O_2} on Rate of Oxygen Usage. Only a minute level of oxygen pressure is required in the cells for normal intracellular chemical reactions to take place. The reason for this is that the respiratory enzyme systems of the cell, which are discussed in Chapter 67, are geared so that when the cellular P_{O_2} is more than 1 mm Hg, oxygen availability is no longer a limiting factor in the rates of the chemical reactions. Instead, the main limiting factor is the *concentration of adenosine diphosphate* (ADP) in the cells. This effect is demonstrated in Figure 40-11, which shows the relation between intracellular P_{O_2} and the rate of oxygen usage at different concentrations of ADP. Note that whenever the intracellular P_{O_2} is above 1 mm Hg, the rate of oxygen usage becomes constant for any given concentration of ADP in the cell. Conversely, when the ADP concentration is altered, the rate of oxygen usage changes in proportion to the change in ADP concentration. As explained in Chapter 3, when adenosine triphosphate (ATP) is used in the cells to provide energy, it is converted into ADP. The increasing concentration of ADP increases the metabolic usage of oxygen as it combines with the various cell nutrients, releasing energy that reconverts the ADP back to ATP. *Under normal operating conditions, the rate of oxygen usage by the cells is controlled ultimately by the rate of energy expenditure within the cells—that is, by the rate at which ADP is formed from ATP.* Effect of Diffusion Distance from the Capillary to the Cell on Oxygen Usage. Tissue cells are seldom more than 50 micrometers away from a capillary, and oxygen normally can diffuse readily enough from the capillary to the cell to supply all the required amounts of oxygen for metabolism. However, occasionally, cells are located farther from the capillaries, and the rate of oxygen diffusion to these cells can become so low that intracellular P_{O_2} falls below the critical level required to maintain maximal intracellular metabolism. Thus, under these conditions, oxygen usage by the cells is said to be *diffusion limited* and is no longer determined by the amount of ADP formed in the cells. But this almost never occurs, except in pathological states. Effect of Blood Flow on Metabolic Use of Oxygen. The total amount of oxygen available each minute for use in any given tissue is determined by (1) the quantity of oxygen that can be transported to the tissue in each 100 ml of blood and (2) the rate of blood flow. If the rate of blood flow falls to zero, the amount of available oxygen also falls to zero. Thus, there are times when the rate of blood flow through a tissue can be so low that tissue P_{O_2} falls below the critical 1 mm Hg required for intracellular metabolism. Under these conditions, the rate of tissue usage of oxygen is *blood flow limited*. Neither diffusion-limited nor blood flow–limited oxygen states can continue for long, because the cells receive less oxygen than is required to continue the life of the cells. Transport of Oxygen in the Dissolved State At the normal arterial P_{O_2} of 95 mm Hg, about 0.29 milliliter of oxygen is dissolved in every 100 milliliters of water in the blood, and when the P_{O_2} of the blood falls to the normal 40 mm Hg in the tissue capillaries, only 0.12 milliliters of oxygen remains dissolved. In other words, 0.17 milliliters of oxygen is normally transported in the dissolved state to the tissues by each 100 milliliters of arterial blood flow. This compares with almost 5 milliliters of oxygen transported by the red cell hemoglobin. Therefore, the amount of oxygen transported to the tissues in the dissolved state is normally slight, only about 3 percent of the total, as compared with 97 percent transported by the hemoglobin. During strenuous exercise, when hemoglobin release of oxygen to the tissues increases another threefold, the relative quantity of oxygen transported in the dissolved state falls to as little as 1.5 percent. But if a person breathes oxygen at very high alveolar P_{O_2} levels, the amount transported in the dissolved state can become much greater, sometimes so much so that a serious excess of oxygen occurs in the tissues, and "oxygen poisoning" ensues. This often leads to brain convulsions and even death, as discussed in detail in Chapter 44 in relation to the high-pressure breath-

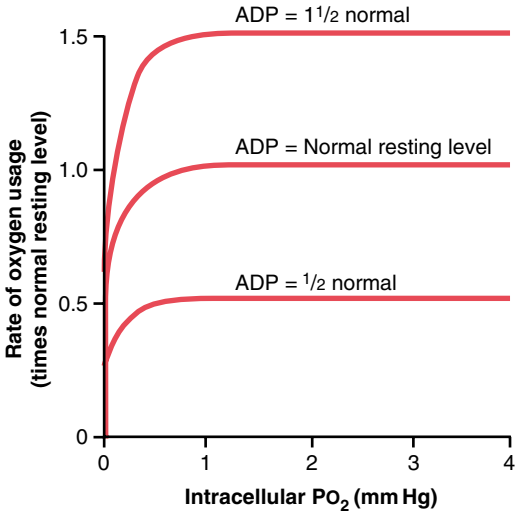


Figure 40-11 Effect of intracellular adenosine diphosphate (ADP) and P_{O_2} on rate of oxygen usage by the cells. Note that as long as the intracellular P_{O_2} remains above 1 mm Hg, the controlling factor for the rate of oxygen usage is the intracellular concentration of ADP.

ing of oxygen among deep-sea divers. Combination of Hemoglobin with Carbon Monoxide—Displacement of Oxygen Carbon monoxide combines with hemoglobin at the same point on the hemoglobin molecule as does oxygen; it can therefore displace oxygen from the hemoglobin, thereby decreasing the oxygen-carrying capacity of blood. Further, it binds with about 250 times as much tenacity as oxygen, which is demonstrated by the carbon monoxide–hemoglobin dissociation curve in Figure 40-12. This curve is almost identical to the oxygen-hemoglobin dissociation curve, except that the carbon monoxide partial pressures, shown on the abscissa, are at a level ½₅₀ of those for the oxygen-hemoglobin dissociation curve of Figure 40-8. Therefore, a carbon monoxide partial pressure of only 0.4 mm Hg in the alveoli, ½₅₀ that of normal alveolar oxygen (100 mm Hg P_{O_2}), allows the carbon monoxide to compete equally with the oxygen for combination with the hemoglobin and causes half the hemoglobin in the blood to become bound with carbon monoxide instead of with oxygen. Therefore, a carbon monoxide pressure of only 0.6 mm Hg (a volume concentration of less than one part per thousand in air) can be lethal. Even though the oxygen content of blood is greatly reduced in carbon monoxide poisoning, the P_{O_2} of the blood may be normal. This makes exposure to carbon monoxide especially dangerous because the blood is bright red and there are no obvious signs of hypoxemia, such as a bluish color of the fingertips or lips (cyanosis). Also, P_{O_2} is not reduced, and the feedback mechanism that usually stimulates increased respiration rate in response to lack of oxygen (usually reflected by a low P_{O_2}) is absent. Because the brain is one of the first organs affected by lack of oxygen, the person may become disoriented and unconscious before becoming aware of the danger. A patient severely poisoned with carbon monoxide can be treated by administering pure oxygen because oxygen at high alveolar pressure can displace carbon monoxide rapidly from its combination with hemoglobin. The patient can also benefit from simultaneous administration of 5 percent carbon dioxide because this strongly stimulates the respiratory center, which increases alveolar ventilation and reduces the alveolar carbon monoxide. With intensive oxygen and carbon dioxide therapy, carbon monoxide can be removed from the blood as much as 10 times as rapidly as without therapy. Transport of Carbon Dioxide in the Blood Transport of carbon dioxide by the blood is not nearly as problematical as transport of oxygen is because even in the most abnormal conditions, carbon dioxide can usually be transported in far greater quantities than oxygen can be. However, the amount of carbon dioxide in the blood has a lot to do with the acid-base balance of the body fluids, which is discussed in Chapter 30. Under normal resting conditions, *an average of 4 milliliters of carbon dioxide is transported from the tissues to the lungs in each 100 milliliters of blood.* Chemical Forms in Which Carbon Dioxide Is Transported To begin the process of carbon dioxide transport, carbon dioxide diffuses out of the tissue cells in the dissolved molecular carbon dioxide form. On entering the tissue capillaries, the carbon dioxide initiates a host of almost instantaneous physical and chemical reactions, shown in Figure 40-13, which are essential for carbon dioxide transport. Transport of Carbon Dioxide in the Dissolved State. A small portion of the carbon dioxide is transported in the dissolved state to the lungs. Recall that the P_{CO_2} of venous blood is 45 mm Hg and that of arterial blood is 40 mm Hg. The amount of carbon dioxide dissolved in the fluid of the blood at 45 mm Hg is about 2.7 ml/dl (2.7 volumes percent). The amount dissolved at 40 mm Hg is about 2.4 milliliters, or a difference of 0.3 milliliter. Therefore, only about 0.3 milliliter of carbon dioxide is transported in the dissolved form by each 100 milliliters of blood flow. This is about 7 percent of all the carbon dioxide normally transported. Transport of

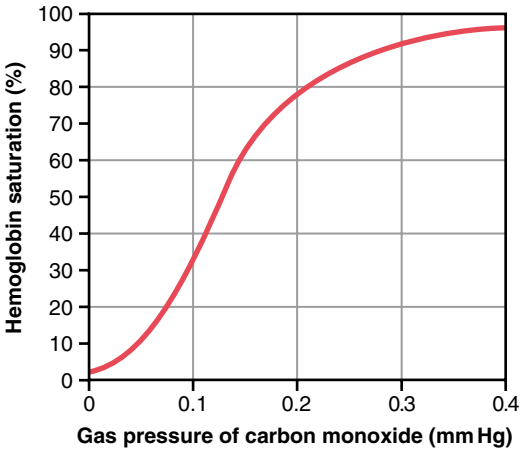


Figure 40-12 Carbon monoxide–hemoglobin dissociation curve. Note the extremely low carbon monoxide pressures at which carbon monoxide combines with hemoglobin.

Carbon Dioxide in the Form of Bicarbonate Ion Reaction of Carbon Dioxide with Water in the Red Blood Cells—Effect of Carbonic Anhydrase. The dissolved carbon dioxide in the blood reacts with water to form *carbonic acid*. This reaction would occur much too slowly to be of importance were it not for the fact that inside the red blood cells is a protein enzyme called *carbonic anhydrase*, which catalyzes the reaction between carbon dioxide and water and accelerates its reaction rate about 5000-fold. Therefore, instead of requiring many seconds or minutes to occur, as is true in the plasma, the reaction occurs so rapidly in the red blood cells that it reaches almost complete equilibrium within a very small fraction of a second. This allows tremendous amounts of carbon dioxide to react with the red blood cell water even before the blood leaves the tissue capillaries. Dissociation of Carbonic Acid into Bicarbonate and Hydrogen Ions. In another fraction of a second, the carbonic acid formed in the red cells (H_2CO_3) dissociates into *hydrogen* and *bicarbonate ions* (H^+ and HCO_3^-). Most of the H^+ ions then combine with the hemoglobin in the red blood cells because the hemoglobin protein is a powerful acid-base buffer. In turn, many of the HCO_3^- ions diffuse from the red cells into the plasma, while chloride ions diffuse into the red cells to take their place. This is made possible by the presence of a special *bicarbonate-chloride carrier protein* in the red cell membrane that shuttles these two ions in opposite directions at rapid velocities. Thus, the chloride content of venous red blood cells is greater than that of arterial red cells, a phenomenon called the *chloride shift*. The reversible combination of carbon dioxide with water in the red blood cells under the influence of carbonic anhydrase accounts for about 70 percent of the carbon dioxide transported from the tissues to the lungs. Thus, this means of transporting carbon dioxide is by far the most important. Indeed, when a carbonic anhydrase inhibitor (acetazolamide) is administered to an animal to block the action of carbonic anhydrase in the red blood cells, carbon dioxide transport from the tissues becomes so poor that the tissue P_{CO_2} can be made to rise to 80 mm Hg instead of the normal 45 mm Hg. Transport of Carbon Dioxide in Combination with Hemoglobin and Plasma Proteins—Carbaminohemoglobin. In addition to reacting with water, carbon dioxide reacts directly with amine radicals of the hemoglobin molecule to form the compound *carbaminohemoglobin* (CO_2Hgb). This combination of carbon dioxide and hemoglobin is a reversible reaction that occurs with a loose bond, so the carbon dioxide is easily released into the alveoli, where the P_{CO_2} is lower than in the pulmonary capillaries. A small amount of carbon dioxide also reacts in the same way with the plasma proteins in the tissue capillaries. This is much less significant for the transport of carbon dioxide because the quantity of these proteins in the blood is only one fourth as great as the quantity of hemoglobin. The quantity of carbon dioxide that can be carried from the peripheral tissues to the lungs by carbamino combination with hemoglobin and plasma proteins is about 30 percent of

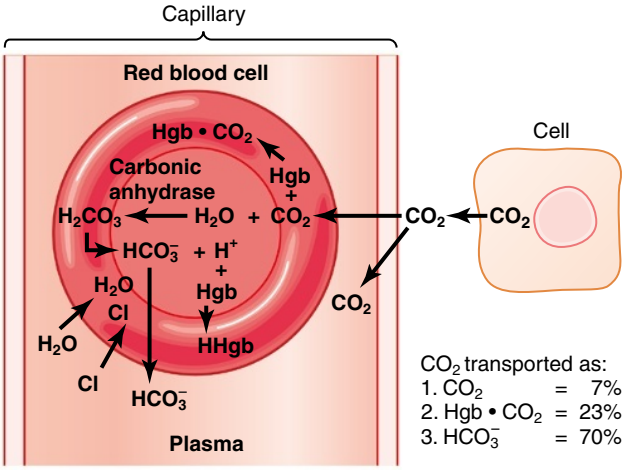


Figure 40-13 Transport of carbon dioxide in the blood.

the total quantity transported—that is, normally about 1.5 milliliters of carbon dioxide in each 100 milliliters of blood. However, because this reaction is much slower than the reaction of carbon dioxide with water inside the red blood cells, it is doubtful that under normal conditions this carbamino mechanism transports more than 20 percent of the total carbon dioxide. Carbon Dioxide Dissociation Curve The curve shown in Figure 40-14—called the *carbon dioxide dissociation curve*—depicts the dependence of total blood carbon dioxide in all its forms on P_{CO_2}. Note that the normal blood P_{CO_2} ranges between the limits of 40 mm Hg in arterial blood and 45 mm Hg in venous blood, which is a very narrow range. Note also that the normal concentration of carbon dioxide in the blood in all its different forms is about 50 volumes percent, but only 4 volumes percent of this is exchanged during normal transport of carbon dioxide from the tissues to the lungs. That is, the concentration rises to about 52 volumes percent as the blood passes through the tissues and falls to about 48 volumes percent as it passes through the lungs. When Oxygen Binds with Hemoglobin, Carbon Dioxide Is Released (the Haldane Effect) to Increase CO_2 Transport Earlier in the chapter, it was pointed out that an increase in carbon dioxide in the blood causes oxygen to be displaced from the hemoglobin (the Bohr effect), which is an important factor in increasing oxygen transport. The reverse is also true: binding of oxygen with hemoglobin tends to displace carbon dioxide from the blood. Indeed, this effect, called the *Haldane effect*, is quantitatively far more important in promoting carbon dioxide transport than is the Bohr effect in promoting oxygen transport. The Haldane effect results from the simple fact that the combination of oxygen with hemoglobin in the lungs causes the hemoglobin to become a stronger acid. This displaces carbon dioxide from the blood and into the alveoli in two ways: (1) The more highly acidic hemoglobin has less tendency to combine with carbon dioxide to form carbaminohemoglobin, thus displacing much of the carbon dioxide that is present in

the carbamino form from the blood. (2) The increased acidity of the hemoglobin also causes it to release an excess of hydrogen ions, and these bind with bicarbonate ions to form carbonic acid; this then dissociates into water and carbon dioxide, and the carbon dioxide is released from the blood into the alveoli and, finally, into the air. Figure 40-15 demonstrates quantitatively the significance of the Haldane effect on the transport of carbon dioxide from the tissues to the lungs. This figure shows small portions of two carbon dioxide dissociation curves: (1) when the P_{O_2} is 100 mm Hg, which is the case in the blood capillaries of the lungs, and (2) when the P_{O_2} is 40 mm Hg, which is the case in the tissue capillaries. Point A shows that the normal P_{CO_2} of 45 mm Hg in the tissues causes 52 volumes percent of carbon dioxide to combine with the blood. On entering the lungs, the P_{CO_2} falls to 40 mm Hg and the P_{O_2} rises to 100 mm Hg. If the carbon dioxide dissociation curve did not shift because of the Haldane effect, the carbon dioxide content of the blood would fall only to 50 volumes percent, which would be a loss of only 2 volumes percent of carbon dioxide. However, the increase in P_{O_2} in the lungs lowers the carbon dioxide dissociation curve from the top curve to the lower curve of the figure, so the carbon dioxide content falls to 48 volumes percent (point B). This represents an additional two volumes percent loss of carbon dioxide. Thus, the Haldane effect approximately doubles the amount of carbon dioxide released from the blood in the lungs and approximately doubles the pickup of carbon dioxide in the tissues. Change in Blood Acidity During Carbon Dioxide Transport The carbonic acid formed when carbon dioxide enters the blood in the peripheral tissues decreases the blood pH. However, reaction of this acid with the acid-base buffers of the blood prevents the H^+ concentration from rising greatly (and the pH from falling greatly). Ordinarily, arterial blood has a pH of about 7.41, and as the blood acquires carbon dioxide in the tissue capillaries, the pH falls to a venous value of about 7.37. In other words, a pH change of 0.04 unit takes place. The reverse occurs when carbon dioxide is released from the blood in the lungs, with the pH rising to the arterial value of 7.41 once again. In heavy exercise or other conditions of high metabolic activity, or when blood flow through the tissues is sluggish, the decrease in pH in the tissue blood (and in the tissues themselves) can be as much as 0.50, about 12 times normal, thus causing significant tissue acidosis. Respiratory Exchange Ratio The discerning student will have noted that normal transport of oxygen from the lungs to the tissues by each 100 milliliters of blood is about 5 milliliters, whereas normal transport of carbon dioxide from the tissues to the lungs is about 4 milliliters. Thus, under normal resting conditions, only about 82 percent as much carbon dioxide is expired from the lungs as oxygen is taken up by the lungs. The ratio of carbon dioxide output to oxygen uptake is called the *respiratory exchange ratio* (R). That is,

$$R = \frac{\text{Rate of carbon dioxide output}}{\text{Rate of oxygen uptake}}$$

The value for R changes under different metabolic conditions. When a person is using exclusively carbohydrates for body metabolism, R rises to 1.00. Conversely, when a person is using exclusively fats for metabolic energy, the R level falls to as low as 0.7. The reason for this difference is that when oxygen is metabolized with carbohydrates, one molecule of carbon dioxide is formed for each molecule of oxygen consumed; when oxygen reacts with fats, a large share of the oxygen combines with hydrogen atoms from the fats to form water instead of carbon dioxide. In other words, when fats are metabolized, the *respiratory quotient of the chemical reactions* in the tissues is about 0.70 instead of 1.00. (The tissue respiratory quotient is discussed in Chapter 71.)

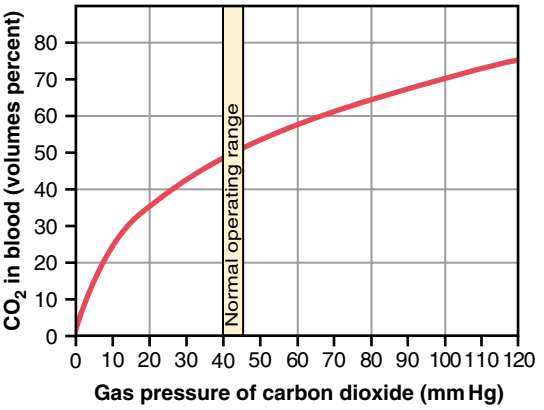


Figure 40-14 Carbon dioxide dissociation curve.

For a person on a normal diet consuming average amounts of carbohydrates, fats, and proteins, the average value for R is considered to be 0.825. Bibliography Albert R, Spiro S, Jett J: *Comprehensive Respiratory Medicine*, Philadelphia, 2002, Mosby. Amann M, Calbet JA: Convective oxygen transport and fatigue, *J Appl Physiol* 104:861, 2008. Geers C, Gros G: Carbon dioxide transport and carbonic anhydrase in blood and muscle, *Physiol Rev* 80:681, 2000. Hopkins SR, Levin DL, Emami K, et al: Advances in magnetic resonance imaging of lung physiology, *J Appl Physiol* 102:1244, 2007. Hughes JM: Assessing gas exchange, *Chron Respir Dis* 4:205, 2007. Jensen FB: Red blood cell pH, the Bohr effect, and other oxygenation-linked phenomena in blood O_2 and CO_2 transport, *Acta Physiol Scand* 182:215, 2004. Maina JN, West JB: Thin and strong! The bioengineering dilemma in the structural and functional design of the blood-gas barrier, *Physiol Rev* 85:811, 2005. Piiper J: Perfusion, diffusion and their heterogeneities limiting blood-tissue O_2 transfer in muscle, *Acta Physiol Scand* 168:603, 2000. Richardson RS: Oxygen transport and utilization: an integration of the muscle systems, *Adv Physiol Educ* 27:183, 2003. Sonveaux P, Lobysheva II, Feron O, et al: Transport and peripheral bioactivities of nitrogen oxides carried by red blood cell hemoglobin: role in oxygen delivery, *Physiology (Bethesda)* 22:97, 2007. Tsai AG, Johnson PC, Intaglietta M: Oxygen gradients in the microcirculation, *Physiol Rev* 83:933, 2003. West JB: *Respiratory Physiology-The Essentials*, ed 8, Baltimore, 2008, Lippincott, Williams & Wilkins.

