Periyar Arts College

PG and Research Department of Zoology

Animal Physiology (MZO 31)

UNIT-II

RESPIRATION AND CIRCULATION

Physiology of respiration in Man. Respiratory Pigments, nervous and chemical control of respiration, BMR.

Circulation - types of hearts - physiology of cardiac muscle - heart beat and its regulation - blood coagulation and theories.

UNIT VII Respiration

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

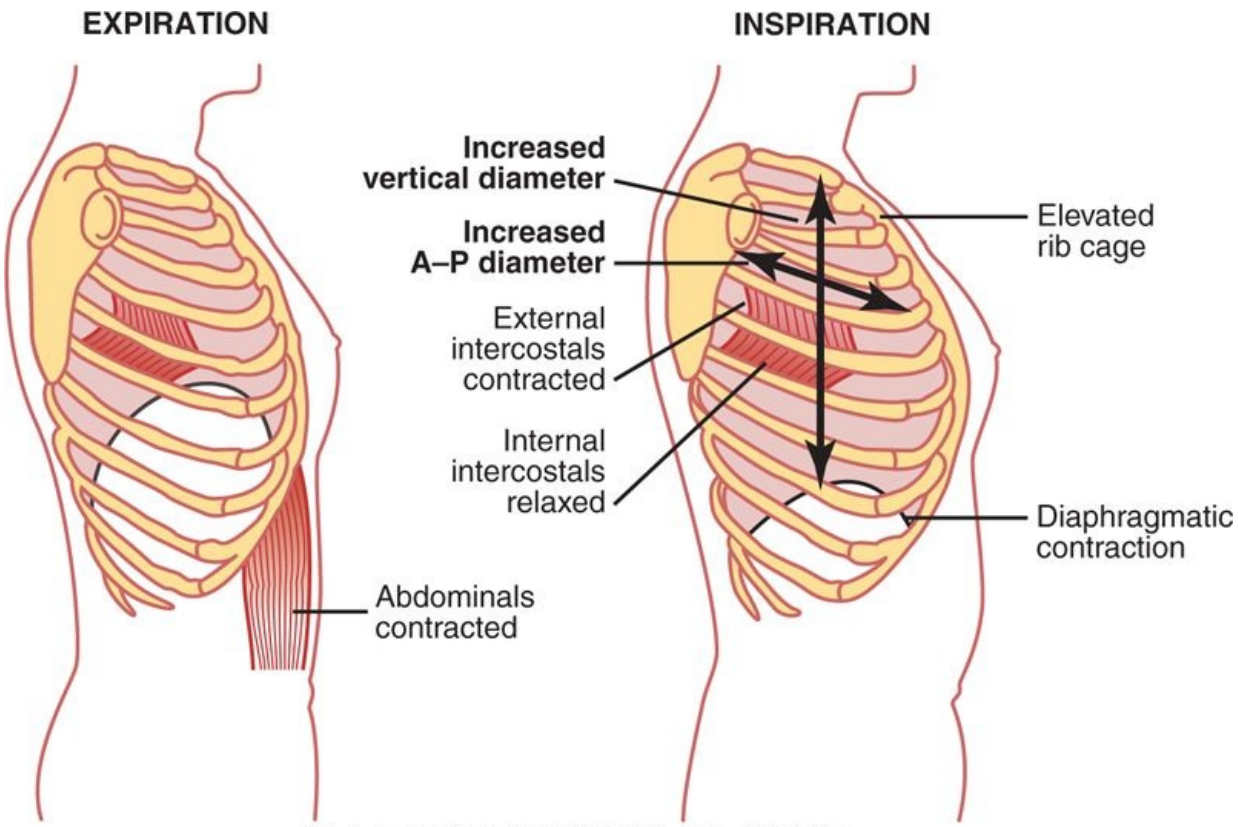

Figure 37-1 Contraction and expansion of the thoracic cage during expiration and inspiration, demonstrating diaphragmatic contraction, function of the intercostal muscles, and elevation and depression of the rib cage.