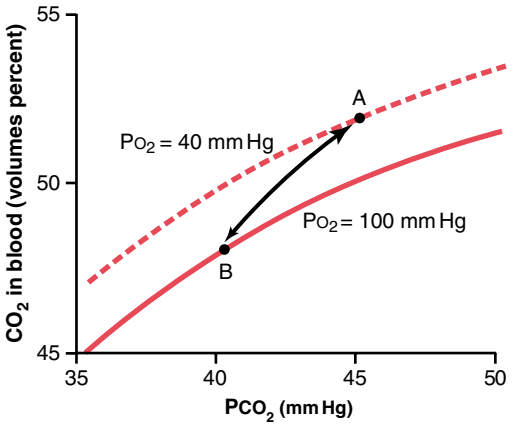
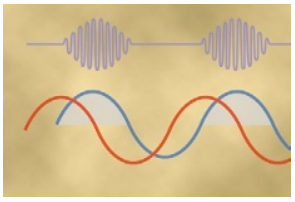


Figure 40-15 Portions of the carbon dioxide dissociation curve when the Po_2 is 100 mm Hg or 40 mm Hg. The arrow represents the Haldane effect on the transport of carbon dioxide, as discussed in the text.

CHAPTER 41

Regulation of Respiration



The nervous system normally adjusts the rate of alveolar ventilation almost exactly to the demands of the body so that the oxygen pressure (P_{O_2}) and carbon dioxide pressure (P_{CO_2}) in the arterial blood are hardly altered, even during heavy exercise and most other types of respiratory stress. This chapter describes the function of this neurogenic system for regulation of respiration.

Respiratory Center

The *respiratory center* is composed of several groups of neurons located *bilaterally* in the *medulla oblongata* and pons of the brain stem, as shown in Figure 41-1. It is divided into three major collections of neurons: (1) a *dorsal respiratory group*, located in the dorsal portion of the medulla, which mainly causes inspiration; (2) a *ventral respiratory group*, located in the ventrolateral part of the medulla, which mainly causes expiration; and (3) the *pneumotaxic center*, located dorsally in the superior portion of the pons, which mainly controls rate and depth of breathing.

Dorsal Respiratory Group of Neurons—Its Control of Inspiration and of Respiratory Rhythm

The dorsal respiratory group of neurons plays the most fundamental role in the control of respiration and extends most of the length of the medulla. Most of its neurons are located within the *nucleus of the tractus solitarius (NTS)*, although additional neurons in the adjacent reticular substance of the medulla also play important roles in respiratory control. The NTS is the sensory termination of both the vagal and the glossopharyngeal nerves, which transmit sensory signals into the respiratory center from (1) peripheral chemoreceptors, (2) baroreceptors, and (3) several types of receptors in the lungs.

Rhythmical Inspiratory Discharges from the Dorsal Respiratory Group. The basic rhythm of respiration is generated mainly in the dorsal respiratory group of neurons. Even when all the peripheral nerves entering the medulla have been sectioned and the brain stem transected both above and below the medulla, this group of neurons still emits repetitive bursts of *inspiratory neuronal action potentials*. The basic cause of these repetitive discharges is unknown. In primitive animals, neural networks have been found in which activity of one set of neurons excites a second set, which in turn inhibits the first. Then, after a period of time, the mechanism repeats itself, continuing throughout the life of the animal. Therefore, most respiratory physiologists believe that some similar network of neurons is present in the human being, located entirely within the medulla; it probably involves not only the dorsal respiratory group but adjacent areas of the medulla as well, and it is responsible for the basic rhythm of respiration.

Inspiratory "Ramp" Signal. The nervous signal that is transmitted to the inspiratory muscles, mainly the diaphragm, is not an instantaneous burst of action potentials. Instead, it begins weakly and increases steadily in a ramp manner for about 2 seconds in normal respiration. Then it ceases abruptly for approximately the next 3 seconds, which turns off the excitation of the diaphragm and allows elastic recoil of the lungs and the chest wall to cause expiration. Next, the inspiratory signal begins again for another cycle; this cycle repeats again and again, with expiration occurring in between. Thus, the inspiratory signal is a *ramp signal*. The obvious advantage of the ramp is that it causes a steady increase in the volume of the lungs during inspiration, rather than inspiratory gasps.

There are two qualities of the inspiratory ramp that are controlled, as follows:

1. Control of the *rate of increase of the ramp signal* so that during heavy respiration, the ramp increases rapidly and therefore fills the lungs rapidly.
2. Control of the *limiting point at which the ramp suddenly ceases*. This is the usual method for controlling the rate of respiration; that is, the earlier the ramp ceases, the

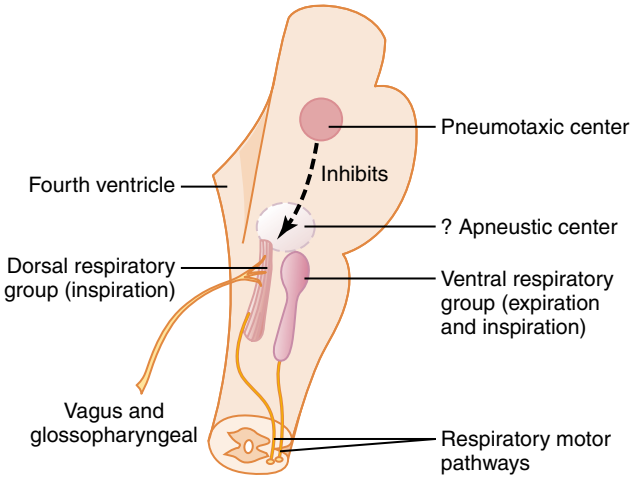


Figure 41-1 Organization of the respiratory center.

shorter the duration of inspiration. This also shortens the duration of expiration. Thus, the frequency of respiration is increased.

A Pneumotaxic Center Limits the Duration of Inspiration and Increases the Respiratory Rate

A *pneumotaxic center*, located dorsally in the *nucleus parabrachialis* of the upper pons, transmits signals to the inspiratory area. The primary effect of this center is to control the "switch-off" point of the inspiratory ramp, thus controlling the duration of the filling phase of the lung cycle. When the pneumotaxic signal is strong, inspiration might last for as little as 0.5 second, thus filling the lungs only slightly; when the pneumotaxic signal is weak, inspiration might continue for 5 or more seconds, thus filling the lungs with a great excess of air.

The function of the pneumotaxic center is primarily to limit inspiration. This has a secondary effect of increasing the rate of breathing because limitation of inspiration also shortens expiration and the entire period of each respiration. A strong pneumotaxic signal can increase the rate of breathing to 30 to 40 breaths per minute, whereas a weak pneumotaxic signal may reduce the rate to only 3 to 5 breaths per minute.

Ventral Respiratory Group of Neurons—Functions in Both Inspiration and Expiration

Located in each side of the medulla, about 5 millimeters anterior and lateral to the dorsal respiratory group of neurons, is the *ventral respiratory group of neurons*, found in the *nucleus ambiguus* rostrally and the *nucleus retroambiguus* caudally. The function of this neuronal group differs from that of the dorsal respiratory group in several important ways:

1. The neurons of the ventral respiratory group remain almost totally *inactive* during normal quiet respiration. Therefore, normal quiet breathing is caused only by repetitive inspiratory signals from the dorsal respiratory group transmitted mainly to the diaphragm, and expiration results from elastic recoil of the lungs and thoracic cage.
2. The ventral respiratory neurons do not appear to participate in the basic rhythmical oscillation that controls respiration.
3. When the respiratory drive for increased pulmonary ventilation becomes greater than normal, respiratory signals spill over into the ventral respiratory neurons from the basic oscillating mechanism of the dorsal respiratory area. As a consequence, the ventral respiratory area contributes extra respiratory drive as well.
4. Electrical stimulation of a few of the neurons in the ventral group causes inspiration, whereas stimulation of others causes expiration. Therefore, these neurons contribute to both inspiration and expiration. They are especially important in providing the powerful expiratory signals to the abdominal muscles during very heavy expiration. Thus, this area operates more or less as an overdrive mechanism when high levels of pulmonary ventilation are required, especially during heavy exercise.

Lung Inflation Signals Limit Inspiration—The Hering-Breuer Inflation Reflex

In addition to the central nervous system respiratory control mechanisms operating entirely within the brain stem, sensory nerve signals from the lungs also help control respiration. Most important, located in the muscular portions of the walls of the bronchi and bronchioles throughout the lungs are *stretch receptors* that transmit signals through the *vagi* into the dorsal respiratory group of neurons when the lungs become overstretched. These signals affect inspiration in much the same way as signals from the pneumotaxic center; that is, when the lungs become overly inflated, the stretch receptors activate an appropriate feedback response that "switches off" the inspiratory ramp and thus stops further inspiration. This is called the *Hering-Breuer inflation reflex*. This reflex also increases the rate of respiration, as is true for signals from the pneumotaxic center.

In humans, the Hering-Breuer reflex probably is not activated until the tidal volume increases to more than three times normal (>≈ 1.5 liters per breath). Therefore, this reflex appears to be mainly a protective mechanism for preventing excess lung inflation rather than an important ingredient in normal control of ventilation.

Control of Overall Respiratory Center Activity

Up to this point, we have discussed the basic mechanisms for causing inspiration and expiration, but it is also important to know how the intensity of the respiratory control signals is increased or decreased to match the ventilatory needs of the body. For example, during heavy exercise, the rates of oxygen usage and carbon dioxide formation are often increased to as much as 20 times normal, requiring

commensurate increases in pulmonary ventilation. The major purpose of the remainder of this chapter is to discuss this control of ventilation in accord with the respiratory needs of the body.

Chemical Control of Respiration

The ultimate goal of respiration is to maintain proper concentrations of oxygen, carbon dioxide, and hydrogen ions in the tissues. It is fortunate, therefore, that respiratory activity is highly responsive to changes in each of these.

Excess carbon dioxide or excess hydrogen ions in the blood mainly act directly on the respiratory center itself, causing greatly increased strength of both the inspiratory and the expiratory motor signals to the respiratory muscles.

Oxygen, in contrast, does not have a significant *direct* effect on the respiratory center of the brain in controlling respiration. Instead, it acts almost entirely on peripheral *chemoreceptors* located in the *carotid* and *aortic bodies*, and these in turn transmit appropriate nervous signals to the respiratory center for control of respiration.

Direct Chemical Control of Respiratory Center Activity by Carbon Dioxide and Hydrogen Ions

Chemosensitive Area of the Respiratory Center. We have discussed mainly three areas of the respiratory center: the dorsal respiratory group of neurons, the ventral respiratory group, and the pneumotaxic center. It is believed that none of these is affected directly by changes in blood carbon dioxide concentration or hydrogen ion concentration. Instead, an additional neuronal area, a *chemosensitive area*, shown in Figure 41-2, is located bilaterally, lying only 0.2 millimeter beneath the ventral surface of the medulla. This area is highly sensitive to changes in either blood P_{CO_2} or hydrogen ion concentration, and it in turn excites the other portions of the respiratory center.

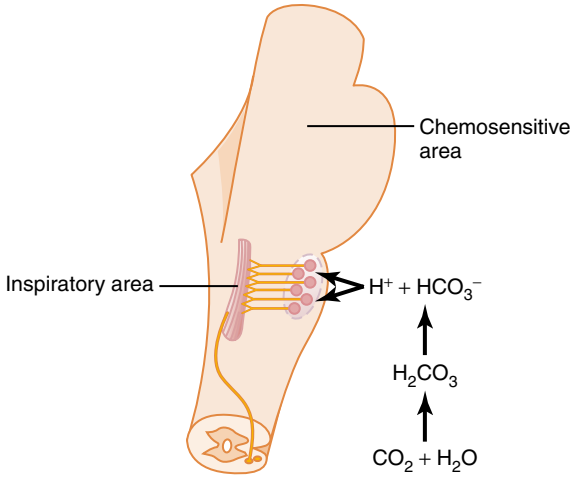


Figure 41-2 Stimulation of the *brain stem inspiratory* area by signals from the ***chemosensitive area*** located bilaterally in the medulla, lying only a fraction of a millimeter beneath the ventral medullary surface. Note also that hydrogen ions stimulate the chemosensitive area, but carbon dioxide in the fluid gives rise to most of the hydrogen ions.

Excitation of the Chemosensitive Neurons by Hydrogen Ions Is Likely the Primary Stimulus

The sensor neurons in the chemosensitive area are especially excited by hydrogen ions; in fact, it is believed that hydrogen ions may be the only important direct stimulus for these neurons. However, hydrogen ions do not easily cross the blood-brain barrier. For this reason, changes in hydrogen ion concentration in the blood have considerably less effect in stimulating the chemosensitive neurons than do changes in blood carbon dioxide, even though carbon dioxide is believed to stimulate these neurons secondarily by changing the hydrogen ion concentration, as explained in the following section.

Carbon Dioxide Stimulates the Chemosensitive Area

Although carbon dioxide has little direct effect in stimulating the neurons in the chemosensitive area, it does have a potent indirect effect. It does this by reacting with the water of the tissues to form carbonic acid, which dissociates into hydrogen and bicarbonate ions; the hydrogen ions then have a potent direct stimulatory effect on respiration. These reactions are shown in Figure 41-2.

Why does blood carbon dioxide have a more potent effect in stimulating the chemosensitive neurons than do blood hydrogen ions? The answer is that the blood-brain barrier is not very permeable to hydrogen ions, but carbon dioxide passes through this barrier almost as if the barrier did not exist. Consequently, whenever the blood P_{CO_2} increases, so does the P_{CO_2} of both the interstitial fluid of the medulla and the cerebrospinal fluid. In both these fluids, the carbon dioxide immediately reacts with the water to form new hydrogen ions. Thus, paradoxically, more hydrogen ions are released into the respiratory chemosensitive sensory area of the medulla when the blood carbon dioxide concentration increases than when the blood hydrogen ion concentration increases. For this reason, respiratory center activity is increased very strongly by changes in blood carbon dioxide, a fact that we subsequently discuss quantitatively.

Decreased Stimulatory Effect of Carbon Dioxide After the First 1 to 2 Days. Excitation of the respiratory center by carbon dioxide is great the first few hours after the blood carbon dioxide first increases, but then it gradually declines over the next 1 to 2 days, decreasing to about one-fifth the initial effect. Part of this decline results from renal readjustment of the hydrogen ion concentration in the circulating blood back toward normal after the carbon dioxide first increases the hydrogen concentration. The kidneys achieve this by increasing the blood bicarbonate, which binds with the hydrogen ions in the blood and cerebrospinal fluid to reduce their concentrations. But even more important, over a period of hours, the bicarbonate ions also slowly diffuse through the blood-brain and blood-cerebrospinal fluid barriers and combine directly

with the hydrogen ions adjacent to the respiratory neurons as well, thus reducing the hydrogen ions back to near normal. A change in blood carbon dioxide concentration therefore has a potent *acute* effect on controlling respiratory drive but only a weak *chronic* effect after a few days' adaptation.

Quantitative Effects of Blood PCO_2 and Hydrogen Ion Concentration on Alveolar Ventilation

Figure 41-3 shows quantitatively the approximate effects of blood P_{CO_2} and blood pH (which is an inverse logarithmic measure of hydrogen ion concentration) on alveolar ventilation. Note especially the very marked increase in ventilation caused by an increase in P_{CO_2} *in the normal range* between 35 and 75 mm Hg. This demonstrates the tremendous effect that carbon dioxide changes have in controlling respiration. By contrast, the change in respiration in the normal blood pH range between 7.3 and 7.5 is less than one-tenth as great.

Changes in Oxygen Have Little Direct Effect on Control of the Respiratory Center

Changes in oxygen concentration have virtually no *direct* effect on the respiratory center itself to alter respiratory drive (although oxygen changes do have an indirect effect, acting through the peripheral chemoreceptors, as explained in the next section).

We learned in Chapter 40 that the hemoglobin-oxygen buffer system delivers almost exactly normal amounts of oxygen to the tissues even when the pulmonary P_{O_2} changes from a value as low as 60 mm Hg up to a value as high as 1000 mm Hg. Therefore, except under special conditions, adequate delivery of oxygen can occur despite changes in lung ventilation ranging from slightly below one-half normal to as high as 20 or more times normal. This is not true for carbon dioxide because both the blood and tissue P_{CO_2} change inversely with the rate of pulmonary ventilation; thus, the processes of animal evolution have made carbon dioxide the major controller of respiration, not oxygen.

Yet for those special conditions in which the tissues get into trouble for lack of oxygen, the body has a special mechanism for respiratory control located in the peripheral chemoreceptors, outside the brain respiratory center; this mechanism responds when the blood oxygen falls too low, mainly below a P_{O_2} of 70 mm Hg, as explained in the next section.

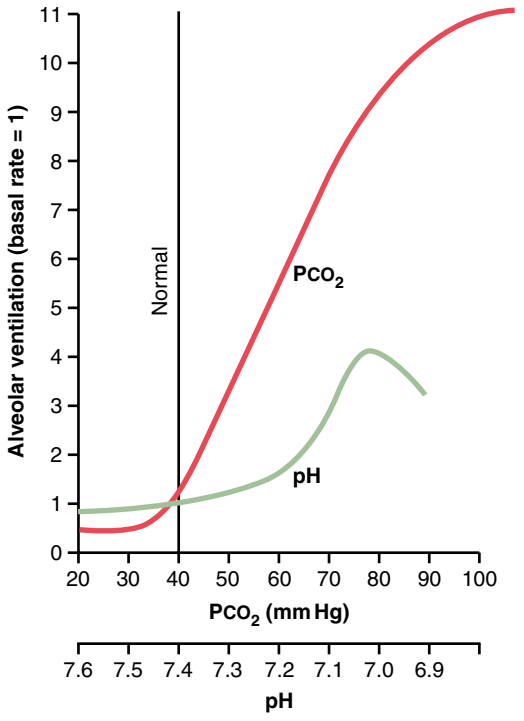


Figure 41-3 Effects of increased arterial blood P_{CO_2} and decreased arterial pH (increased hydrogen ion concentration) on the rate of alveolar ventilation.

Peripheral Chemoreceptor System for Control of Respiratory Activity—Role of Oxygen in Respiratory Control

In addition to control of respiratory activity by the respiratory center itself, still another mechanism is available for controlling respiration. This is the *peripheral chemoreceptor system*, shown in Figure 41-4. Special nervous chemical receptors, called *chemoreceptors*, are located in several areas outside the brain. They are especially important for detecting changes in oxygen in the blood, although they also respond to a lesser extent to changes in carbon dioxide and hydrogen ion concentrations. The chemoreceptors transmit nervous signals to the respiratory center in the brain to help regulate respiratory activity.

Most of the chemoreceptors are in the *carotid bodies*. However, a few are also in the *aortic bodies*, shown in the lower part of Figure 41-4, and a very few are located elsewhere in association with other arteries of the thoracic and abdominal regions.

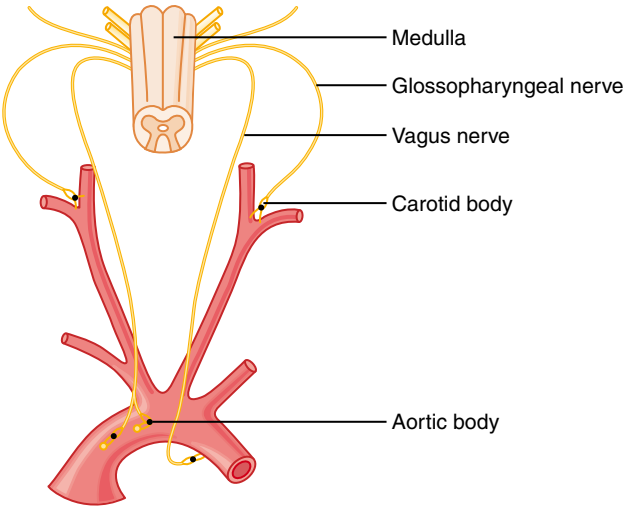


Figure 41-4 Respiratory control by peripheral chemoreceptors in the carotid and aortic bodies.

The *carotid bodies* are located bilaterally in the bifurcations of the common carotid arteries. Their afferent nerve fibers pass through Hering's nerves to the *glossopharyngeal nerves* and then to the dorsal respiratory area of the medulla. The *aortic bodies* are located along the arch of the aorta; their afferent nerve fibers pass through the *vagi*, also to the dorsal medullary respiratory area.

Each of the chemoreceptor bodies receives its own special blood supply through a minute artery directly from the adjacent arterial trunk. Further, blood flow through these bodies is extreme, 20 times the weight of the bodies themselves each minute. Therefore, the percentage of oxygen removed from the flowing blood is virtually zero. This means that *the chemoreceptors are exposed at all times to arterial blood*, not venous blood, and their P_{O_2}s are arterial P_{O_2}s.