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 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

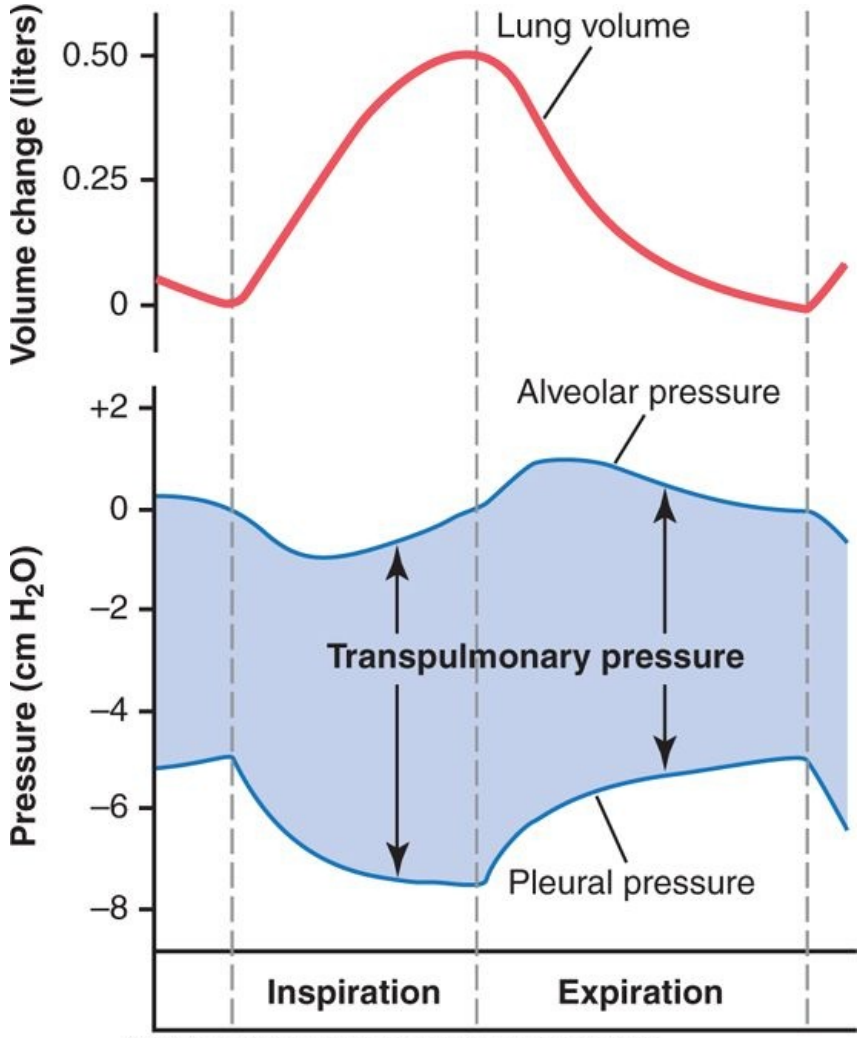

Figure 37-2 Changes in lung volume, alveolar pressure, pleural pressure, and transpulmonary pressure during normal breathing.

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 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.

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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.

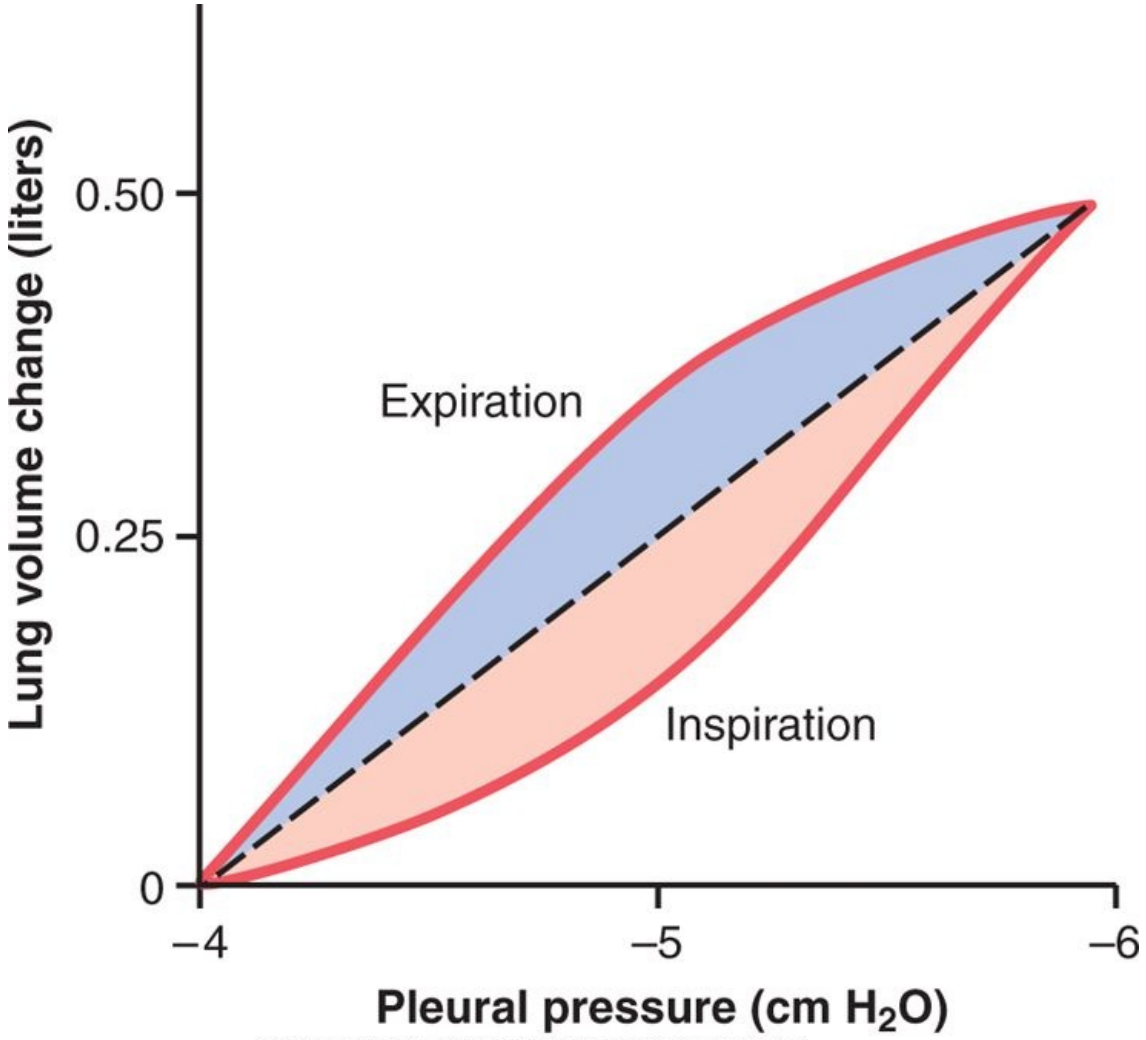

Figure 37-3 Compliance diagram in a healthy person. This diagram shows compliance of the lungs alone.