***Decreased* Arterial Oxygen Stimulates the Chemoreceptors.** When the oxygen concentration in the arterial blood falls below normal, the chemoreceptors become strongly stimulated. This is demonstrated in Figure 41-5, which shows the effect of different levels of *arterial* P_{O_2} on the rate of nerve impulse transmission from a carotid body. Note that the impulse rate is particularly sensitive to changes in arterial P_{O_2} in the range of 60 down to 30 mm Hg, a range in which hemoglobin saturation with oxygen decreases rapidly.

***Increased* Carbon Dioxide and Hydrogen Ion Concentration Stimulates the Chemoreceptors.** An increase in either carbon dioxide concentration or hydrogen ion concentration also excites the chemoreceptors and, in this way, indirectly increases respiratory activity. However, the direct effects of both these factors in the respiratory center itself are much more powerful than their effects mediated through the chemoreceptors (about seven times as powerful). Yet there is one difference between the peripheral and central effects of carbon dioxide: The stimulation by way of the peripheral chemoreceptors occurs as much as five times as rapidly as central stimulation, so the peripheral chemoreceptors might be especially important in increasing the rapidity of response to carbon dioxide at the onset of exercise.

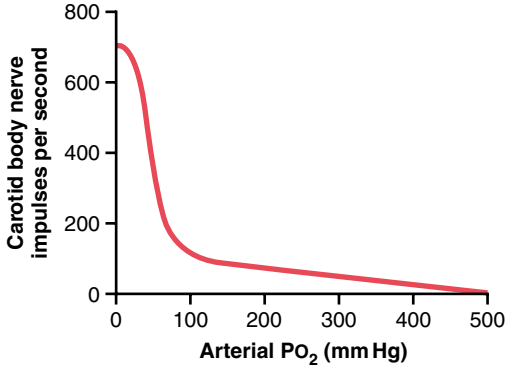


Figure 41-5 Effect of arterial P_{O_2} on impulse rate from the carotid body.

Basic Mechanism of Stimulation of the Chemoreceptors by Oxygen Deficiency. The exact means by which low P_{O_2} excites the nerve endings in the carotid and aortic bodies are still unknown. However, these bodies have multiple highly characteristic glandular-like cells, called *glomus cells*, which synapse directly or indirectly with the nerve endings. Some investigators have suggested that these glomus cells might function as the chemoreceptors and then stimulate the nerve endings. But other studies suggest that the nerve endings themselves are directly sensitive to the low P_{O_2}.

Effect of Low Arterial P_{O_2} to Stimulate Alveolar Ventilation When Arterial Carbon Dioxide and Hydrogen Ion Concentrations Remain Normal

Figure 41-6 shows the effect of low arterial P_{O_2} on alveolar ventilation when the P_{CO_2} and the hydrogen ion concentration are kept constant at their normal levels. In other words, in this figure, only the ventilatory drive, due to the effect of low oxygen on the chemoreceptors, is active. The figure shows almost no effect on ventilation as long as the arterial P_{O_2} remains greater than 100 mm Hg. But at pressures lower than 100 mm Hg, ventilation approximately doubles when the arterial P_{O_2} falls to 60 mm Hg and can increase as much as fivefold at very low P_{O_2}s. Under these conditions, low arterial P_{O_2} obviously drives the ventilatory process quite strongly.

Because the effect of hypoxia on ventilation is modest for P_{O_2}s greater than 60 to 80 mm Hg, the P_{CO_2} and the hydrogen ion response are mainly responsible for regulating ventilation in healthy humans at sea level.

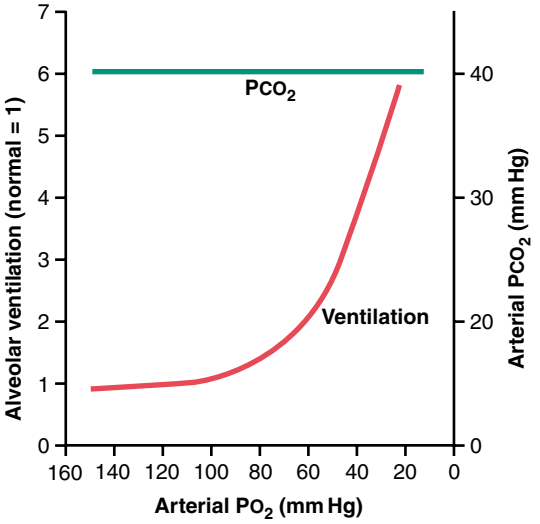


Figure 41-6 The lower curve demonstrates the effect of different levels of arterial P_{O_2} on alveolar ventilation, showing a sixfold increase in ventilation as the P_{O_2} decreases from the normal level of 100 mm Hg to 20 mm Hg. The upper line shows that the arterial P_{CO_2} was kept at a constant level during the measurements of this study; pH also was kept constant.

Chronic Breathing of Low Oxygen Stimulates Respiration Even More—The Phenomenon of "Acclimatization"

Mountain climbers have found that when they ascend a mountain slowly, over a period of days rather than a period of hours, they breathe much more deeply and therefore can withstand far lower atmospheric oxygen concentrations than when they ascend rapidly. This is called *acclimatization*.

The reason for acclimatization is that, within 2 to 3 days, the respiratory center in the brain stem loses about four fifths of its sensitivity to changes in P_{CO_2} and hydrogen ions. Therefore, the excess ventilatory blow-off of carbon dioxide that normally would inhibit an increase in respiration fails to occur, and low oxygen can drive the respiratory system to a much higher level of alveolar ventilation than under acute conditions. Instead of the 70 percent increase in ventilation that might occur after acute exposure to low oxygen, the alveolar ventilation often increases 400 to 500 percent after 2 to 3 days of low oxygen; this helps immensely in supplying additional oxygen to the mountain climber.

Composite Effects of P_{CO_2}, pH, and P_{O_2} on Alveolar Ventilation

Figure 41-7 gives a quick overview of the manner in which the chemical factors P_{O_2}, P_{CO_2}, and pH together affect alveolar ventilation. To understand this diagram, first observe the four red curves. These curves were recorded at different levels of arterial P_{O_2}—40 mm Hg, 50 mm Hg, 60 mm Hg, and 100 mm Hg. For each of these curves, the P_{CO_2} was changed from lower to higher levels. Thus, this "family" of red curves represents the combined effects of alveolar P_{CO_2} and P_{O_2} on ventilation.

Now observe the green curves. The red curves were measured at a blood pH of 7.4; the green curves were measured at a pH of 7.3. We now have two families of curves representing the combined effects of P_{CO_2} and P_{O_2} on ventilation at two different pH values. Still other families of curves would be displaced to the right at higher pHs and displaced to the left at lower pHs. Thus, using this diagram, one can predict the level of alveolar ventilation for most combinations of alveolar P_{CO_2}, alveolar P_{O_2}, and arterial pH.

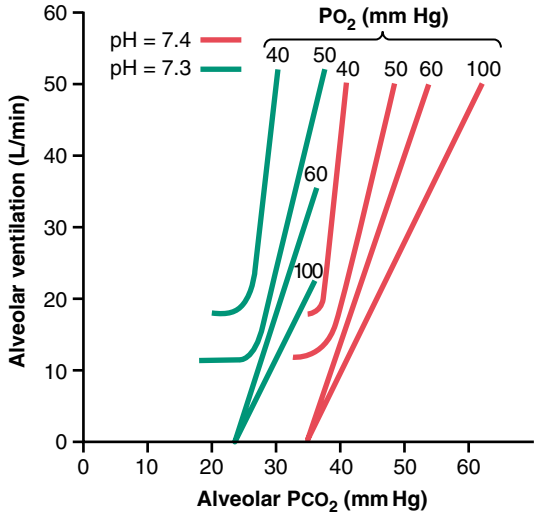


Figure 41-7 Composite diagram showing the interrelated effects of P_{CO_2}, P_{O_2}, and pH on alveolar ventilation. (Drawn from data in Cunningham DJC, Lloyd BB: The Regulation of Human Respiration. Oxford: Blackwell Scientific Publications, 1963.)

Regulation of Respiration During Exercise

In strenuous exercise, oxygen consumption and carbon dioxide formation can increase as much as 20-fold. Yet, as illustrated in Figure 41-8, in the healthy athlete, alveolar ventilation ordinarily increases almost exactly in step with the increased level of oxygen metabolism. The arterial P_{O_2}, P_{CO_2}, and pH remain *almost exactly normal*.

In trying to analyze what causes the increased ventilation during exercise, one is tempted to ascribe this to increases in blood carbon dioxide and hydrogen ions, plus a decrease in blood oxygen. However, this is questionable because measurements of arterial P_{CO_2}, pH, and P_{O_2} show that none of these values changes significantly during exercise, so none of them becomes abnormal enough to stimulate respiration so vigorously as observed during strenuous exercise. Therefore, the question must be asked: What causes intense ventilation during exercise? At least one effect seems to be predominant. The brain, on transmitting motor impulses to the exercising muscles, is believed to transmit at the same time collateral impulses into the brain stem to excite the respiratory center. This is analogous to the stimulation of the vasomotor center of the brain stem during exercise that causes a simultaneous increase in arterial pressure.

Actually, when a person begins to exercise, a large share of the total increase in ventilation begins immediately on initiation of the exercise, before any blood chemicals have had time to change. It is likely that most of the increase in respiration results from neurogenic signals transmitted directly into the brain stem respiratory center at the same time that signals go to the body muscles to cause muscle contraction.

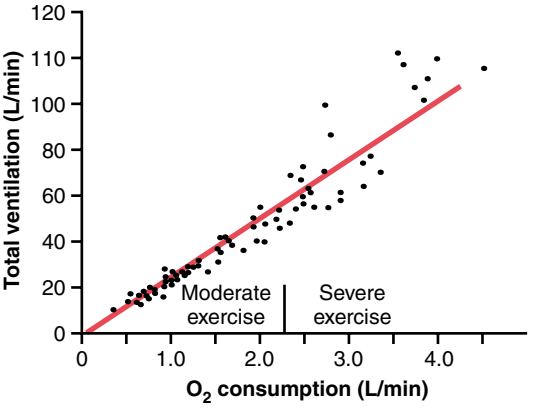


Figure 41-8 Effect of exercise on oxygen consumption and ventilatory rate. (From Gray JS: Pulmonary Ventilation and Its Physiological Regulation. Springfield, Ill: Charles C Thomas, 1950.)

Interrelation Between Chemical Factors and Nervous Factors in the Control of Respiration During Exercise. When a person exercises, direct nervous signals presumably stimulate the respiratory center *almost* the proper amount to supply the extra oxygen required for exercise and to blow off extra carbon dioxide. Occasionally, however, the nervous respiratory control signals are either too strong or too weak. Then chemical factors play a significant role in bringing about the final adjustment of respiration required to keep the oxygen, carbon dioxide, and hydrogen ion concentrations of the body fluids as nearly normal as possible.

This is demonstrated in Figure 41-9, which shows in the lower curve changes in alveolar ventilation during a 1-minute period of exercise and in the upper curve changes in arterial P_{CO_2}. Note that at the onset of exercise, the alveolar ventilation increases almost instantaneously, without an initial increase in arterial P_{CO_2}. In fact, this increase in ventilation is usually great enough so that at first it actually *decreases* arterial P_{CO_2} below normal, as shown in the figure. The presumed reason that the ventilation forges ahead of the buildup of blood carbon dioxide is that the brain provides an "anticipatory" stimulation of respiration at the onset of exercise, causing extra alveolar ventilation even before it is necessary. However, after about 30 to 40 seconds, the amount of carbon dioxide released into the blood from the active muscles approximately matches the increased rate of ventilation, and the arterial P_{CO_2} returns essentially to normal even as the exercise continues, as shown toward the end of the 1-minute period of exercise in the figure.

Figure 41-10 summarizes the control of respiration during exercise in still another way, this time more quantitatively. The lower curve of this figure shows the

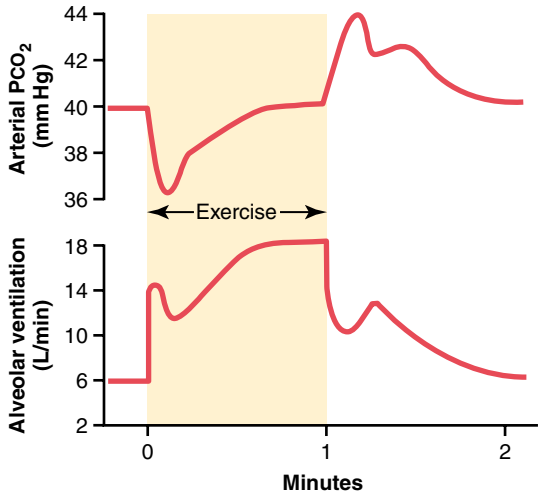


Figure 41-9 Changes in alveolar ventilation (*bottom curve*) and arterial PCO_2 (*top curve*) during a 1-minute period of exercise and also after termination of exercise. (Extrapolated to the human from data in dogs in Bainton CR: Effect of speed vs grade and shivering on ventilation in dogs during active exercise. J Appl Physiol 33:778, 1972.)

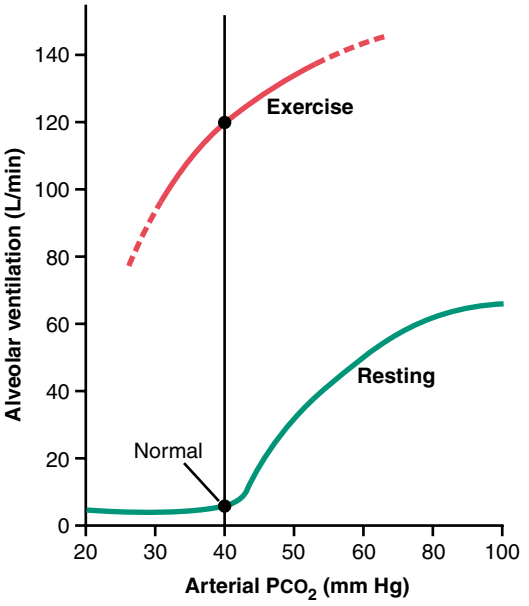


Figure 41-10 Approximate effect of maximum exercise in an athlete to shift the alveolar P_{CO_2}-ventilation response curve to a level much higher than normal. The shift, believed to be caused by neurogenic factors, is almost exactly the right amount to maintain arterial P_{CO_2} at the normal level of 40 mm Hg both in the resting state and during heavy exercise.

effect of different levels of arterial P_{CO_2} on alveolar ventilation when the body is at rest—that is, not exercising. The upper curve shows the approximate shift of this ventilatory curve caused by neurogenic drive from the respiratory center that occurs during heavy exercise. The points indicated on the two curves show the arterial P_{CO_2} first in the resting state and then in the exercising state. Note in both instances that the P_{CO_2} is at the normal level of 40 mm Hg. In other words, the neurogenic factor shifts the curve about 20-fold in the upward direction, so ventilation almost matches the rate of carbon dioxide release, thus keeping arterial P_{CO_2} near its normal value. The upper curve of Figure 41-10 also shows that if, during exercise, the arterial P_{CO_2} does change from its normal value of 40 mm Hg, it has an extra stimulatory effect on ventilation at a P_{CO_2} greater than 40 mm Hg and a depressant effect at a P_{CO_2} less than 40 mm Hg.

Neurogenic Control of Ventilation During Exercise May Be Partly a Learned Response. Many experiments suggest that the brain's ability to shift the ventilatory response curve during exercise, as shown in Figure 41-10, is at least partly a *learned* response. That is, with repeated periods of exercise, the brain becomes progressively more able to provide the proper signals required to keep the blood P_{CO_2} at its normal level. Also, there is reason to believe that even the cerebral cortex is involved in this learning because experiments that block only the cortex also block the learned response.

Other Factors That Affect Respiration

Voluntary Control of Respiration. Thus far, we have discussed the involuntary system for the control of respiration. However, we all know that for short periods of time, respiration can be controlled voluntarily and that one can hyperventilate or hypoventilate to such an extent that serious derangements in P_{CO_2}, pH, and P_{O_2} can occur in the blood.

Effect of Irritant Receptors in the Airways. The epithelium of the trachea, bronchi, and bronchioles is supplied with sensory nerve endings called *pulmonary irritant receptors* that are stimulated by many incidents. These cause coughing and sneezing, as discussed in Chapter 39. They may also cause bronchial constriction in such diseases as asthma and emphysema.

Function of Lung "J Receptors". A few sensory nerve endings have been described in the alveolar walls in *juxtaposition* to the pulmonary capillaries—hence the name "J receptors." They are stimulated especially when the pulmonary capillaries become engorged with blood or when pulmonary edema occurs in such conditions as congestive heart failure. Although the functional role of the J receptors is not clear, their excitation may give the person a feeling of dyspnea.

Brain Edema Depresses the Respiratory Center. The activity of the respiratory center may be depressed or even inactivated by acute brain edema resulting from brain concussion. For instance, the head might be struck against some solid object, after which the damaged brain tissues swell, compressing the cerebral arteries against the cranial vault and thus partially blocking cerebral blood supply.

Occasionally, respiratory depression resulting from brain edema can be relieved temporarily by intravenous injection of hypertonic solutions such as highly concentrated mannitol solution. These solutions osmotically remove some of the fluids of the brain, thus relieving intracranial pressure and sometimes re-establishing respiration within a few minutes.

Anesthesia. Perhaps the most prevalent cause of respiratory depression and respiratory arrest is overdosage with anesthetics or narcotics. For instance, sodium pentobarbital depresses the respiratory center considerably more than many other anesthetics, such as halothane. At one time, morphine was used as an anesthetic, but this drug is now used only as an adjunct to anesthetics because it greatly depresses the respiratory center while having less ability to anesthetize the cerebral cortex.

Periodic Breathing. An abnormality of respiration called *periodic breathing* occurs in a number of disease conditions. The person breathes deeply for a short interval and then breathes slightly or not at all for an additional interval, with the cycle repeating itself over and over. One type of periodic breathing, *Cheyne-Stokes breathing*, is characterized by slowly waxing and waning respiration occurring about every 40 to 60 seconds, as illustrated in Figure 41-11.

Basic Mechanism of Cheyne-Stokes Breathing. The basic cause of Cheyne-Stokes breathing is the following: When a person overbreathes, thus blowing off too much carbon dioxide from the pulmonary blood while at the same time increasing blood oxygen, it takes several seconds before the changed pulmonary blood can be transported to the brain and inhibit the excess ventilation. By this time, the person has already overventilated for an extra few seconds.

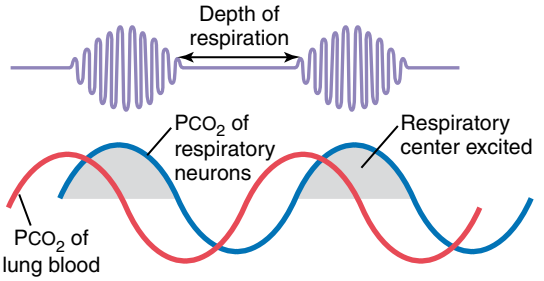


Figure 41-11 Cheyne-Stokes breathing, showing changing P_{CO_2} in the pulmonary blood (*red line*) and delayed changes in the P_{CO_2} of the fluids of the respiratory center (*blue line*).

Therefore, when the overventilated blood finally reaches the brain respiratory center, the center becomes depressed to an excessive amount. Then the opposite cycle begins. That is, carbon dioxide increases and oxygen decreases in the alveoli. Again, it takes a few seconds before the brain can respond to these new changes. When the brain does respond, the person breathes hard once again and the cycle repeats.

The basic cause of Cheyne-Stokes breathing occurs in everyone. However, under normal conditions, this mechanism is highly "damped." That is, the fluids of the blood and the respiratory center control areas have large amounts of dissolved and chemically bound carbon dioxide and oxygen. Therefore, normally, the lungs cannot build up enough extra carbon dioxide or depress the oxygen sufficiently in a few seconds to cause the next cycle of the periodic breathing. But under two separate conditions, the damping factors can be overridden and Cheyne-Stokes breathing does occur:

1. When a *long delay occurs for transport of blood from the lungs to the brain*, changes in carbon dioxide and oxygen in the alveoli can continue for many more seconds than usual. Under these conditions, the storage capacities of the alveoli and pulmonary blood for these gases are exceeded; then, after a few more seconds, the periodic respiratory drive becomes extreme and Cheyne-Stokes breathing begins. This type of Cheyne-Stokes breathing often occurs in patients with *severe cardiac failure* because blood flow is slow, thus delaying the transport of blood gases from the lungs to the brain. In fact, in patients with chronic heart failure, Cheyne-Stokes breathing can sometimes occur on and off for months.
2. A second cause of Cheyne-Stokes breathing is *increased negative feedback gain* in the respiratory control areas. This means that a change in blood carbon dioxide or oxygen causes a far greater change in ventilation than normally. For instance, instead of the normal 2- to 3-fold increase in ventilation that occurs when the P_{CO_2} rises 3 mm Hg, the same 3 mm Hg rise might increase ventilation 10- to 20-fold. The brain feedback tendency for periodic breathing is now strong enough to cause Cheyne-Stokes breathing without extra blood flow delay between the lungs and brain. This type of Cheyne-Stokes breathing occurs mainly in patients with *brain damage*. The brain damage often turns off the respiratory drive entirely for a few seconds; then an extra intense increase in blood carbon dioxide turns it back on with great force. Cheyne-Stokes breathing of this type is frequently a prelude to death from brain malfunction.

Typical records of changes in pulmonary and respiratory center P_{CO_2} during Cheyne-Stokes breathing are shown in Figure 41-11. Note that the P_{CO_2} of the pulmonary blood changes *in advance* of the P_{CO_2} of the respiratory neurons. But the depth of respiration corresponds with the P_{CO_2} in the brain, not with the P_{CO_2} in the pulmonary blood where the ventilation is occurring.

Sleep Apnea

The term *apnea* means absence of spontaneous breathing. Occasional apneas occur during normal sleep, but in persons with *sleep apnea*, the frequency and duration are greatly increased, with episodes of apnea lasting for 10 seconds or longer and occurring 300 to 500 times each night. Sleep apneas can be caused by obstruction of the upper airways, especially the pharynx, or by impaired central nervous system respiratory drive.

Obstructive Sleep Apnea Is Caused by Blockage of the Upper Airway. The muscles of the pharynx normally keep this passage open to allow air to flow into the lungs during inspiration. During sleep, these muscles usually relax, but the airway passage remains open enough to permit adequate airflow. Some individuals have an especially narrow passage, and relaxation of these muscles during sleep causes the pharynx to completely close so that air cannot flow into the lungs.

In persons with sleep apnea, loud *snoring* and *labored breathing* occur soon after falling asleep. The snoring proceeds, often becoming louder, and is then interrupted by a long silent period during which no breathing (apnea) occurs. These periods of apnea result in significant decreases in P_{O_2} and increases in P_{CO_2}, which greatly stimulate respiration. This, in turn, causes sudden attempts to breathe, which result in loud snorts and gasps followed by snoring and repeated episodes of apnea. The periods of apnea and labored breathing are repeated several hundred times during the night, resulting in fragmented, restless sleep. Therefore, patients with sleep apnea usually have excessive daytime *drowsiness*, as well as other disorders, including increased sympathetic activity, high heart rates, pulmonary and systemic hypertension, and a greatly elevated risk for cardiovascular disease.

Obstructive sleep apnea most commonly occurs in older, obese persons in whom there is increased fat deposition in the soft tissues of the pharynx or compression of the pharynx due to excessive fat masses in the neck. In a few individuals, sleep apnea may be associated with nasal obstruction, a very large tongue, enlarged tonsils, or certain shapes of the palate that greatly increase resistance to the flow of air to the lungs during inspiration. The most common treatments of obstructive sleep apnea include (1) surgery to remove excess fat tissue at the back of the throat (a procedure called *uvulopalatopharyngoplasty*), to remove enlarged tonsils or adenoids, or to create an opening in the trachea (tracheostomy) to bypass the obstructed airway during sleep, and (2) nasal ventilation with *continuous positive airway pressure* (CPAP).

"Central" Sleep Apnea Occurs When the Neural Drive to Respiratory Muscles Is Transiently Abolished. In a few persons with sleep apnea, the central nervous system drive to the ventilatory muscles transiently ceases. Disorders that can cause cessation of the ventilatory drive during sleep include *damage to the central respiratory centers or abnormalities of the respiratory neuromuscular apparatus*. Patients affected by central sleep apnea may have decreased ventilation when they are awake, although they are fully capable of normal voluntary breathing. During sleep, their breathing disorders usually worsen, resulting in more frequent episodes of apnea that decrease P_{O_2} and increase P_{CO_2} until a critical level is reached that eventually stimulates respiration. These transient instabilities of respiration cause restless sleep and clinical features similar to those observed in obstructive sleep apnea.

In most patients the cause of central sleep apnea is unknown, although instability of the respiratory drive can result from strokes or other disorders that make the respiratory centers of the brain less responsive to the stimulatory effects of carbon dioxide and hydrogen ions. Patients with this disease are extremely sensitive to even small doses of sedatives or narcotics, which further reduce the responsiveness of the respiratory centers to the stimulatory effects of carbon dioxide. Medications that stimulate the respiratory centers can sometimes be helpful, but ventilation with CPAP at night is usually necessary.

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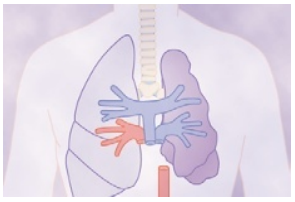
Respiratory Insufficiency—Pathophysiology, Diagnosis, Oxygen Therapy



Diagnosis and treatment of most respiratory disorders depend heavily on understanding the basic physiologic principles of respiration and gas exchange. Some respiratory diseases result from inadequate ventilation. Others result from abnormalities of diffusion through the pulmonary membrane or abnormal blood transport of gases between the lungs and tissues. Therapy is often entirely different for these diseases, so it is no longer satisfactory simply to make a diagnosis of "respiratory insufficiency."

Useful Methods for Studying Respiratory Abnormalities

In the previous few chapters, we have discussed several methods for studying respiratory abnormalities, including measuring vital capacity, tidal air, functional residual capacity, dead space, physiologic shunt, and physiologic dead space. This array of measurements is only part of the armamentarium of the clinical pulmonary physiologist. Some other tools are described here.

Study of Blood Gases and Blood pH

Among the most fundamental of all tests of pulmonary performance are determinations of the blood P_{O_2}, CO_2, and pH. It is often important to make these measurements rapidly as an aid in determining appropriate therapy for acute respiratory distress or acute abnormalities of acid-base balance. Several simple and rapid methods have been developed to make these measurements within minutes, using no more than a few drops of blood. They are the following.

Determination of Blood pH. Blood pH is measured using a glass pH electrode of the type used in all chemical laboratories. However, the electrodes used for this purpose are miniaturized. The voltage generated by the glass electrode is a direct measure of pH, and this is generally read directly from a voltmeter scale, or it is recorded on a chart.

Determination of Blood CO_2. A glass electrode pH meter can also be used to determine blood CO_2 in the following way: When a weak solution of sodium bicarbonate is exposed to carbon dioxide gas, the carbon dioxide dissolves in the solution until an equilibrium state is established. In this equilibrium state, the pH of the solution is a function of the carbon dioxide and bicarbonate ion concentrations in accordance with the Henderson-Hasselbalch equation that is explained in Chapter 30; that is,

$$pH = 6.1 + \log \frac{HCO_3^-}{CO_2}$$

When the glass electrode is used to measure CO_2 in blood, a miniature glass electrode is surrounded by a thin plastic membrane. In the space between the electrode and plastic membrane is a solution of sodium bicarbonate of known concentration. Blood is then superfused onto the outer surface of the plastic membrane, allowing carbon dioxide to diffuse from the blood into the bicarbonate solution. Only a drop or so of blood is required. Next, the pH is measured by the glass electrode, and the CO_2 is calculated by use of the previously given formula.

Determination of Blood PO_2. The concentration of oxygen in a fluid can be measured by a technique called *polarography*. Electric current is made to flow between a small negative electrode and the solution. If the voltage of the electrode is more than −0.6 volt different from the voltage of the solution, oxygen will deposit on the electrode. Furthermore, the rate of current flow through the electrode will be directly proportional to the concentration of oxygen (and therefore to PO_2 as well). In practice, a negative platinum electrode with a surface area of about 1 square millimeter is used, and this is separated from the blood by a thin plastic membrane that allows diffusion of oxygen but not diffusion of proteins or other substances that will "poison" the electrode.

Often all three of the measuring devices for pH, CO_2, and P_{O_2} are built into the same apparatus, and all these

measurements can be made within a minute or so using a single, droplet-size sample of blood. Thus, changes in the blood gases and pH can be followed almost moment by moment at the bedside.

Measurement of Maximum Expiratory Flow

In many respiratory diseases, particularly in asthma, the resistance to airflow becomes especially great during expiration, sometimes causing tremendous difficulty in breathing. This has led to the concept called *maximum expiratory flow*, which can be defined as follows: When a person expires with great force, the expiratory airflow reaches a maximum flow beyond which the flow cannot be increased any more, even with greatly increased additional force. This is the maximum expiratory flow. The maximum expiratory flow is much greater when the lungs are filled with a large volume of air than when they are almost empty. These principles can be understood by referring to Figure 42-1.

Figure 42-1*A* shows the effect of increased pressure applied to the outsides of the alveoli and air passageways caused by compressing the chest cage. The arrows indicate that the same pressure compresses the outsides of both the alveoli and the bronchioles. Therefore, not only does this pressure force air from the alveoli toward the bronchioles, but it also tends to collapse the bronchioles at the same time, which will oppose movement of air to the exterior. Once the bronchioles have almost completely collapsed, further expiratory force can still greatly increase the alveolar pressure, but it also increases the degree of bronchiolar collapse and airway resistance by an equal amount, thus preventing further increase in flow.

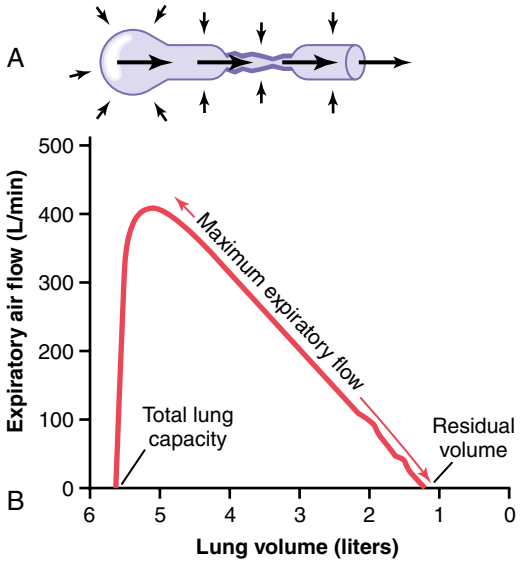


Figure 42-1 *A*, Collapse of the respiratory passageway during maximum expiratory effort, an effect that limits expiratory flow rate. *B*, Effect of lung volume on the maximum expiratory air flow, showing decreasing maximum expiratory air flow as the lung volume becomes smaller.

Therefore, beyond a critical degree of expiratory force, a maximum expiratory flow has been reached.

Figure 42-1*B* shows the effect of different degrees of lung collapse (and therefore of bronchiolar collapse as well) on the maximum expiratory flow. The curve recorded in this section shows the maximum expiratory flow at all levels of lung volume after a healthy person first inhales as much air as possible and then expires with maximum expiratory effort until he or she can expire at no greater rate. Note that the person quickly reaches a *maximum expiratory airflow* of more than 400 L/min. But regardless of how much additional expiratory effort the person exerts, this is still the maximum flow rate that he or she can achieve.

Note also that as the lung volume becomes smaller, the maximum expiratory flow rate also becomes less. The main reason for this is that in the enlarged lung the bronchi and bronchioles are held open partially by way of elastic pull on their outsides by lung structural elements; however, as the lung becomes smaller, these structures are relaxed so that the bronchi and bronchioles are collapsed more easily by external chest pressure, thus progressively reducing the maximum expiratory flow rate as well.

Abnormalities of the Maximum Expiratory Flow-Volume Curve. Figure 42-2 shows the normal maximum expiratory flow-volume curve, along with two additional flow-volume curves recorded in two types of lung diseases: constricted lungs and partial airway obstruction. Note that the *constricted lungs* have both reduced total lung capacity (TLC) and reduced residual volume (RV). Furthermore, because the lung cannot expand to a normal maximum volume, even with the greatest possible expiratory effort, the maximal expiratory flow cannot rise to equal that of the normal curve. Constricted lung diseases include fibrotic diseases of the lung itself, such as *tuberculosis* and *silicosis*, and diseases that constrict the chest cage, such as *kyphosis, scoliosis*, and *fibrotic pleurisy*.

In diseases with *airway obstruction*, it is usually much more difficult to expire than to inspire because the closing tendency of the airways is greatly increased by the extra

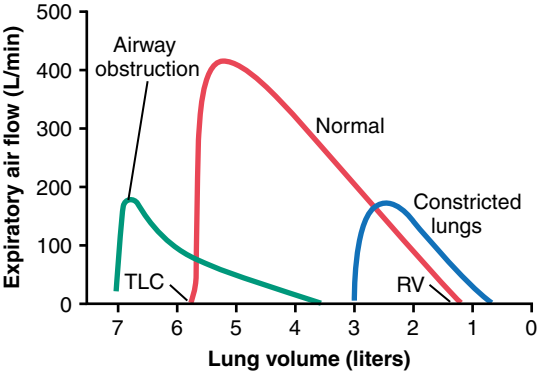


Figure 42-2 Effect of two respiratory abnormalities—constricted lungs and airway obstruction—on the maximum expiratory flow-volume curve. TLC, total lung capacity; RV, residual volume.

positive pressure required in the chest to cause expiration. By contrast, the extra negative pleural pressure that occurs during inspiration actually "pulls" the airways open at the same time that it expands the alveoli. Therefore, air tends to enter the lung easily but then becomes trapped in the lungs. Over a period of months or years, this effect increases both the TLC and the RV, as shown by the green curve in Figure 42-2. Also, because of the obstruction of the airways and because they collapse more easily than normal airways, the maximum expiratory flow rate is greatly reduced.

The classic disease that causes severe airway obstruction is *asthma*. Serious airway obstruction also occurs in some stages of *emphysema*.

Forced Expiratory Vital Capacity and Forced Expiratory Volume

Another exceedingly useful clinical pulmonary test, and one that is also simple, is to record on a spirometer the *forced expiratory vital capacity* (FVC). Such a recording is shown in Figure 42-3*A* for a person with normal lungs and in Figure 42-3*B* for a person with partial airway obstruction. In performing the FVC maneuver, the person first inspires maximally to the total lung capacity and then exhales into the spirometer with maximum expiratory effort as rapidly and as completely as possible. The total distance of the downslope of the lung volume record represents the FVC, as shown in the figure.

Now, study the difference between the two records (1) for normal lungs and (2) for *partial* airway obstruction. The total volume changes of the FVCs are not greatly different, indicating only a moderate difference in basic lung volumes in the two persons. There is, however, a *major difference in the amounts of air that these persons can expire each second*, especially during the first second. Therefore, it is customary to compare the recorded forced expiratory volume during the first second (FEV_1) with the normal. In the normal person (see Figure 42-3*A*), the percentage of the FVC that is expired in the first second divided by the total FVC (FEV_1/FVC%) is 80 percent. However, note in Figure 42-3*B* that, with airway obstruction, this value decreased to only 47 percent. In serious airway obstruction, as often occurs in acute asthma, this can decrease to less than 20 percent.

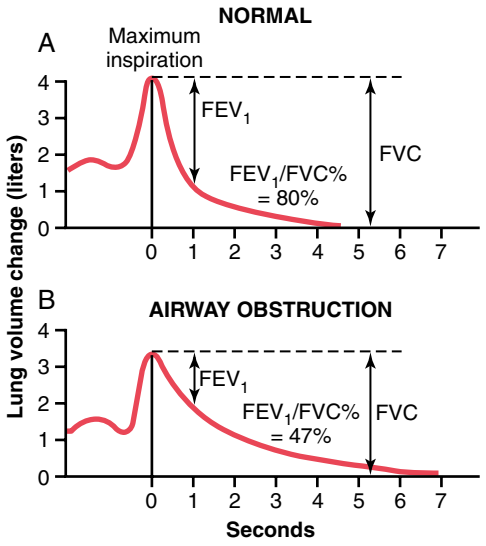


Figure 42-3 Recordings during the forced vital capacity maneuver: *A*, in a healthy person and *B*, in a person with partial airway obstruction. (The "zero" on the volume scale is residual volume.)

Pathophysiology of Specific Pulmonary Abnormalities

Chronic Pulmonary Emphysema

The term *pulmonary emphysema* literally means excess air in the lungs. However, this term is usually used to describe complex obstructive and destructive process of the lungs caused by many years of smoking. It results from the following major pathophysiologic changes in the lungs:

1. *Chronic infection*, caused by inhaling smoke or other substances that irritate the bronchi and bronchioles. The chronic infection seriously deranges the normal protective mechanisms of the airways, including partial paralysis of the cilia of the respiratory epithelium, an effect caused by nicotine. As a result, mucus cannot be moved easily out of the passageways. Also, stimulation of excess mucus secretion occurs, which further exacerbates the condition. Inhibition of the alveolar macrophages also occurs, so they become less effective in combating infection.
2. The infection, excess mucus, and inflammatory edema of the bronchiolar epithelium together cause *chronic obstruction* of many of the smaller airways.
3. The obstruction of the airways makes it especially difficult to expire, thus causing *entrapment of air in the alveoli* and overstretching them. This, combined with the lung infection, causes *marked destruction of as much as 50 to 80 percent of the alveolar walls*. Therefore, the final picture of the emphysematous lung is that shown in Figures 42-4 *(top)* and 42-5.

The physiologic effects of chronic emphysema are variable, depending on the severity of the disease and the relative degrees of bronchiolar obstruction versus lung parenchymal destruction. Among the different abnormalities are the following:

1. The bronchiolar obstruction *increases airway resistance* and results in greatly increased work of breathing. It is especially difficult for the person to move air through the bronchioles during expiration because the compressive force on the outside of the lung not only compresses the alveoli but also compresses the bronchioles, which further increases their resistance during expiration.

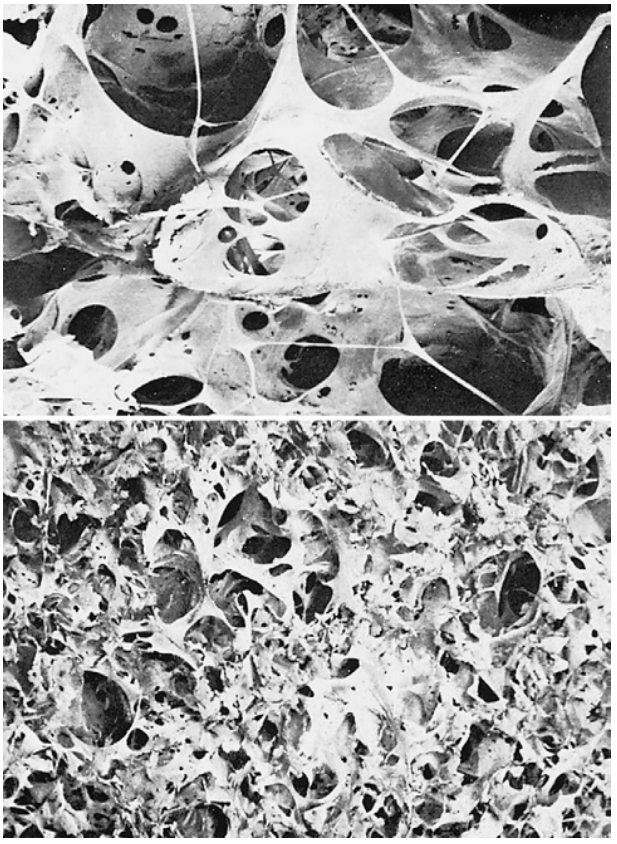


Figure 42-4 Contrast of the emphysematous lung (***top figure***) with the normal lung (***bottom figure***), showing extensive alveolar destruction in emphysema. (Reproduced with permission of Patricia Delaney and the Department of Anatomy, The Medical College of Wisconsin.)

2. The marked loss of alveolar walls greatly *decreases the diffusing capacity* of the lung, which reduces the ability of the lungs to oxygenate the blood and remove carbon dioxide from the blood.
3. The obstructive process is frequently much worse in some parts of the lungs than in other parts, so some portions of the lungs are well ventilated, whereas other portions are poorly ventilated. This often causes *extremely abnormal ventilation-perfusion ratios*, with a very low $\dot{V}a/\dot{Q}$ in some parts *(physiologic shunt)*, resulting in poor aeration of the blood, and very high $\dot{V}a/\dot{Q}$ in other parts *(physiologic dead space)*, resulting in wasted ventilation, both effects occurring in the same lungs.
4. Loss of large portions of the alveolar walls also decreases the number of pulmonary capillaries through which blood can pass. As a result, the pulmonary vascular resistance often increases markedly, causing *pulmonary hypertension*. This in turn overloads the right side of the heart and frequently causes right-sided heart failure.

Chronic emphysema usually progresses slowly over many years. The person develops both hypoxia and hypercapnia because of hypoventilation of many alveoli plus loss of alveolar walls. The net result of all these effects is severe, prolonged, devastating *air hunger* that can last for years until the hypoxia and hypercapnia cause death—a high penalty to pay for smoking.

Pneumonia

The term *pneumonia* includes any inflammatory condition of the lung in which some or all of the alveoli are filled with fluid and blood cells, as shown in Figure 42-5. A common type of pneumonia is *bacterial pneumonia*, caused most frequently by *pneumococci*. This disease begins with infection in the alveoli; the pulmonary membrane becomes inflamed and highly porous so that fluid and even red and white blood cells leak out of the blood into the alveoli. Thus, the infected alveoli become progressively filled with fluid and cells, and the infection spreads by extension of bacteria or virus from alveolus to alveolus. Eventually, large areas of the lungs, sometimes whole lobes or even a whole lung, become "consolidated," which means that they are filled with fluid and cellular debris.