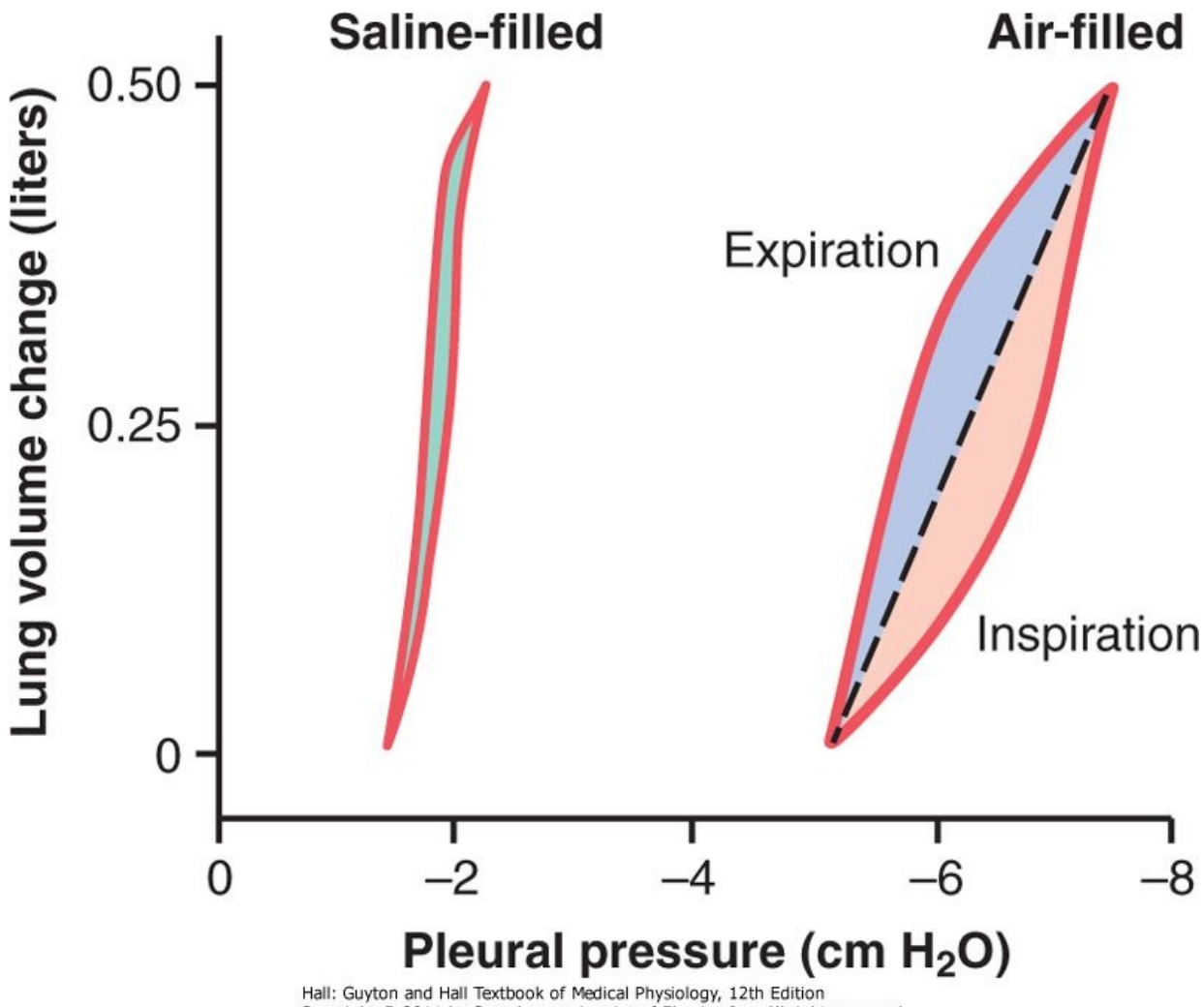

Figure 37-4 Comparison of the compliance diagrams of saline-filled and air-filled lungs when the alveolar pressure is maintained at atmospheric pressure (0 cm H_2O) and pleural pressure is changed.

The elastic forces 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.

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

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

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:

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*. Atypical 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*.

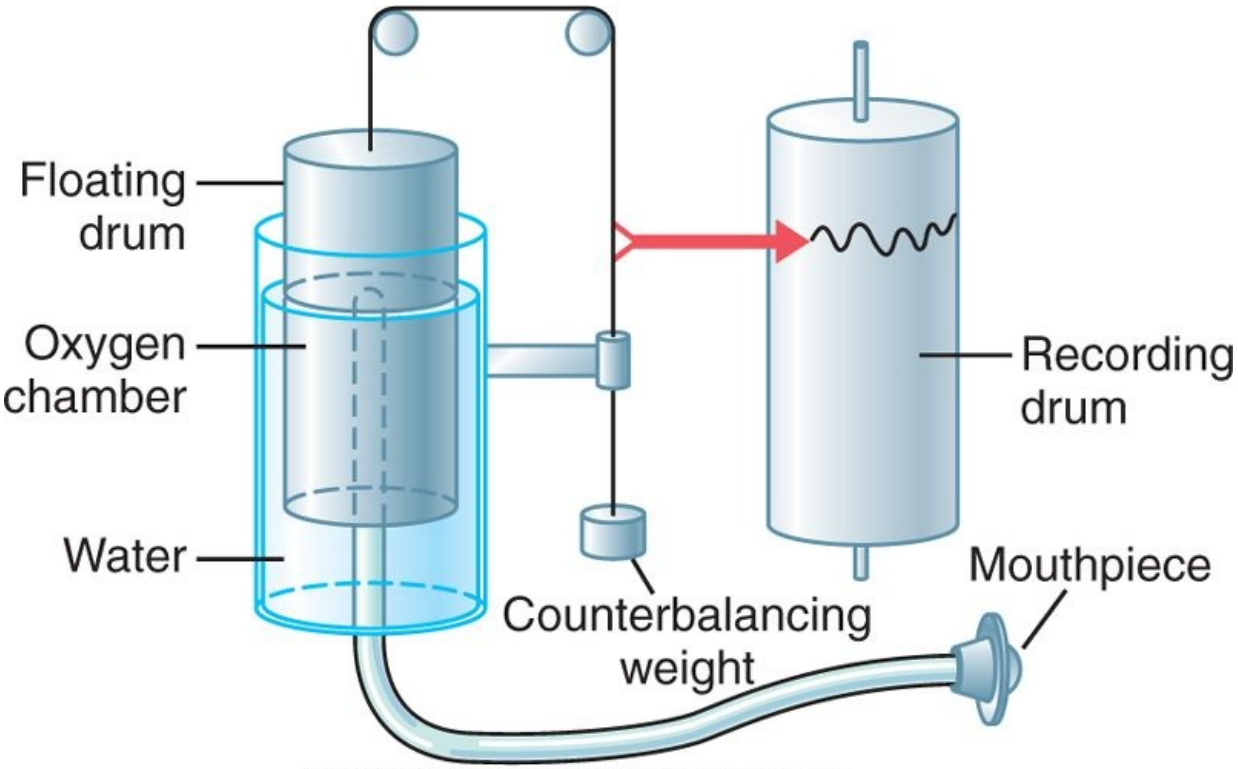

Figure 37-5 Spirometer.

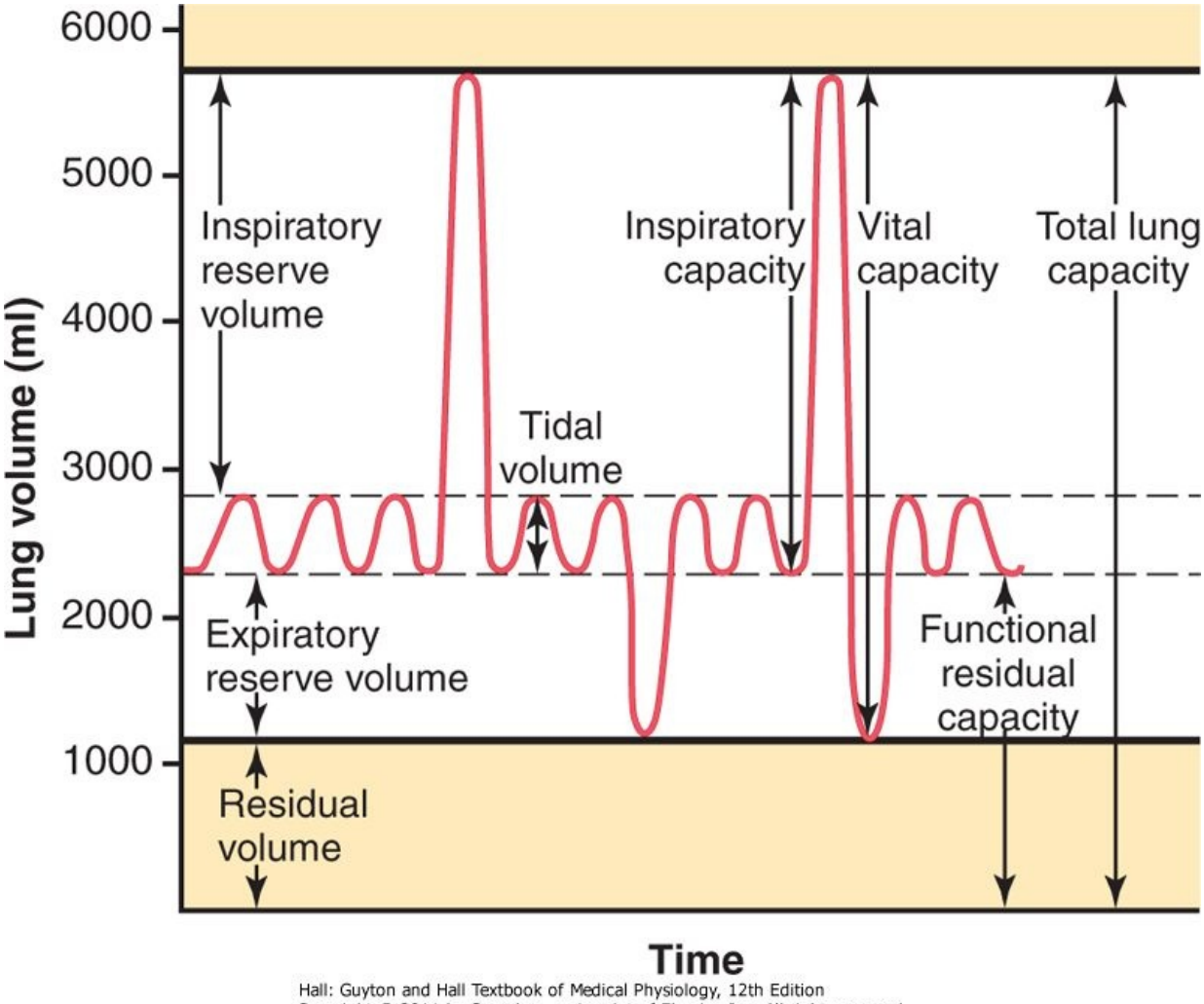

Figure 37-6 Diagram showing respiratory excursions during normal breathing and during maximal inspiration and maximal expiration.