In pneumonia, the gas exchange functions of the lungs decline in different stages of the disease. In early stages, the pneumonia process might well be localized to only one lung, with alveolar ventilation reduced while blood flow through the lung continues normally. This causes two major pulmonary abnormalities: (1) reduction in the total available surface area of the respiratory membrane

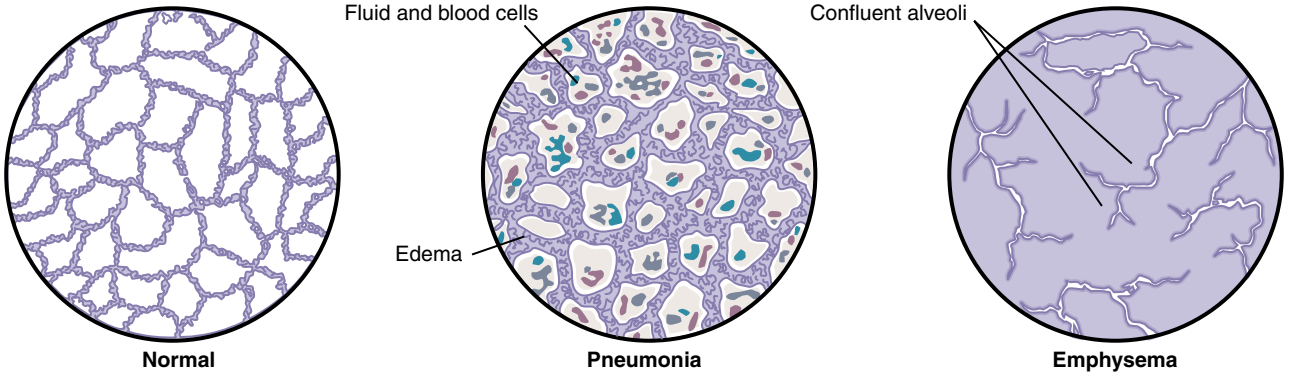


Figure 42-5 Lung alveolar changes in pneumonia and emphysema.

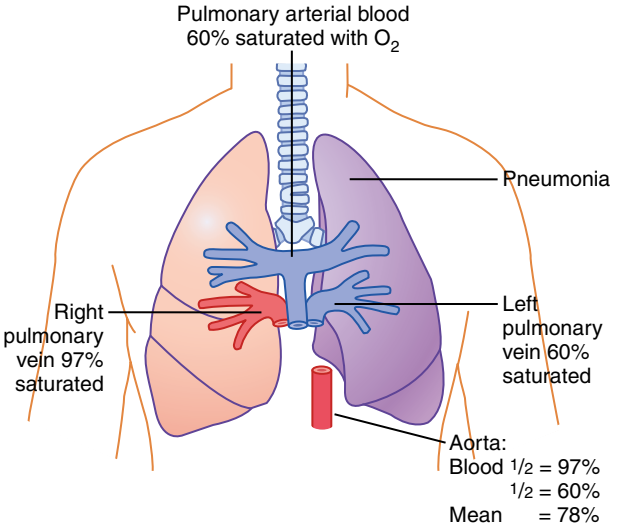


Figure 42-6 Effect of pneumonia on percentage saturation of oxygen in the pulmonary artery, the right and left pulmonary veins, and the aorta.

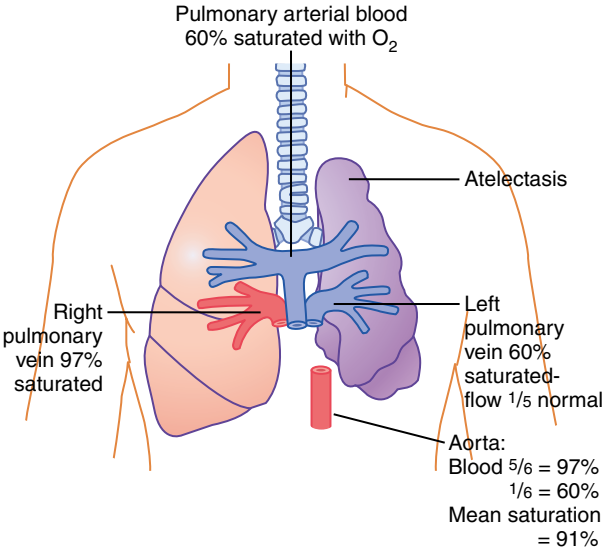


Figure 42-7 Effect of atelectasis on aortic blood oxygen saturation.

and (2) decreased ventilation-perfusion ratio. Both these effects cause *hypoxemia* (low blood oxygen) and *hypercapnia* (high blood carbon dioxide).

Figure 42-6 shows the effect of the decreased ventilation-perfusion ratio in pneumonia, showing that the blood passing through the aerated lung becomes 97 percent saturated with oxygen, whereas that passing through the unaerated lung is about 60 percent saturated. Therefore, the average saturation of the blood pumped by the left heart into the aorta is only about 78 percent, which is far below normal.

Atelectasis

Atelectasis means collapse of the alveoli. It can occur in localized areas of a lung or in an entire lung. Common causes of atelectasis are (1) total obstruction of the airway or (2) lack of surfactant in the fluids lining the alveoli.

Airway Obstruction Causes Lung Collapse. The airway obstruction type of atelectasis usually results from (1) blockage of many small bronchi with mucus or (2) obstruction of a major bronchus by either a large mucus plug or some solid object such as a tumor. The air entrapped beyond the block is absorbed within minutes to hours by the blood flowing in the pulmonary capillaries. If the lung tissue is pliable enough, this will lead simply to collapse of the alveoli. However, if the lung is rigid because of fibrotic tissue and cannot collapse, absorption of air from the alveoli creates very negative pressures within the alveoli, which pull fluid out of the pulmonary capillaries into the alveoli, thus causing the alveoli to fill completely with edema fluid. This almost always is the effect that occurs when an entire lung becomes atelectatic, a condition called *massive collapse* of the lung.

The effects on overall pulmonary function caused by *massive collapse* (atelectasis) of an entire lung are shown in Figure 42-7. Collapse of the lung tissue not only occludes the alveoli but also almost always increases the *resistance to blood flow* through the pulmonary vessels of the collapsed lung. This resistance increase occurs partially because of the lung collapse itself, which compresses and folds the vessels as the volume of the lung decreases. In addition, hypoxia in the collapsed alveoli causes additional vasoconstriction, as explained in Chapter 38.

Because of the vascular constriction, blood flow through the atelectatic lung is greatly reduced. Fortunately, most of the blood is routed through the ventilated lung and therefore becomes well aerated. In the situation shown in Figure 42-7, five sixths of the blood passes through the aerated lung and only one sixth through the unaerated lung. As a result, the overall ventilation-perfusion ratio is only moderately compromised, so the aortic blood has only mild oxygen desaturation despite total loss of ventilation in an entire lung.

Lack of "Surfactant" as a Cause of Lung Collapse. The secretion and function of *surfactant* in the alveoli were discussed in Chapter 37. It was pointed out that the surfactant is secreted by special alveolar epithelial cells into the fluids that coat the inside surface of the alveoli. The surfactant in turn decreases the surface tension in the alveoli 2- to 10-fold, which normally plays a major role in preventing alveolar collapse. However, in a number of conditions, such as in *hyaline membrane disease* (also called *respiratory distress syndrome*), which often occurs in newborn premature babies, the quantity of surfactant secreted by the alveoli is so greatly depressed that the surface tension of the alveolar fluid becomes several times normal. This causes a serious tendency for the lungs of these babies to collapse or to become filled with fluid. As explained in Chapter 37, many of these infants die of suffocation when large portions of the lungs become atelectatic.

Asthma—Spasmodic Contraction of Smooth Muscles in Bronchioles

Asthma is characterized by spastic contraction of the smooth muscle in the bronchioles, which partially obstructs the bronchioles and causes extremely difficult breathing. It occurs in 3 to 5 percent of all people at some time in life.

The usual cause of asthma is contractile hypersensitivity of the bronchioles in response to foreign substances in the air. In about 70 percent of patients younger than age 30 years, the asthma is caused by allergic hypersensitivity, especially sensitivity to plant pollens. In older people, the cause is almost always hypersensitivity to nonallergenic types of irritants in the air, such as irritants in smog.

The allergic reaction that occurs in the allergic type of asthma is believed to occur in the following way: The typical allergic person tends to form abnormally large amounts of IgE antibodies, and these antibodies cause allergic reactions when they react with the specific antigens that have caused them to develop in the first place, as explained in Chapter 34. In asthma, these *antibodies are mainly attached to mast cells* that are present in the lung interstitium in close association with the bronchioles and small bronchi. When the asthmatic person breathes in pollen to which he or she is sensitive (i.e., to which the person has developed IgE antibodies), the pollen reacts with the mast cell–attached antibodies and causes the mast cells to release several different substances. Among them are (a) *histamine*, (b) *slow-reacting substance of anaphylaxis* (which is a mixture of leukotrienes), (c) *eosinophilic chemotactic factor*, and (d) *bradykinin*. The combined effects of all these factors, especially the slow-reacting substance of anaphylaxis, are to produce (1) localized edema in the walls of the small bronchioles, as well as secretion of thick mucus into the bronchiolar lumens, and (2) spasm of the bronchiolar smooth muscle. Therefore, the airway resistance increases greatly.

As discussed earlier in this chapter, the bronchiolar diameter becomes more reduced during expiration than during inspiration in asthma, caused by bronchiolar collapse during expiratory effort that compresses the outsides of the bronchioles. Because the bronchioles of the asthmatic lungs are already partially occluded, further occlusion resulting from the external pressure creates especially severe obstruction during expiration. That is, the asthmatic person often can inspire quite adequately but has great difficulty expiring. Clinical measurements show (1) greatly reduced maximum expiratory rate and (2) reduced timed expiratory volume. Also, all of this together results in dyspnea, or "air hunger," which is discussed later in this chapter.

The *functional residual capacity* and *residual volume* of the lung become especially increased during the acute asthmatic attack because of the difficulty in expiring air from the lungs. Also, over a period of years, the chest cage becomes permanently enlarged, causing a "barrel chest," and both the functional residual capacity and lung residual volume become permanently increased.

Tuberculosis

In tuberculosis, the tubercle bacilli cause a peculiar tissue reaction in the lungs, including (1) invasion of the infected tissue by macrophages and (2) "walling off" of the lesion by fibrous tissue to form the so-called *tubercle*. This walling-off process helps to limit further transmission of the tubercle bacilli in the lungs and therefore is part of the protective process against extension of the infection. However, in about 3 percent of all people who develop tuberculosis, if untreated, the walling-off process fails and tubercle bacilli spread throughout the lungs, often causing extreme destruction of lung tissue with formation of large abscess cavities.

Thus, tuberculosis in its late stages is characterized by many areas of fibrosis throughout the lungs, as well as reduced total amount of functional lung tissue. These effects cause (1) *increased "work"* on the part of the respiratory muscles to cause pulmonary ventilation and *reduced vital capacity and breathing capacity*; (2) *reduced total respiratory membrane surface area* and *increased thickness of the respiratory membrane*, causing progressively *diminished pulmonary diffusing capacity*; and (3) *abnormal ventilation-perfusion ratio* in the lungs, further reducing overall pulmonary diffusion of oxygen and carbon dioxide.

Hypoxia and Oxygen Therapy

Almost any of the conditions discussed in the past few sections of this chapter can cause serious degrees of cellular hypoxia throughout the body. Sometimes, oxygen therapy is of great value; other times, it is of moderate value; and, at still other times, it is of almost no value. Therefore, it is important to understand the different types of hypoxia; then we can discuss the physiologic principles of oxygen therapy. The following is a descriptive classification of the causes of hypoxia:

1. Inadequate oxygenation of the blood in the lungs because of extrinsic reasons
   - **a.** Deficiency of oxygen in the atmosphere
   - **b.** Hypoventilation (neuromuscular disorders)
2. Pulmonary disease
   - **a.** Hypoventilation caused by increased airway resistance or decreased pulmonary compliance
   - **b.** Abnormal alveolar ventilation-perfusion ratio (including either increased physiologic dead space or increased physiologic shunt)
   - **c.** Diminished respiratory membrane diffusion
3. Venous-to-arterial shunts ("right-to-left" cardiac shunts)
4. Inadequate oxygen transport to the tissues by the blood
   - **a.** Anemia or abnormal hemoglobin
   - **b.** General circulatory deficiency

c. Localized circulatory deficiency (peripheral, cerebral, coronary vessels)

d. Tissue edema

5. Inadequate tissue capability of using oxygen

a. Poisoning of cellular oxidation enzymes

b. Diminished cellular metabolic capacity for using oxygen, because of toxicity, vitamin deficiency, or other factors

This classification of the types of hypoxia is mainly self-evident from the discussions earlier in the chapter. Only one type of hypoxia in the classification needs further elaboration: the hypoxia caused by inadequate capability of the body's tissue cells to use oxygen.

Inadequate Tissue Capability to Use Oxygen. The classic cause of inability of the tissues to use oxygen is *cyanide poisoning*, in which the action of the enzyme *cytochrome oxidase* is completely blocked by the cyanide—to such an extent that the tissues simply cannot use oxygen even when plenty is available. Also, deficiencies of some of the *tissue cellular oxidative enzymes* or of other elements in the tissue oxidative system can lead to this type of hypoxia. A special example occurs in the disease *beriberi*, in which several important steps in tissue utilization of oxygen and formation of carbon dioxide are compromised because of *vitamin B deficiency*.

Effects of Hypoxia on the Body. Hypoxia, if severe enough, can cause death of cells throughout the body, but in less severe degrees it causes principally (1) depressed mental activity, sometimes culminating in coma, and (2) reduced work capacity of the muscles. These effects are specifically discussed in Chapter 43 in relation to high-altitude physiology.

Oxygen Therapy in Different Types of Hypoxia

Oxygen can be administered by (1) placing the patient's head in a "tent" that contains air fortified with oxygen, (2) allowing the patient to breathe either pure oxygen or high concentrations of oxygen from a mask, or (3) administering oxygen through an intranasal tube.

Recalling the basic physiologic principles of the different types of hypoxia, one can readily decide when oxygen therapy will be of value and, if so, how valuable.

In *atmospheric hypoxia*, oxygen therapy can completely correct the depressed oxygen level in the inspired gases and, therefore, provide 100 percent effective therapy.

In *hypoventilation hypoxia*, a person breathing 100 percent oxygen can move five times as much oxygen into the alveoli with each breath as when breathing normal air. Therefore, here again oxygen therapy can be extremely beneficial. (However, this provides no benefit for the excess blood carbon dioxide also caused by the hypoventilation.)

In *hypoxia caused by impaired alveolar membrane diffusion*, essentially the same result occurs as in hypoventilation hypoxia because oxygen therapy can increase the

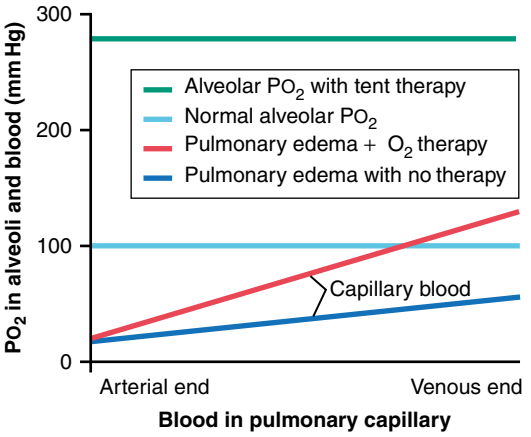


Figure 42-8 Absorption of oxygen into the pulmonary capillary blood in pulmonary edema with and without oxygen tent therapy.

P_{O_2} in the lung alveoli from the normal value of about 100 mm Hg to as high as 600 mm Hg. This raises the oxygen pressure gradient for diffusion of oxygen from the alveoli to the blood from the normal value of 60 mm Hg to as high as 560 mm Hg, an increase of more than 800 percent. This highly beneficial effect of oxygen therapy in diffusion hypoxia is demonstrated in Figure 42-8, which shows that the pulmonary blood in this patient with pulmonary edema picks up oxygen three to four times as rapidly as would occur with no therapy.

In *hypoxia caused by anemia, abnormal hemoglobin transport of oxygen, circulatory deficiency, or physiologic shunt*, oxygen therapy is of much less value because normal oxygen is already available in the alveoli. The problem instead is that one or more of the mechanisms for transporting oxygen from the lungs to the tissues are deficient. Even so, a small amount of extra oxygen, between 7 and 30 percent, can be *transported in the dissolved state* in the blood when alveolar oxygen is increased to maximum even though the amount transported by the hemoglobin is hardly altered. This small amount of extra oxygen may be the difference between life and death.

In the different types of *hypoxia caused by inadequate tissue use of oxygen*, there is abnormality neither of oxygen pickup by the lungs nor of transport to the tissues. Instead, the tissue metabolic enzyme system is simply incapable of using the oxygen that is delivered. Therefore, oxygen therapy provides no measurable benefit.

Cyanosis

The term *cyanosis* means blueness of the skin, and its cause is excessive amounts of deoxygenated hemoglobin in the skin blood vessels, especially in the capillaries. This deoxygenated hemoglobin has an intense dark blue–purple color that is transmitted through the skin.

In general, definite cyanosis appears whenever the *arterial blood* contains more than 5 grams of deoxygenated hemoglobin in each 100 milliliters of blood. A person with *anemia* almost never becomes cyanotic because there is not enough hemoglobin for 5 grams to be deoxygenated

in 100 milliliters of arterial blood. Conversely, in a person with excess red blood cells, as occurs in *polycythemia vera*, the great excess of available hemoglobin that can become deoxygenated leads frequently to cyanosis, even under otherwise normal conditions.

Hypercapnia—Excess Carbon Dioxide in the Body Fluids

One might suspect, on first thought, that any respiratory condition that causes hypoxia would also cause hypercapnia. However, hypercapnia usually occurs in association with hypoxia only when the hypoxia is caused by *hypoventilation* or *circulatory deficiency*. The reasons for this are the following.

Hypoxia caused by *too little oxygen in the air, too little hemoglobin*, or *poisoning of the oxidative enzymes* has to do only with the availability of oxygen or use of oxygen by the tissues. Therefore, it is readily understandable that hypercapnia is *not* a concomitant of these types of hypoxia.

In hypoxia resulting from poor diffusion through the pulmonary membrane or through the tissues, serious hypercapnia usually does not occur at the same time because carbon dioxide diffuses 20 times as rapidly as oxygen. If hypercapnia does begin to occur, this immediately stimulates pulmonary ventilation, which corrects the hypercapnia but not necessarily the hypoxia.

Conversely, in hypoxia caused by hypoventilation, carbon dioxide transfer between the alveoli and the atmosphere is affected as much as is oxygen transfer. Hypercapnia then occurs along with the hypoxia. And in circulatory deficiency, diminished flow of blood decreases carbon dioxide removal from the tissues, resulting in tissue hypercapnia in addition to tissue hypoxia. However, the transport capacity of the blood for carbon dioxide is more than three times that for oxygen, so that the resulting tissue hypercapnia is much less than the tissue hypoxia.

When the alveolar P_{CO_2} rises above about 60 to 75 mm Hg, an otherwise normal person by then is breathing about as rapidly and deeply as he or she can, and "air hunger," also called *dyspnea*, becomes severe.

If the P_{CO_2} rises to 80 to 100 mm Hg, the person becomes lethargic and sometimes even semicomatose. Anesthesia and death can result when the P_{CO_2} rises to 120 to 150 mm Hg. At these higher levels of P_{CO_2}, the excess carbon dioxide now begins to depress respiration rather than stimulate it, thus causing a vicious circle: (1) more carbon dioxide, (2) further decrease in respiration, (3) then more carbon dioxide, and so forth—culminating rapidly in a respiratory death.

Dyspnea

Dyspnea means mental anguish associated with inability to ventilate enough to satisfy the demand for air. A common synonym is *air hunger*.

At least three factors often enter into the development of the sensation of dyspnea. They are (1) abnormality of respiratory gases in the body fluids, especially hypercapnia and, to a much less extent, hypoxia; (2) the amount of work that must be performed by the respiratory muscles to provide adequate ventilation; and (3) state of mind.

A person becomes very dyspneic, especially from excess buildup of carbon dioxide in the body fluids. At times, however, the levels of both carbon dioxide and oxygen in the body fluids are normal, but to attain this normality of the respiratory gases, the person has to breathe forcefully. In these instances, the forceful activity of the respiratory muscles frequently gives the person a sensation of dyspnea.

Finally, the person's respiratory functions may be normal and still dyspnea may be experienced because of an abnormal state of mind. This is called *neurogenic dyspnea* or *emotional dyspnea*. For instance, almost anyone momentarily thinking about the act of breathing may suddenly start taking breaths a little more deeply than ordinarily because of a feeling of mild dyspnea. This feeling is greatly enhanced in people who have a psychological fear of not being able to receive a sufficient quantity of air, such as on entering small or crowded rooms.

Artificial Respiration

Resuscitator. Many types of respiratory resuscitators are available, and each has its own characteristic principles of operation. The resuscitator shown in Figure 42-9*A* consists of a tank supply of oxygen or air; a mechanism for applying intermittent positive pressure and, with some

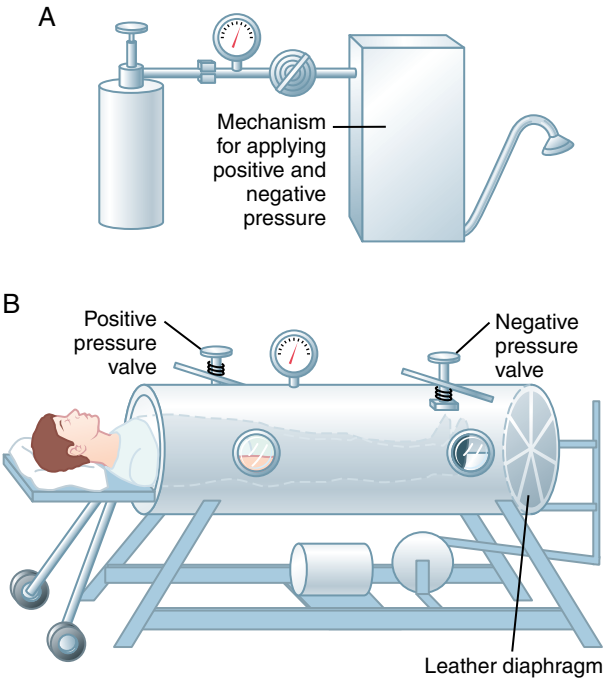


Figure 42-9 *A*, Resuscitator. *B*, Tank respirator.

machines, negative pressure as well; and a mask that fits over the face of the patient or a connector for joining the equipment to an endotracheal tube. This apparatus forces air through the mask or endotracheal tube into the lungs of the patient during the positive-pressure cycle of the resuscitator and then usually allows the air to flow passively out of the lungs during the remainder of the cycle.

Earlier resuscitators often caused damage to the lungs because of excessive positive pressure. Their usage was at one time greatly decried. However, resuscitators now have adjustable positive-pressure limits that are commonly set at 12 to 15 cm H_2O pressure for normal lungs (but sometimes much higher for noncompliant lungs).

Tank Respirator (the "Iron-Lung"). Figure 42-9*B* shows the tank respirator with a patient's body inside the tank and the head protruding through a flexible but airtight collar. At the end of the tank opposite the patient's head, a motor-driven leather diaphragm moves back and forth with sufficient excursion to raise and lower the pressure inside the tank. As the leather diaphragm moves inward, positive pressure develops around the body and causes expiration; as the diaphragm moves outward, negative pressure causes inspiration. Check valves on the respirator control the positive and negative pressures. Ordinarily these pressures are adjusted so that the negative pressure that causes inspiration falls to −10 to −20 cm H_2O and the positive pressure rises to 0 to +5 cm H_2O.

Effect of the Resuscitator and the Tank Respirator on Venous Return. When air is forced into the lungs under positive pressure by a resuscitator, or when the pressure around the patient's body is *reduced* by the tank respirator, the pressure inside the lungs becomes greater than pressure everywhere else in the body. Flow of blood into the chest and heart from the peripheral veins becomes impeded. As a result, use of excessive pressures with either the resuscitator or the tank respirator can reduce the cardiac output—sometimes to lethal levels. For instance, continuous exposure for more than a few minutes to greater than 30 mm Hg positive pressure in the lungs can cause death because of inadequate venous return to the heart.

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UNIT VIII

Aviation, Space, and Deep-Sea Diving Physiology

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CHAPTER 43

Aviation, High Altitude, and Space Physiology

As humans have ascended to higher and higher altitudes in aviation, mountain climbing, and space vehicles, it has become progressively more important to understand the effects of altitude and low gas pressures on the human body. This chapter deals with these problems, as well as acceleratory forces, weightlessness, and other challenges to body homeostasis that occur at high altitude and in space flight.

Effects of Low Oxygen Pressure on the Body

Barometric Pressures at Different Altitudes. Table 43-1 gives the approximate *barometric* and *oxygen pressures* at different altitudes, showing that at sea level, the barometric pressure is 760 mm Hg; at 10,000 feet, only 523 mm Hg; and at 50,000 feet, 87 mm Hg. This decrease in barometric pressure is the basic cause of all the hypoxia problems in high-altitude physiology because, as the barometric pressure decreases, the atmospheric oxygen partial pressure (P_{O_2}) decreases proportionately, remaining at all times slightly less than 21 percent of the total barometric pressure; at sea level P_{O_2} is about 159 mm Hg, but at 50,000 feet P_{O_2} is only 18 mm Hg.

Alveolar P_{O_2} at Different Elevations

Carbon Dioxide and Water Vapor Decrease the Alveolar Oxygen. Even at high altitudes, carbon dioxide is continually excreted from the pulmonary blood into the alveoli. Also, water vaporizes into the inspired air from the respiratory surfaces. These two gases dilute the oxygen in the alveoli, thus reducing the oxygen concentration. Water vapor pressure in the alveoli remains at 47 mm Hg as long as the body temperature is normal, regardless of altitude.

In the case of carbon dioxide, during exposure to very high altitudes, the alveolar P_{CO_2} falls from the sea-level value of 40 mm Hg to lower values. In the *acclimatized* person, who increases his or her ventilation about fivefold, the P_{CO_2} falls to about 7 mm Hg because of increased respiration.

Now let us see how the pressures of these two gases affect the alveolar oxygen. For instance, assume that the barometric pressure falls from the normal sea-level value of 760 mm Hg to 253 mm Hg, which is the usual measured value at the top of 29,028-foot Mount Everest. Forty-seven mm Hg of this must be water vapor, leaving only 206 mm Hg for all the other gases. In the *acclimatized* person, 7 mm of the 206 mm Hg must be carbon dioxide, leaving only 199 mm Hg. If there were no use of oxygen by the body, one fifth of this 199 mm Hg would be oxygen and four fifths would be nitrogen; that is, the P_{O_2} in the alveoli would be 40 mm Hg. However, some of this remaining alveolar oxygen is continually being absorbed into the blood, leaving about 35 mm Hg oxygen pressure in the alveoli. At the summit of Mount Everest, only the best of acclimatized people can barely survive when breathing air. But the effect is very different when the person is breathing pure oxygen, as we see in the following discussions.

Alveolar P_{O_2} at Different Altitudes. The fifth column of Table 43-1 shows the approximate P_{O_2}s in the alveoli at different altitudes when one is breathing air for both the *unacclimatized* and the *acclimatized* person. At sea level, the alveolar P_{O_2} is 104 mm Hg; at 20,000 feet altitude, it falls to about 40 mm Hg in the unacclimatized person but only to 53 mm Hg in the acclimatized person. The difference between these two is that alveolar ventilation increases much more in the acclimatized person than in the unacclimatized person, as we discuss later.

Saturation of Hemoglobin with Oxygen at Different Altitudes. Figure 43-1 shows arterial blood oxygen saturation at different altitudes while a person is breathing air and while breathing oxygen. Up to an altitude of about 10,000 feet, even when air is breathed, the arterial oxygen saturation remains at least as high as 90 percent. Above 10,000 feet, the arterial oxygen saturation falls rapidly, as shown by the blue curve of the figure, until it is slightly less than 70 percent at 20,000 feet and much less at still higher altitudes.

Table 43-1 Effects of Acute Exposure to Low Atmospheric Pressures on Alveolar Gas Concentrations and Arterial Oxygen Saturation*

Altitude (ft/meters)	Barometric Pressure (mm Hg)	P_{O_2} in Air (mm Hg)	Breathing Air			Breathing Pure Oxygen		
			P_{CO_2} in Alveoli (mm Hg)	*P_{O_2} in Alveoli (mm Hg)*	*Arterial Oxygen Saturation (%)*	*P_{CO_2} in Alveoli (mm Hg)*	*P_{O_2} in Alveoli (mm Hg)*	*Arterial Oxygen Saturation (%)*
0	760	159	40 (40)	104 (104)	97 (97)	40	673	100
10,000/3048	523	110	36 (23)	67 (77)	90 (92)	40	436	100
20,000/6096	349	73	24 (10)	40 (53)	73 (85)	40	262	100
30,000/9144	226	47	24 (7)	18 (30)	24 (38)	40	139	99
40,000/12,192	141	29				36	58	84
50,000/15,240	87	18				24	16	15

*Numbers in parentheses are acclimatized values.

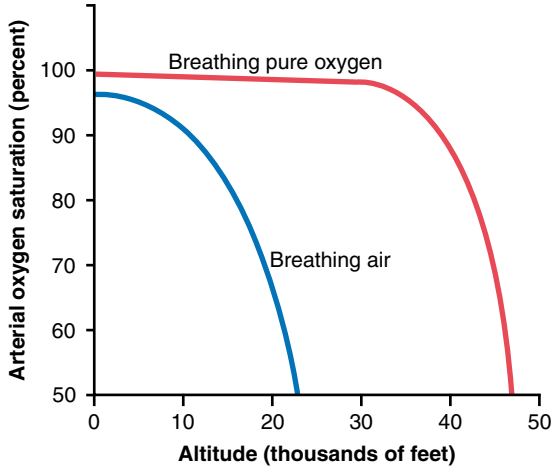

Figure 43-1 Effect of high altitude on arterial oxygen saturation when breathing air and when breathing pure oxygen.

Effect of Breathing Pure Oxygen on Alveolar P_{O_2} at Different Altitudes

When a person breathes pure oxygen instead of air, most of the space in the alveoli formerly occupied by nitrogen becomes occupied by oxygen. At 30,000 feet, an aviator could have an alveolar P_{O_2} as high as 139 mm Hg instead of the 18 mm Hg when breathing air (see Table 43-1).

The red curve of Figure 43-1 shows arterial blood hemoglobin oxygen saturation at different altitudes when one is breathing pure oxygen. Note that the saturation remains above 90 percent until the aviator ascends to about 39,000 feet; then it falls rapidly to about 50 percent at about 47,000 feet.

The "Ceiling" When Breathing Air and When Breathing Oxygen in an Unpressurized Airplane

Comparing the two arterial blood oxygen saturation curves in Figure 43-1, one notes that an aviator breathing pure oxygen in an unpressurized airplane can ascend to far higher altitudes than one breathing air. For instance, the arterial saturation at 47,000 feet when one is breathing oxygen is about 50 percent and is equivalent to the arterial oxygen saturation at 23,000 feet when one is breathing air. In addition, because an unacclimatized person usually can remain conscious until the arterial oxygen saturation falls to 50 percent, for short exposure times the ceiling for an aviator in an unpressurized airplane when breathing air is about 23,000 feet and when breathing pure oxygen is about 47,000 feet, provided the oxygen-supplying equipment operates perfectly.

Acute Effects of Hypoxia

Some of the important acute effects of hypoxia in the unacclimatized person breathing air, beginning at an altitude of about 12,000 feet, are drowsiness, lassitude, mental and muscle fatigue, sometimes headache, occasionally nausea, and sometimes euphoria. These effects progress to a stage of twitchings or seizures above 18,000 feet and end, above 23,000 feet in the unacclimatized person, in coma, followed shortly thereafter by death.

One of the most important effects of hypoxia is decreased mental proficiency, which decreases judgment, memory, and performance of discrete motor movements. For instance, if an unacclimatized aviator stays at 15,000 feet for 1 hour, mental proficiency ordinarily falls to about 50 percent of normal, and after 18 hours at this level it falls to about 20 percent of normal.

Acclimatization to Low P_{O_2}

A person remaining at high altitudes for days, weeks, or years becomes more and more *acclimatized* to the low P_{O_2}, so it causes fewer deleterious effects on the body. And it becomes possible for the person to work harder without hypoxic effects or to ascend to still higher altitudes.

The principal means by which acclimatization comes about are (1) a great increase in pulmonary ventilation, (2) increased numbers of red blood cells, (3) increased diffusing capacity of the lungs, (4) increased vascularity of the

peripheral tissues, and (5) increased ability of the tissue cells to use oxygen despite low P_{O_2}.

Increased Pulmonary Ventilation—Role of Arterial Chemoreceptors. Immediate exposure to low P_{O_2} stimulates the arterial chemoreceptors, and this increases alveolar ventilation to a maximum of about 1.65 times normal. Therefore, compensation occurs within seconds for the high altitude, and it alone allows the person to rise several thousand feet higher than would be possible without the increased ventilation. Then, if the person remains at very high altitude for several days, the chemoreceptors increase ventilation still more, up to about five times normal.

The immediate increase in pulmonary ventilation on rising to a high altitude blows off large quantities of carbon dioxide, reducing the P_{CO_2} and increasing the pH of the body fluids. These changes *inhibit* the brain stem respiratory center and thereby *oppose the effect of low* P_{O_2} *to stimulate respiration by way of the peripheral arterial chemoreceptors in the carotid and aortic bodies*. But during the ensuing 2 to 5 days, this inhibition fades away, allowing the respiratory center to respond with full force to the peripheral chemoreceptor stimulus from hypoxia, and ventilation increases to about five times normal.

The cause of this fading inhibition is believed to be mainly a reduction of bicarbonate ion concentration in the cerebrospinal fluid, as well as in the brain tissues. This in turn decreases the pH in the fluids surrounding the chemosensitive neurons of the respiratory center, thus increasing the respiratory stimulatory activity of the center.

An important mechanism for the gradual decrease in bicarbonate concentration is compensation by the kidneys for the respiratory alkalosis, as discussed in Chapter 30. The kidneys respond to decreased P_{CO_2} by reducing hydrogen ion secretion and increasing bicarbonate excretion. This metabolic compensation for the respiratory alkalosis gradually reduces plasma and cerebrospinal fluid bicarbonate concentration and pH toward normal and removes part of the inhibitory effect on respiration of low hydrogen ion concentration. Thus, the respiratory centers are much more responsive to the peripheral chemoreceptor stimulus caused by the hypoxia after the kidneys compensate for the alkalosis.

Increase in Red Blood Cells and Hemoglobin Concentration During Acclimatization. As discussed in Chapter 32, hypoxia is the principal stimulus for causing an increase in red blood cell production. Ordinarily, when a person remains exposed to low oxygen for weeks at a time, the hematocrit rises slowly from a normal value of 40 to 45 to an average of about 60, with an average increase in whole blood hemoglobin concentration from normal of 15 g/dl to about 20 g/dl.

In addition, the blood volume also increases, often by 20 to 30 percent, and this increase times the increased blood hemoglobin concentration gives an increase in total body hemoglobin of 50 or more percent.

Increased Diffusing Capacity After Acclimatization. The normal diffusing capacity for oxygen through the pulmonary membrane is about 21 ml/mm Hg/min, and this diffusing capacity can increase as much as threefold during exercise. A similar increase in diffusing capacity occurs at high altitude.

Part of the increase results from increased pulmonary capillary blood volume, which expands the capillaries and increases the surface area through which oxygen can diffuse into the blood. Another part results from an increase in lung air volume, which expands the surface area of the alveolar-capillary interface still more. A final part results from an increase in pulmonary arterial blood pressure; this forces blood into greater numbers of alveolar capillaries than normally—especially in the upper parts of the lungs, which are poorly perfused under usual conditions.

Peripheral Circulatory System Changes During Acclimatization—Increased Tissue Capillarity. The cardiac output often increases as much as 30 percent immediately after a person ascends to high altitude but then decreases back toward normal *over a period of weeks as the blood hematocrit increases*, so the amount of oxygen transported to the peripheral body tissues remains about normal.

Another circulatory adaptation is *growth of increased numbers of systemic circulatory capillaries* in the nonpulmonary tissues, which is called *increased tissue capillarity* (or *angiogenesis*). This occurs especially in animals born and bred at high altitudes but less so in animals that later in life become exposed to high altitude.

In active tissues exposed to chronic hypoxia, the increase in capillarity is especially marked. For instance, capillary density in right ventricular muscle increases markedly because of the combined effects of hypoxia and excess workload on the right ventricle caused by pulmonary hypertension at high altitude.

Cellular Acclimatization. In animals native to altitudes of 13,000 to 17,000 feet, cell mitochondria and cellular oxidative enzyme systems are slightly more plentiful than in sea-level inhabitants. Therefore, it is presumed that the tissue cells of high altitude–acclimatized human beings also can use oxygen more effectively than can their sea-level counterparts.

Natural Acclimatization of Native Human Beings Living at High Altitudes

Many native human beings in the Andes and in the Himalayas live at altitudes above 13,000 feet—one group in the Peruvian Andes lives at an altitude of 17,500 feet and works a mine at an altitude of 19,000 feet. Many of these natives are born at these altitudes and live there all their lives. In all aspects of acclimatization, the natives are superior to even the best-acclimatized lowlanders, even though the lowlanders might also have lived at high altitudes for 10 or more years. Acclimatization of the natives

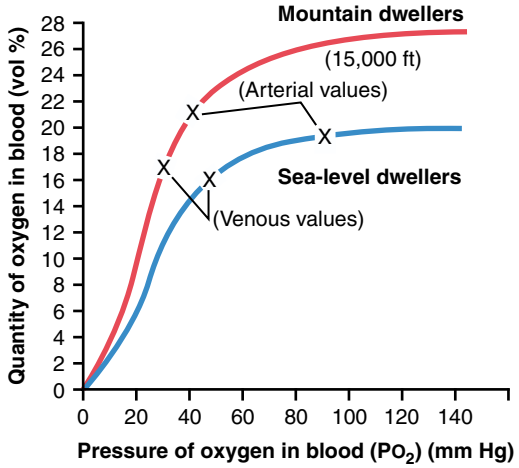

Figure 43-2 Oxygen-hemoglobin dissociation curves for blood of high-altitude residents (*red curve*) and sea-level residents (*blue curve*), showing the respective arterial and venous Po_2 levels and oxygen contents as recorded in their native surroundings. (Data from Oxygen-dissociation curves for bloods of high-altitude and sea-level residents. PAHO Scientific Publication No. 140, Life at High Altitudes, 1966.)

begins in infancy. The chest size, especially, is greatly increased, whereas the body size is somewhat decreased, giving a high ratio of ventilatory capacity to body mass. In addition, their hearts, which from birth onward pump extra amounts of cardiac output, are considerably larger than the hearts of lowlanders.

Delivery of oxygen by the blood to the tissues is also highly facilitated in these natives. For instance, Figure 43-2 shows oxygen-hemoglobin dissociation curves for natives who live at sea level and for their counterparts who live at 15,000 feet. Note that the arterial oxygen Po_2 in the natives at high altitude is only 40 mm Hg, but because of the greater quantity of hemoglobin, the quantity of oxygen in their arterial blood is greater than that in the blood of the natives at the lower altitude. Note also that the venous Po_2 in the high-altitude natives is only 15 mm Hg less than the venous Po_2 for the lowlanders, despite the very low arterial Po_2, indicating that oxygen transport to the tissues is exceedingly effective in the naturally acclimatized high-altitude natives.

Reduced Work Capacity at High Altitudes and Positive Effect of Acclimatization

In addition to the mental depression caused by hypoxia, as discussed earlier, the work capacity of all muscles is greatly decreased in hypoxia. This includes not only skeletal muscles but also cardiac muscles.

In general, work capacity is reduced in direct proportion to the decrease in maximum rate of oxygen uptake that the body can achieve.

To give an idea of the importance of acclimatization in increasing work capacity, consider the large differences in work capacities as percent of normal for unacclimatized and acclimatized people at an altitude of 17,000 feet:

	Work capacity (percent of normal)
Unacclimatized	50
Acclimatized for 2 months	68
Native living at 13,200 feet but working at 17,000 feet	87

Thus, naturally acclimatized native persons can achieve a daily work output even at high altitude almost equal to that of a lowlander at sea level, but even well-acclimatized lowlanders can almost never achieve this result.

Acute Mountain Sickness and High-Altitude Pulmonary Edema

A small percentage of people who ascend rapidly to high altitudes become acutely sick and can die if not given oxygen or removed to a low altitude. The sickness begins from a few hours up to about 2 days after ascent. Two events frequently occur:

1. *Acute cerebral edema*. This is believed to result from local vasodilation of the cerebral blood vessels, caused by the hypoxia. Dilation of the arterioles increases blood flow into the capillaries, thus increasing capillary pressure, which in turn causes fluid to leak into the cerebral tissues. The cerebral edema can then lead to severe disorientation and other effects related to cerebral dysfunction.
2. *Acute pulmonary edema*. The cause of this is still unknown, but one explanation is the following: The severe hypoxia causes the pulmonary arterioles to constrict potently, but the constriction is much greater in some parts of the lungs than in other parts, so more and more of the pulmonary blood flow is forced through fewer and fewer still unconstricted pulmonary vessels. The postulated result is that the capillary pressure in these areas of the lungs becomes especially high and local edema occurs. Extension of the process to progressively more areas of the lungs leads to spreading pulmonary edema and severe pulmonary dysfunction that can be lethal. Allowing the person to breathe oxygen usually reverses the process within hours.

Chronic Mountain Sickness

Occasionally, a person who remains at high altitude too long develops *chronic mountain sickness*, in which the following effects occur: (1) The red cell mass and hematocrit become exceptionally high, (2) the pulmonary arterial pressure becomes elevated even more than the normal elevation that occurs during acclimatization, (3) the right side of the heart becomes greatly enlarged, (4) the peripheral arterial pressure begins to fall, (5) congestive heart failure ensues, and (6) death often follows unless the person is removed to a lower altitude.