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

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
V_I	inspired volume of ventilation per minute	Q	cardiac output
V_E	expired volume of ventilation per minute		
V_s	shunt flow		
V_A	alveolar ventilation per minute	Ca_{O_2}	concentration of oxygen in arterial blood
VO_2	rate of oxygen uptake per minute	Cv_{O_2}	concentration of oxygen in mixed venous blood
VCO_2	amount of carbon dioxide eliminated per minute	S_{O_2}	percentage saturation of hemoglobin with oxygen
VCO	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		

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.

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

Aspirometer 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: 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.

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$$RV = FRC - ERV$$

and

$$TLC = FRC + IC$$

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,

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

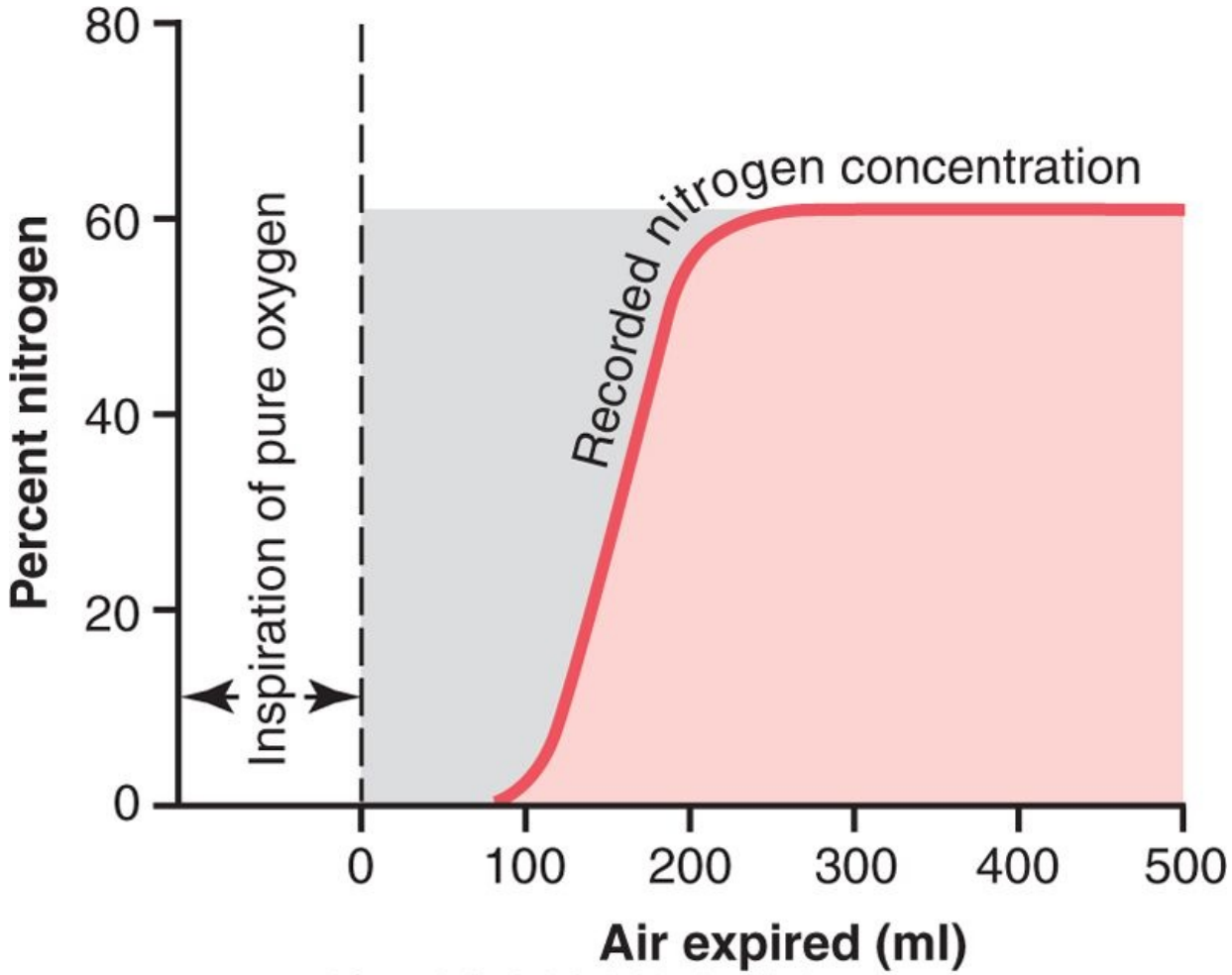
The ultimate importance of pulmonary ventilation is to continually renew the air in the gas exchange areas of the lungs, where air is in proximity to the pulmonary blood. These areas include the alveoli, alveolar sacs, alveolar ducts, and respiratory bronchioles. The rate at which new air reaches these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



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

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.

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

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

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

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

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

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. where 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 × (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.

Integration link: Histology of the intrapulmonary bronchial tree

Taken from Histology & Cell Biology: An introduction to Pathology 2E

Muscular Wall of the Bronchi and Bronchioles and Its Control

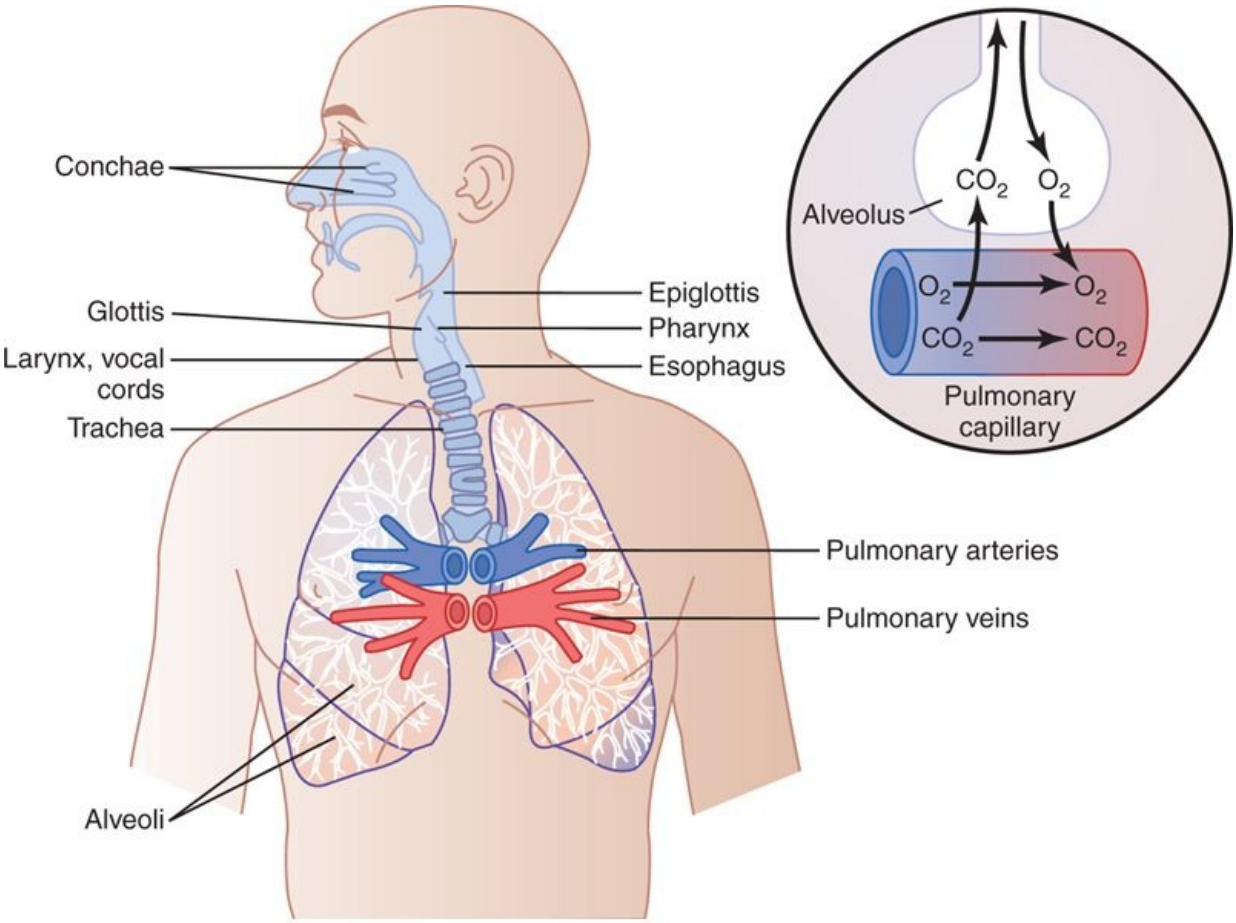


Figure 37-8 Respiratory passages.