The causes of this sequence of events are probably threefold: First, the red cell mass becomes so great that the blood viscosity increases severalfold; this increased viscosity tends to *decrease* tissue blood flow so that oxygen delivery also begins to decrease. Second, the pulmonary arterioles become vasoconstricted because of the lung hypoxia. This results from the hypoxic vascular constrictor effect that normally operates to divert blood flow from low-oxygen to high-oxygen alveoli, as explained in Chapter 38. But because *all* the alveoli are now in the low-oxygen state, all the arterioles become constricted, the pulmonary arterial pressure rises excessively, and the right side of the heart fails. Third, the alveolar arteriolar spasm diverts much of the blood flow through nonalveolar pulmonary vessels, thus causing an excess of pulmonary shunt blood flow where the blood is poorly oxygenated; this further compounds the problem. Most of these people recover within days or weeks when they are moved to a lower altitude.

Effects of Acceleratory Forces on the Body in Aviation and Space Physiology

Because of rapid changes in velocity and direction of motion in airplanes or spacecraft, several types of acceleratory forces affect the body during flight. At the beginning of flight, simple linear acceleration occurs; at the end of flight, deceleration; and every time the vehicle turns, centrifugal acceleration.

Centrifugal Acceleratory Forces

When an airplane makes a turn, the force of centrifugal acceleration is determined by the following relation:

$$f = \frac{mv^2}{r}$$

in which f is centrifugal acceleratory force, m is the mass of the object, v is velocity of travel, and r is radius of curvature of the turn. From this formula, it is obvious that as the velocity increases, the *force of centrifugal acceleration increases in proportion to the square of the velocity*. It is also obvious that the force of acceleration is *directly proportional to the sharpness of the turn (the less the radius)*.

Measurement of Acceleratory Force—"G." When an aviator is simply sitting in his seat, the force with which he is pressing against the seat results from the pull of gravity and is equal to his weight. The intensity of this force is said to be +1G because it is equal to the pull of gravity. If the force with which he presses against the seat becomes five times his normal weight during pull-out from a dive, the force acting on the seat is +5 G.

If the airplane goes through an outside loop so that the person is held down by his seat belt, *negative G* is applied to his body; if the force with which he is held down by his belt is equal to the weight of his body, the negative force is −1G.

Effects of Centrifugal Acceleratory Force on the Body—(Positive G)

Effects on the Circulatory System. The most important effect of centrifugal acceleration is on the circulatory system, because blood is mobile and can be translocated by centrifugal forces.

When an aviator is subjected to *positive G*, blood is centrifuged toward the lowermost part of the body. Thus, if the centrifugal acceleratory force is +5 G and the person is in an immobilized standing position, the pressure in the veins of the feet becomes greatly increased (to about 450 mm Hg). In the sitting position, the pressure becomes nearly 300 mm Hg. And, as pressure in the vessels of the lower body increases, these vessels passively dilate so that a major portion of the blood from the upper body is translocated into the lower vessels. Because the heart cannot pump unless blood returns to it, the greater the quantity of blood "pooled" in this way in the lower body, the less that is available for the cardiac output.

Figure 43-3 shows the changes in systolic and diastolic arterial pressures (top and bottom curves, respectively) in the upper body when a centrifugal acceleratory force of +3.3 G is suddenly applied to a sitting person. Note that both these pressures fall below 22 mm Hg for the first few seconds after the acceleration begins but then return to a systolic pressure of about 55 mm Hg and a diastolic pressure of 20 mm Hg within another 10 to 15 seconds. This secondary recovery is caused mainly by activation of the baroreceptor reflexes.

Acceleration greater than 4 to 6 G causes "blackout" of vision within a few seconds and unconsciousness shortly thereafter. If this great degree of acceleration is continued, the person will die.

Effects on the Vertebrae. Extremely high acceleratory forces for even a fraction of a second can fracture the vertebrae. The degree of positive acceleration that the average person can withstand in the sitting position before vertebral fracture occurs is about 20 G.

Negative G. The effects of negative G on the body are less dramatic acutely but possibly more damaging permanently than the effects of positive G. An aviator can

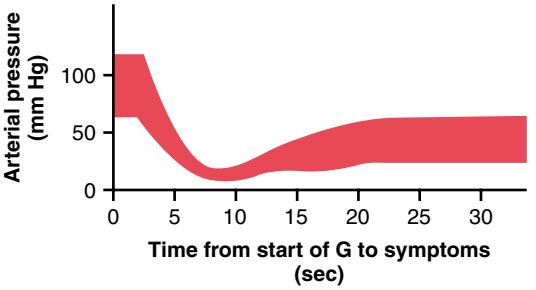

Figure 43-3 Changes in systolic (*top of curve*) and diastolic (*bottom of curve*) arterial pressures after abrupt and continuing exposure of a sitting person to an acceleratory force from top to bottom of 3.3 G. (Data from Martin EE, Henry JP: Effects of time and temperature upon tolerance to positive acceleration. J Aviation Med 22:382, 1951.)

usually go through outside loops up to negative accelerator forces of −4 to −5 G without causing permanent harm, although causing intense momentary hyperemia of the head. Occasionally, psychotic disturbances lasting for 15 to 20 minutes occur as a result of brain edema.

Occasionally, negative G forces can be so great (−20 G, for instance) and centrifugation of the blood into the head is so great that the cerebral blood pressure reaches 300 to 400 mm Hg, sometimes causing small vessels on the surface of the head and in the brain to rupture. However, the vessels inside the cranium show less tendency for rupture than would be expected for the following reason: The cerebrospinal fluid is centrifuged toward the head at the same time that blood is centrifuged toward the cranial vessels, and the greatly increased pressure of the cerebrospinal fluid acts as a cushioning buffer on the outside of the brain to prevent intracerebral vascular rupture.

Because the eyes are not protected by the cranium, intense hyperemia occurs in them during strong negative G. As a result, the eyes often become temporarily blinded with "red-out."

Protection of the Body Against Centrifugal Accelerator Forces. Specific procedures and apparatus have been developed to protect aviators against the circulatory collapse that might occur during positive G. First, if the aviator tightens his or her abdominal muscles to an extreme degree and leans forward to compress the abdomen, some of the pooling of blood in the large vessels of the abdomen can be prevented, delaying the onset of blackout. Also, special "anti-G" suits have been devised to prevent pooling of blood in the lower abdomen and legs. The simplest of these applies positive pressure to the legs and abdomen by inflating compression bags as the G increases. Theoretically, a pilot submerged in a tank or suit of water might experience little effect of G forces on the circulation because the pressures developed in the water pressing on the outside of the body during centrifugal acceleration would almost exactly balance the forces acting in the body. However, the presence of air in the lungs still allows displacement of the heart, lung tissues, and diaphragm into seriously abnormal positions despite submersion in water. Therefore, even if this procedure were used, the limit of safety almost certainly would still be less than 10 G.

Effects of Linear Acceleratory Forces on the Body

Acceleratory Forces in Space Travel. Unlike an airplane, a spacecraft cannot make rapid turns; therefore, centrifugal acceleration is of little importance except when the spacecraft goes into abnormal gyrations. However, blast-off acceleration and landing deceleration can be tremendous; both of these are types of *linear acceleration*, one positive and the other negative.

Figure 43-4 shows an approximate profile of acceleration during blast-off in a three-stage spacecraft, demonstrating that the first-stage booster causes acceleration as high as 9 G, and the second-stage booster as high as 8 G. In the standing position, the human body could not withstand this much acceleration, but in a semireclining position *transverse to the axis of acceleration*, this amount of acceleration can be withstood with ease despite the fact that the acceleratory forces continue for as long as several minutes at a time. Therefore, we see the reason for the reclining seats used by astronauts.

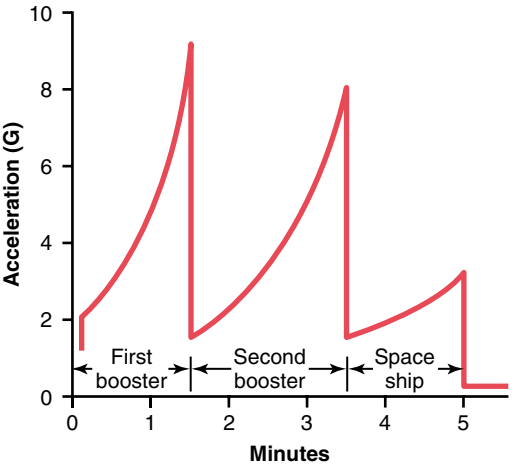

Figure 43-4 Acceleratory forces during takeoff of a spacecraft.

Problems also occur during deceleration when the spacecraft re-enters the atmosphere. A person traveling at Mach 1 (the speed of sound and of fast airplanes) can be safely decelerated in a distance of about 0.12 mile, whereas a person traveling at a speed of Mach 100 (a speed possible in interplanetary space travel) would require a distance of about 10,000 miles for safe deceleration. The principal reason for this difference is that the total amount of energy that must be dispelled during deceleration is proportional to the *square* of the velocity, which alone increases the required distance for decelerations between Mach 1 versus Mach 100 about 10,000-fold. Therefore, deceleration must be accomplished much more slowly from high velocities than is necessary at lower velocities.

Deceleratory Forces Associated with Parachute Jumps. When the parachuting aviator leaves the airplane, his velocity of fall is at first exactly 0 feet per second. However, because of the acceleratory force of gravity, within 1 second his velocity of fall is 32 feet per second (if there is no air resistance); in 2 seconds it is 64 feet per second; and so on. As the velocity of fall increases, the air resistance tending to slow the fall also increases. Finally, the deceleratory force of the air resistance exactly balances the acceleratory force of gravity, so after falling for about 12 seconds, the person will be falling at a "terminal velocity" of 109 to 119 miles per hour (175 feet per second). If the parachutist has already reached terminal velocity before opening his parachute, an "opening shock load" of up to 1200 pounds can occur on the parachute shrouds.

The usual-sized parachute slows the fall of the parachutist to about one-ninth the terminal velocity. In other words, the speed of landing is about 20 feet per second, and the force of impact against the earth is 1/81 the impact

force without a parachute. Even so, the force of impact is still great enough to cause considerable damage to the body unless the parachutist is properly trained in landing. Actually, the force of impact with the earth is about the same as that which would be experienced by jumping without a parachute from a height of about 6 feet. Unless forewarned, the parachutist will be tricked by his senses into striking the earth with extended legs, and this will result in tremendous deceleratory forces along the skeletal axis of the body, resulting in fracture of his pelvis, vertebrae, or leg. Consequently, the trained parachutist strikes the earth with knees bent but muscles taut to cushion the shock of landing.

"Artificial Climate" in the Sealed Spacecraft

Because there is no atmosphere in outer space, an artificial atmosphere and climate must be produced in a spacecraft. Most important, the oxygen concentration must remain high enough and the carbon dioxide concentration low enough to prevent suffocation. In some earlier space missions, a capsule atmosphere containing pure oxygen at about 260 mm Hg pressure was used, but in the modern space shuttle, gases about equal to those in normal air are used, with four times as much nitrogen as oxygen and a total pressure of 760 mm Hg. The presence of nitrogen in the mixture greatly diminishes the likelihood of fire and explosion. It also protects against development of local patches of lung atelectasis that often occur when breathing pure oxygen because oxygen is absorbed rapidly when small bronchi are temporarily blocked by mucous plugs.

For space travel lasting more than several months, it is impractical to carry along an adequate oxygen supply. For this reason, recycling techniques have been proposed for use of the same oxygen over and over again. Some recycling processes depend on purely physical procedures, such as electrolysis of water to release oxygen. Others depend on biological methods, such as use of algae with their large store of chlorophyll to release oxygen from carbon dioxide by the process of photosynthesis. A completely satisfactory system for recycling has yet to be achieved.

Weightlessness in Space

A person in an orbiting satellite or a nonpropelled spacecraft experiences *weightlessness*, or a state of near-zero G force, which is sometimes called *microgravity*. That is, the person is not drawn toward the bottom, sides, or top of the spacecraft but simply floats inside its chambers. The cause of this is not failure of gravity to pull on the body because gravity from any nearby heavenly body is still active. However, the gravity acts on both the spacecraft and the person at the same time so that both are pulled with exactly the same acceleratory forces and in the same direction. For this reason, the person simply is not attracted toward any specific wall of the spacecraft.

Physiologic Problems of Weightlessness (Microgravity). The physiologic problems of weightlessness have not proved to be of much significance, as long as the period of weightlessness is not too long. Most of the problems that do occur are related to three effects of the weightlessness: (1) motion sickness during the first few days of travel, (2) translocation of fluids within the body because of failure of gravity to cause normal hydrostatic pressures, and (3) diminished physical activity because no strength of muscle contraction is required to oppose the force of gravity.

Almost 50 percent of astronauts experience motion sickness, with nausea and sometimes vomiting, during the first 2 to 5 days of space travel. This probably results from an unfamiliar pattern of motion signals arriving in the equilibrium centers of the brain, and at the same time lack of gravitational signals.

The observed effects of prolonged stay in space are the following: (1) decrease in blood volume, (2) decrease in red blood cell mass, (3) decrease in muscle strength and work capacity, (4) decrease in maximum cardiac output, and (5) loss of calcium and phosphate from the bones, as well as loss of bone mass. Most of these same effects also occur in people who lie in bed for an extended period of time. For this reason, exercise programs are carried out by astronauts during prolonged space missions.

In previous space laboratory expeditions in which the exercise program had been less vigorous, the astronauts had severely decreased work capacities for the first few days after returning to earth. They also tended to faint (and still do, to some extent) when they stood up during the first day or so after return to gravity because of diminished blood volume and diminished responses of the arterial pressure control mechanisms.

Cardiovascular, Muscle, and Bone "Deconditioning" During Prolonged Exposure to Weightlessness. During very long space flights and prolonged exposure to microgravity, gradual "deconditioning" effects occur on the cardiovascular system, skeletal muscles, and bone despite rigorous exercise during the flight. Studies of astronauts on space flights lasting several months have shown that they may lose as much 1.0 percent of their bone mass each month even though they continue to exercise. Substantial atrophy of cardiac and skeletal muscles also occurs during prolonged exposure to a microgravity environment.

One of the most serious effects is cardiovascular "deconditioning," which includes decreased work capacity, reduced blood volume, impaired baroreceptor reflexes, and reduced orthostatic tolerance. These changes greatly limit the astronauts' ability to stand upright or perform normal daily activities after returning to the full gravity of Earth.

Astronauts returning from space flights lasting 4 to 6 months are also susceptible to bone fractures and may require several weeks before they return to preflight cardiovascular, bone, and muscle fitness. As space flights become longer in preparation for possible human exploration of other planets, such as Mars, the effects of prolonged microgravity could pose a very serious threat to astronauts after they land, especially in the event of an emergency landing. Therefore, considerable research effort has been directed toward developing countermeasures, in addition to exercise, that can prevent or more effectively attenuate these changes. One such countermeasure that is being tested is the application of intermittent "artificial gravity" caused by short periods (e.g., 1 hour each day) of centrifugal acceleration of the astronauts while they sit in specially designed short-arm centrifuges that create forces of up to 2 to 3 G.

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Physiology of Deep-Sea Diving and Other Hyperbaric Conditions

When human beings descend beneath the sea, the pressure around them increases tremendously. To keep the lungs from collapsing, air must be supplied at very high pressure to keep them inflated. This exposes the blood in the lungs to extremely high alveolar gas pressure, a condition called *hyperbarism*. Beyond certain limits, these high pressures cause tremendous alterations in body physiology and can be lethal.

Relationship of Pressure to Sea Depth. A column of seawater 33 feet (10.1 meters) deep exerts the same pressure at its bottom as the pressure of the atmosphere above the sea. Therefore, a person 33 feet beneath the ocean surface is exposed to 2 atmospheres pressure, 1 atmosphere of pressure caused by the weight of the air above the water and the second atmosphere by the weight of the water itself. At 66 feet the pressure is 3 atmospheres, and so forth, in accord with the table in Figure 44-1.

Effect of Sea Depth on the Volume of Gases—Boyle's Law. Another important effect of depth is compression of gases to smaller and smaller volumes. The lower part of Figure 44-1 shows a bell jar at sea level containing 1 liter of air. At 33 feet beneath the sea, where the pressure is 2 atmospheres, the volume has been compressed to only one-half liter, and at 8 atmospheres (233 feet) to one-eighth liter. Thus, the volume to which a given quantity of gas is compressed is inversely proportional to the pressure. This is a principle of physics called *Boyle's law*, which is extremely important in diving physiology because increased pressure can collapse the air chambers of the diver's body, especially the lungs, and often causes serious damage.

Many times in this chapter it is necessary to refer to *actual volume* versus *sea-level volume*. For instance, we might speak of an actual volume of 1 liter at a depth of 300 feet; this is the same *quantity* of air as a sea-level volume of 10 liters.

Effect of High Partial Pressures of Individual Gases on the Body

The individual gases to which a diver is exposed when breathing air are *nitrogen*, *oxygen*, and *carbon dioxide*; each of these at times can cause significant physiologic effects at high pressures.

Nitrogen Narcosis at High Nitrogen Pressures

About four fifths of the air is nitrogen. At sea-level pressure, the nitrogen has no significant effect on bodily function, but at high pressures it can cause varying degrees of narcosis. When the diver remains beneath the sea for an hour or more and is breathing compressed air, the depth at which the first symptoms of mild narcosis appear is about 120 feet. At this level the diver begins to exhibit joviality and to lose many of his or her cares. At 150 to 200 feet, the diver becomes drowsy. At 200 to 250 feet, his or her strength wanes considerably, and the diver often becomes too clumsy to perform the work required. Beyond 250 feet (8.5 atmospheres pressure), the diver usually becomes almost useless as a result of nitrogen narcosis if he or she remains at these depths too long.

Nitrogen narcosis has characteristics similar to those of alcohol intoxication, and for this reason it has frequently been called "raptures of the depths." The mechanism of the narcotic effect is believed to be the same as that of most other gas anesthetics. That is, it dissolves in the fatty substances in neuronal membranes and, because of its *physical* effect on altering ionic conductance through the membranes, reduces neuronal excitability.

Oxygen Toxicity at High Pressures

Effect of Very High P_{O_2} on Blood Oxygen Transport. When the P_{O_2} in the blood rises above 100 mm Hg, the amount of oxygen dissolved in the water of the blood increases markedly. This is shown in Figure 44-2, which depicts the same oxygen-hemoglobin dissociation curve as that shown in Chapter 40 but with the alveolar P_{O_2} extended to more than 3000 mm Hg. Also depicted by the lowest curve in the figure is the *volume of oxygen dissolved in the fluid of the blood* at each P_{O_2} level. Note that

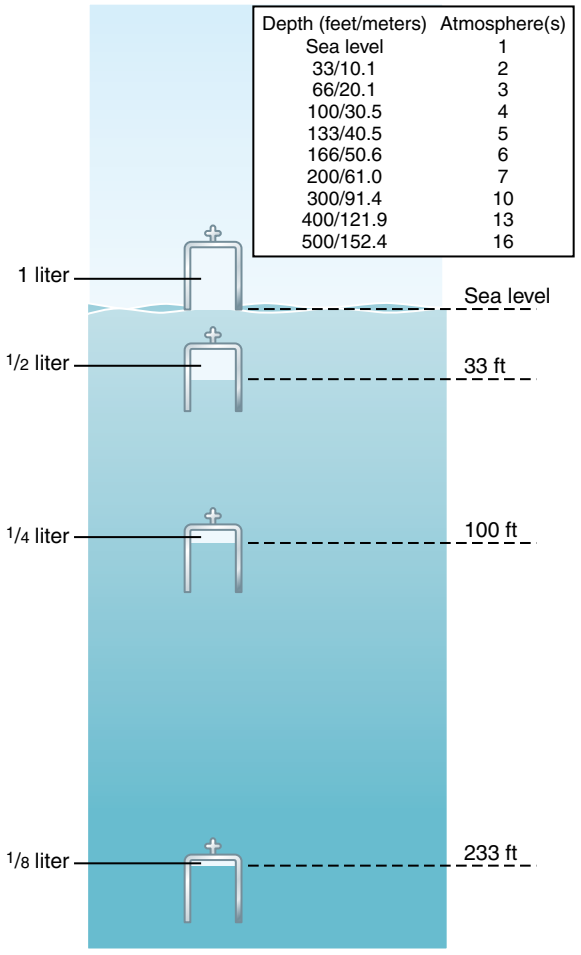

Figure 44-1 Effect of sea depth on pressure (*top table*) and on gas volume (*bottom*).

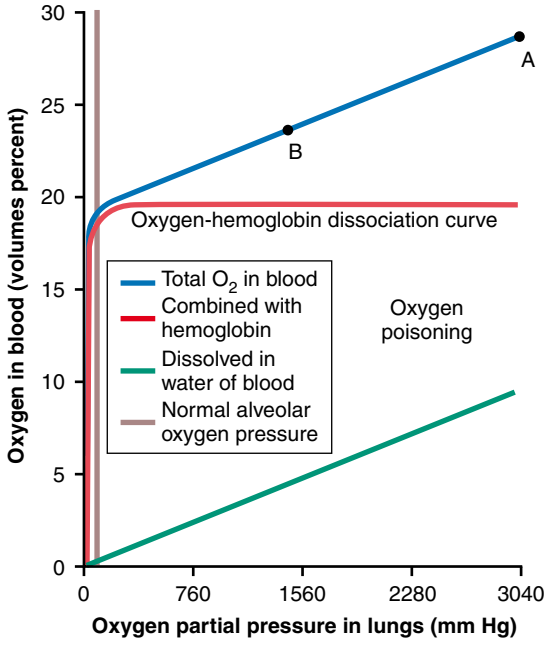

Figure 44-2 Quantity of oxygen dissolved in the fluid of the blood and in combination with hemoglobin at very high P_{O_2}s.

in the normal range of alveolar P_{O_2} (below 120 mm Hg), almost none of the total oxygen in the blood is accounted for by dissolved oxygen, but as the oxygen pressure rises into the thousands of millimeters of mercury, a large portion of the total oxygen is then dissolved in the water of the blood, in addition to that bound with hemoglobin.

Effect of High Alveolar P_{O_2} on Tissue P_{O_2}. Let us assume that the P_{O_2} in the lungs is about 3000 mm Hg (4 atmospheres pressure). Referring to Figure 44-2, one finds that this represents a total oxygen content in each 100 milliliters of blood of about 29 volumes percent, as demonstrated by point A in the figure—this means 20 volumes percent bound with hemoglobin and 9 volumes percent dissolved in the blood water. As this blood passes through the tissue capillaries and the tissues use their normal amount of oxygen, about 5 milliliters from each 100 milliliters of blood, the oxygen content on leaving the tissue capillaries is still 24 volumes percent (point B in the figure). At this point, the P_{O_2} is approximately 1200 mm Hg, which means that oxygen is delivered to the tissues at this extremely high pressure instead of at the normal value of 40 mm Hg. Thus, once the alveolar P_{O_2} rises above a critical level, the hemoglobin-oxygen buffer mechanism (discussed in Chapter 40) is no longer capable of keeping the tissue P_{O_2} in the normal, safe range between 20 and 60 mm Hg.

Acute Oxygen Poisoning. The extremely high tissue P_{O_2} that occurs when oxygen is breathed at very high alveolar oxygen pressure can be detrimental to many of the body's tissues. For instance, breathing oxygen at 4 atmospheres pressure of oxygen (P_{O_2} = 3040 mm Hg) will cause brain *seizures followed by coma* in most people within 30 to 60 minutes. The seizures often occur without warning and, for obvious reasons, are likely to be lethal to divers submerged beneath the sea.

Other symptoms encountered in acute oxygen poisoning include nausea, muscle twitchings, dizziness, disturbances of vision, irritability, and disorientation. Exercise greatly increases the diver's susceptibility to oxygen toxicity, causing symptoms to appear much earlier and with far greater severity than in the resting person.

Excessive Intracellular Oxidation as a Cause of Nervous System Oxygen Toxicity—"Oxidizing Free Radicals." Molecular oxygen (O_2) has little capability of oxidizing other chemical compounds. Instead, it must first be converted into an "active" form of oxygen. There are several forms of active oxygen called *oxygen free radicals*. One of the most important of these is the *superoxide free radical* O_2^-, and another is the *peroxide radical* in the form of *hydrogen peroxide*. Even when the tissue P_{O_2} is normal at the level of 40 mm Hg, small amounts of free radicals are continually being formed from the dissolved molecular oxygen. Fortunately, the tissues also contain multiple enzymes that rapidly remove these free radicals, including *peroxidases, catalases*, and *superoxide*

dismutases. Therefore, so long as the hemoglobin-oxygen buffering mechanism maintains a normal tissue P_{O_2}, the oxidizing free radicals are removed rapidly enough that they have little or no effect in the tissues.

Above a critical alveolar P_{O_2} (above about 2 atmospheres P_{O_2}), the hemoglobin-oxygen buffering mechanism fails, and the tissue P_{O_2} can then rise to hundreds or thousands of millimeters of mercury. At these high levels, the amounts of oxidizing free radicals literally swamp the enzyme systems designed to remove them, and now they can have serious destructive and even lethal effects on the cells. One of the principal effects is to oxidize the polyunsaturated fatty acids that are essential components of many of the cell membranes. Another effect is to oxidize some of the cellular enzymes, thus damaging severely the cellular metabolic systems. The nervous tissues are especially susceptible because of their high lipid content. Therefore, most of the acute lethal effects of acute oxygen toxicity are caused by brain dysfunction.

Chronic Oxygen Poisoning Causes Pulmonary Disability. A person can be exposed to only 1 atmosphere pressure of oxygen almost indefinitely without developing the *acute* oxygen toxicity of the nervous system just described. However, after only about 12 hours of 1 atmosphere oxygen exposure, *lung passageway congestion, pulmonary edema*, and *atelectasis* caused by damage to the linings of the bronchi and alveoli begin to develop. The reason for this effect in the lungs but not in other tissues is that the air spaces of the lungs are directly exposed to the high oxygen pressure, but oxygen is delivered to the other body tissues at almost normal P_{O_2} because of the hemoglobin-oxygen buffer system.

Carbon Dioxide Toxicity at Great Depths in the Sea

If the diving gear is properly designed and functions properly, the diver has no problem due to carbon dioxide toxicity because depth alone does not increase the carbon dioxide partial pressure in the alveoli. This is true because depth does not increase the rate of carbon dioxide production in the body, and as long as the diver continues to breathe a normal tidal volume and expires the carbon dioxide as it is formed, alveolar carbon dioxide pressure will be maintained at a normal value.

In certain types of diving gear, however, such as the diving helmet and some types of rebreathing apparatuses, carbon dioxide can build up in the dead space air of the apparatus and be rebreathed by the diver. Up to an alveolar carbon dioxide pressure (P_{CO_2}) of about 80 mm Hg, twice that in normal alveoli, the diver usually tolerates this buildup by increasing the minute respiratory volume a maximum of 8- to 11-fold to compensate for the increased carbon dioxide. Beyond 80 mm Hg alveolar P_{CO_2}, the situation becomes intolerable, and eventually the respiratory center begins to be depressed, rather than excited, because of the negative tissue metabolic effects of high P_{CO_2}. The diver's respiration then begins to fail rather than to compensate. In addition, the diver develops severe respiratory acidosis and varying degrees of lethargy, narcosis, and finally even anesthesia, as discussed in Chapter 42.

Decompression of the Diver After Excess Exposure to High Pressure

When a person breathes air under high pressure for a long time, the amount of nitrogen dissolved in the body fluids increases. The reason for this is the following: Blood flowing through the pulmonary capillaries becomes saturated with nitrogen to the same high pressure as that in the alveolar breathing mixture. And over several more hours, enough nitrogen is carried to all the tissues of the body to raise their tissue P_{n_2} also to equal the P_{n_2} in the breathing air.

Because nitrogen is not metabolized by the body, it remains dissolved in all the body tissues until the nitrogen pressure in the lungs is decreased back to some lower level, at which time the nitrogen can be removed by the reverse respiratory process; however, this removal often takes hours to occur and is the source of multiple problems collectively called *decompression sickness*.

Volume of Nitrogen Dissolved in the Body Fluids at Different Depths. At sea level, almost exactly 1 liter of nitrogen is dissolved in the entire body. Slightly less than one half of this is dissolved in the water of the body and a little more than one half in the fat of the body. This is true because nitrogen is five times as soluble in fat as in water.

After the diver has become saturated with nitrogen, the *sea-level volume of nitrogen* dissolved in the body at different depths is as follows:

Feet	Liters
0	1
33	2
100	4
200	7
300	10

Several hours are required for the gas pressures of nitrogen in all the body tissues to come nearly to equilibrium with the gas pressure of nitrogen in the alveoli. The reason for this is that the blood does not flow rapidly enough and the nitrogen does not diffuse rapidly enough to cause instantaneous equilibrium. The nitrogen dissolved in the water of the body comes to almost complete equilibrium in less than 1 hour, but the fat tissue, requiring five times as much transport of nitrogen and having a relatively poor blood supply, reaches equilibrium only after several hours. For this reason, if a person remains at deep levels for only a few minutes, not much nitrogen dissolves in the body fluids and tissues, whereas if the person remains at a deep level for several hours, both the body water and body fat become saturated with nitrogen.

Decompression Sickness (Synonyms: Bends, Compressed Air Sickness, Caisson Disease, Diver's Paralysis, Dysbarism). If a diver has been beneath the sea long enough that large amounts of nitrogen have dissolved in his or her body and the diver then suddenly comes back to the surface of the sea, significant quantities of nitrogen bubbles can develop in the body fluids either intracellularly or extracellularly and can cause minor or serious damage in almost any area of the body, depending on the number and sizes of bubbles formed; this is called *decompression sickness*.

The principles underlying bubble formation are shown in Figure 44-3. In Figure 44-3*A*, the diver's tissues have become equilibrated to a high *dissolved nitrogen pressure* (Pn_2 = 3918 mm Hg), about 6.5 times the normal amount of nitrogen in the tissues. As long as the diver remains deep beneath the sea, the pressure against the outside of his or her body (5000 mm Hg) compresses all the body tissues sufficiently to keep the excess nitrogen gas dissolved. But when the diver suddenly rises to sea level (Figure 44-3*B*), the pressure on the outside of the body becomes only 1 atmosphere (760 mm Hg), while the gas pressure inside the body fluids is the sum of the pressures of water vapor, carbon dioxide, oxygen, and nitrogen, or a total of 4065 mm Hg, 97 percent of which is caused by the nitrogen. Obviously, this total value of 4065 mm Hg is far greater than the 760 mm Hg pressure on the outside of the body. Therefore, the gases can escape from the dissolved state and form actual bubbles, composed almost entirely of nitrogen, both in the tissues and in the blood where they plug many small blood vessels. The bubbles may not appear for many minutes to hours because sometimes the gases can remain dissolved in the "supersaturated" state for hours before bubbling.

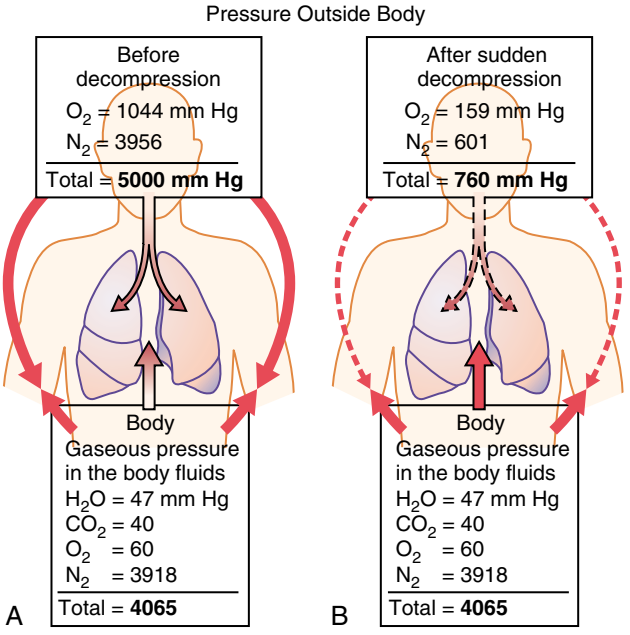

Figure 44-3 Gaseous pressures both inside and outside the body, showing (*A*) saturation of the body to high gas pressures when breathing air at a total pressure of 5000 mm Hg, and (*B*) the great excesses of intrabody pressures that are responsible for bubble formation in the tissues when the lung intra-alveolar pressure body is suddenly returned from 5000 mm Hg to normal pressure of 760 mm Hg.

Symptoms of Decompression Sickness ("Bends"). The symptoms of decompression sickness are caused by gas bubbles blocking many blood vessels in different tissues. At first, only the smallest vessels are blocked by minute bubbles, but as the bubbles coalesce, progressively larger vessels are affected. Tissue ischemia and sometimes tissue death result.

In most people with decompression sickness, the symptoms are pain in the joints and muscles of the legs and arms, affecting 85 to 90 percent of those persons who develop decompression sickness. The joint pain accounts for the term "bends" that is often applied to this condition.

In 5 to 10 percent of people with decompression sickness, nervous system symptoms occur, ranging from dizziness in about 5 percent to paralysis or collapse and unconsciousness in as many as 3 percent. The paralysis may be temporary, but in some instances, damage is permanent.

Finally, about 2 percent of people with decompression sickness develop "the chokes," caused by massive numbers of microbubbles plugging the capillaries of the lungs; this is characterized by serious shortness of breath, often followed by severe pulmonary edema and, occasionally, death.

Nitrogen Elimination from the Body; Decompression Tables. If a diver is brought to the surface slowly, enough of the dissolved nitrogen can usually be eliminated by expiration through the lungs to prevent decompression sickness. About two thirds of the total nitrogen is liberated in 1 hour and about 90 percent in 6 hours.

Decompression tables that detail procedures for safe decompression have been prepared by the U.S. Navy. To give the student an idea of the decompression process, a diver who has been breathing air and has been on the sea bottom for 60 minutes at a depth of 190 feet is decompressed according to the following schedule:

10 minutes at 50 feet depth
17 minutes at 40 feet depth
19 minutes at 30 feet depth
50 minutes at 20 feet depth
84 minutes at 10 feet depth

Thus, for a work period on the bottom of only 1 hour, the total time for decompression is about 3 hours.

Tank Decompression and Treatment of Decompression Sickness. Another procedure widely used for decompression of professional divers is to put the diver into a pressurized tank and then to lower the pressure gradually back to normal atmospheric pressure, using essentially the same time schedule as noted earlier.

Tank decompression is even more important for treating people in whom symptoms of decompression sickness develop minutes or even hours after they have returned to the surface. In this case, the diver is recompressed immediately to a deep level. Then decompression is carried out over a period several times as long as the usual decompression period.

"Saturation Diving" and Use of Helium-Oxygen Mixtures in Deep Dives. When divers must work at very deep levels—between 250 feet and nearly 1000 feet—they frequently live in a large compression tank for days or weeks at a time, remaining compressed at a pressure level near that at which they will be working. This keeps the tissues and fluids of the body saturated with the gases to which they will be exposed while diving. Then, when they return to the same tank after working, there are no significant changes in pressure, so decompression bubbles do not occur.

In very deep dives, especially during saturation diving, helium is usually used in the gas mixture instead of nitrogen for three reasons: (1) it has only about one-fifth the narcotic effect of nitrogen; (2) only about one half as much volume of helium dissolves in the body tissues as nitrogen, and the volume that does dissolve diffuses out of the tissues during decompression several times as rapidly as does nitrogen, thus reducing the problem of decompression sickness; and (3) the low density of helium (one seventh the density of nitrogen) keeps the airway resistance for breathing at a minimum, which is very important because highly compressed nitrogen is so dense that airway resistance can become extreme, sometimes making the work of breathing beyond endurance.

Finally, in very deep dives it is important to reduce the oxygen concentration in the gaseous mixture because otherwise oxygen toxicity would result. For instance, at a depth of 700 feet (22 atmospheres of pressure), a 1 percent oxygen mixture will provide all the oxygen required by the diver, whereas a 21 percent mixture of oxygen (the percentage in air) delivers a P_{O_2} to the lungs of more than 4 atmospheres, a level very likely to cause seizures in as little as 30 minutes.

Scuba (Self-Contained Underwater Breathing Apparatus) Diving

Before the 1940s, almost all diving was done using a diving helmet connected to a hose through which air was pumped to the diver from the surface. Then, in 1943, French explorer Jacques Cousteau popularized a *self-contained underwater breathing apparatus*, known as the SCUBA apparatus. The type of SCUBA apparatus used in more than 99 percent of all sports and commercial diving is the *open-circuit demand system* shown in Figure 44-4. This system consists of the following components: (1) one or more tanks of compressed air or some other breathing mixture, (2) a first-stage "reducing" valve for reducing the very high pressure from the tanks to a low pressure level, (3) a combination inhalation "demand" valve and exhalation valve that allows air to be pulled into the lungs with slight negative pressure of breathing and then to be exhaled into the sea at a pressure level slightly positive to the surrounding water pressure, and (4) a mask and tube system with small "dead space."

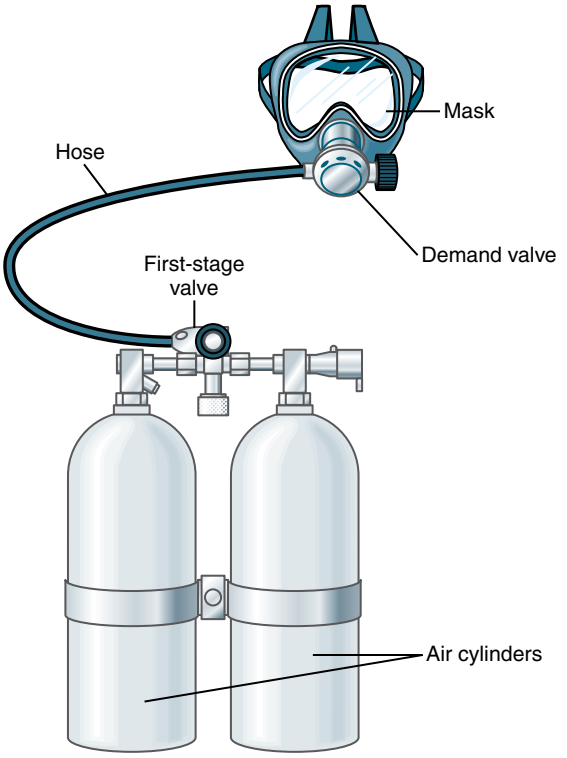

Figure 44-4 Open-circuit demand type of SCUBA apparatus.

The demand system operates as follows: The first-stage reducing valve reduces the pressure from the tanks so that the air delivered to the mask has a pressure only a few mm Hg greater than the surrounding water pressure. The breathing mixture does not flow continually into the mask. Instead, with each inspiration, slight extra negative pressure in the demand valve of the mask pulls the diaphragm of the valve open, and this automatically releases air from the tank into the mask and lungs. In this way, only the amount of air needed for inhalation enters the mask. Then, on expiration, the air cannot go back into the tank but instead is expired into the sea.

The most important problem in use of the self-contained underwater breathing apparatus is the limited amount of time one can remain beneath the sea surface; for instance, only a few minutes are possible at a 200-foot depth. The reason for this is that tremendous airflow from the tanks is required to wash carbon dioxide out of the lungs—the greater the depth, the greater the airflow in terms of *quantity* of air per minute that is required, because the *volumes* have been compressed to small sizes.

Special Physiologic Problems in Submarines

Escape from Submarines. Essentially the same problems encountered in deep-sea diving are often met in relation to submarines, especially when it is necessary to escape from a submerged submarine. Escape is possible from as deep as 300 feet without using any apparatus. However, proper use of rebreathing devices, especially when using helium, theoretically can allow escape from as deep as 600 feet or perhaps more.

One of the major problems of escape is prevention of air embolism. As the person ascends, the gases in the lungs expand and sometimes rupture a pulmonary blood vessel, forcing the gases to enter the vessel and cause air embolism of the circulation. Therefore, as the person ascends, he or she must make a special effort to exhale continually.

Health Problems in the Submarine Internal Environment. Except for escape, submarine medicine generally centers on several engineering problems to keep hazards out of the internal environment. First, in atomic submarines, there exists the problem of radiation hazards, but with appropriate shielding, the amount of radiation received by the crew submerged beneath the sea has been less than normal radiation received above the surface of the sea from cosmic rays.

Second, poisonous gases on occasion escape into the atmosphere of the submarine and must be controlled rapidly. For instance, during several weeks' submergence, cigarette smoking by the crew can liberate enough carbon monoxide, if not removed rapidly, to cause carbon monoxide poisoning. And, on occasion, even Freon gas has been found to diffuse out of refrigeration systems in sufficient quantity to cause toxicity.

Hyperbaric Oxygen Therapy

The intense oxidizing properties of high-pressure oxygen (*hyperbaric oxygen*) can have valuable therapeutic effects in several important clinical conditions. Therefore, large pressure tanks are now available in many medical centers into which patients can be placed and treated with hyperbaric oxygen. The oxygen is usually administered at Po_2s of 2 to 3 atmospheres of pressure through a mask or intratracheal tube, whereas the gas around the body is normal air compressed to the same high-pressure level.

It is believed that the same oxidizing free radicals responsible for oxygen toxicity are also responsible for at least some of the therapeutic benefits. Some of the conditions in which hyperbaric oxygen therapy has been especially beneficial follow.

Probably the most successful use of hyperbaric oxygen has been for treatment of *gas gangrene*. The bacteria that cause this condition, *clostridial organisms*, grow best under anaerobic conditions and stop growing at oxygen pressures greater than about 70 mm Hg. Therefore, hyperbaric oxygenation of the tissues can frequently stop the infectious process entirely and thus convert a condition that formerly was almost 100 percent fatal into one that is cured in most instances by early treatment with hyperbaric therapy.

Other conditions in which hyperbaric oxygen therapy has been either valuable or possibly valuable include decompression sickness, arterial gas embolism, carbon monoxide poisoning, osteomyelitis, and myocardial infarction.

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