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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 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 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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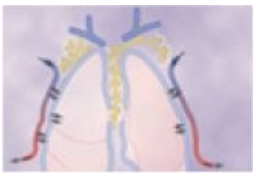
38 Pulmonary Circulation, Pulmonary Edema, Pleural Fluid



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.

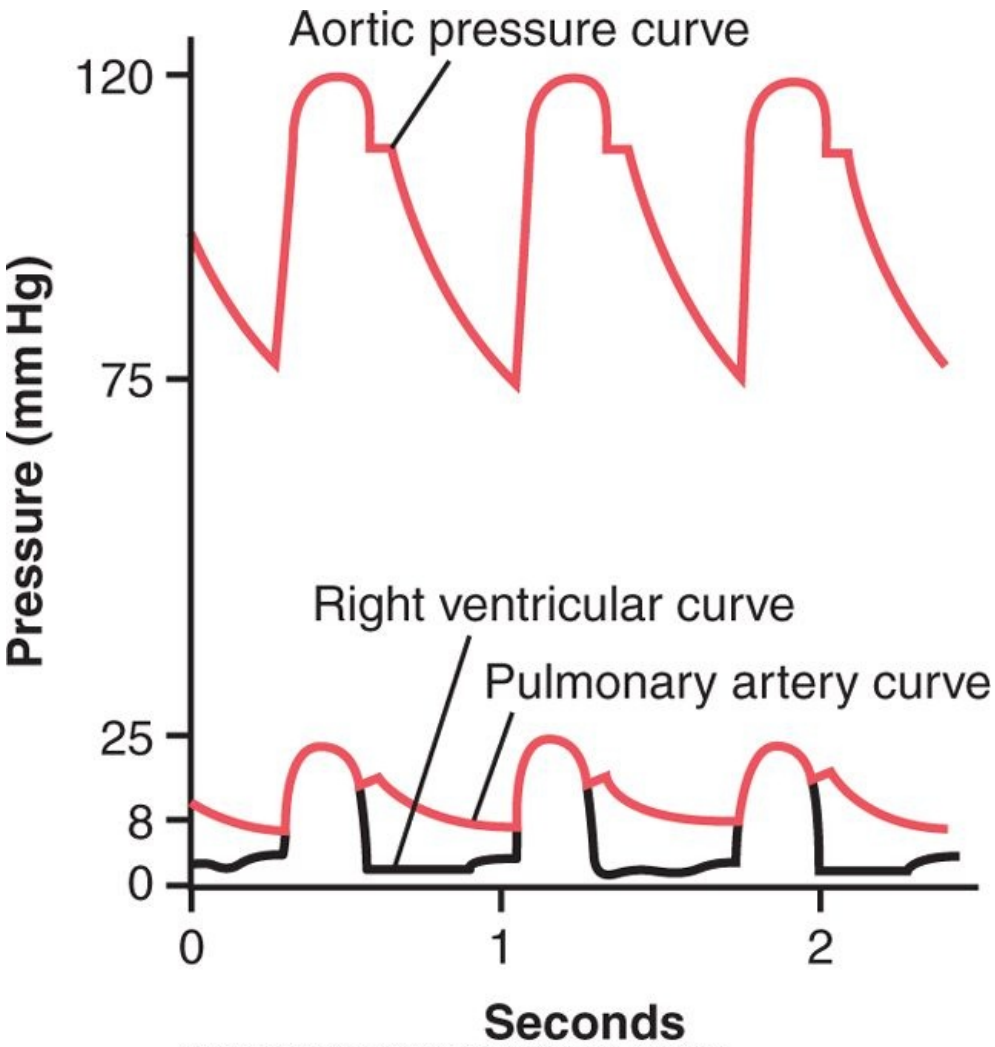


Figure 38-1 Pressure pulse contours in the right ventricle, pulmonary artery, and aorta.

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

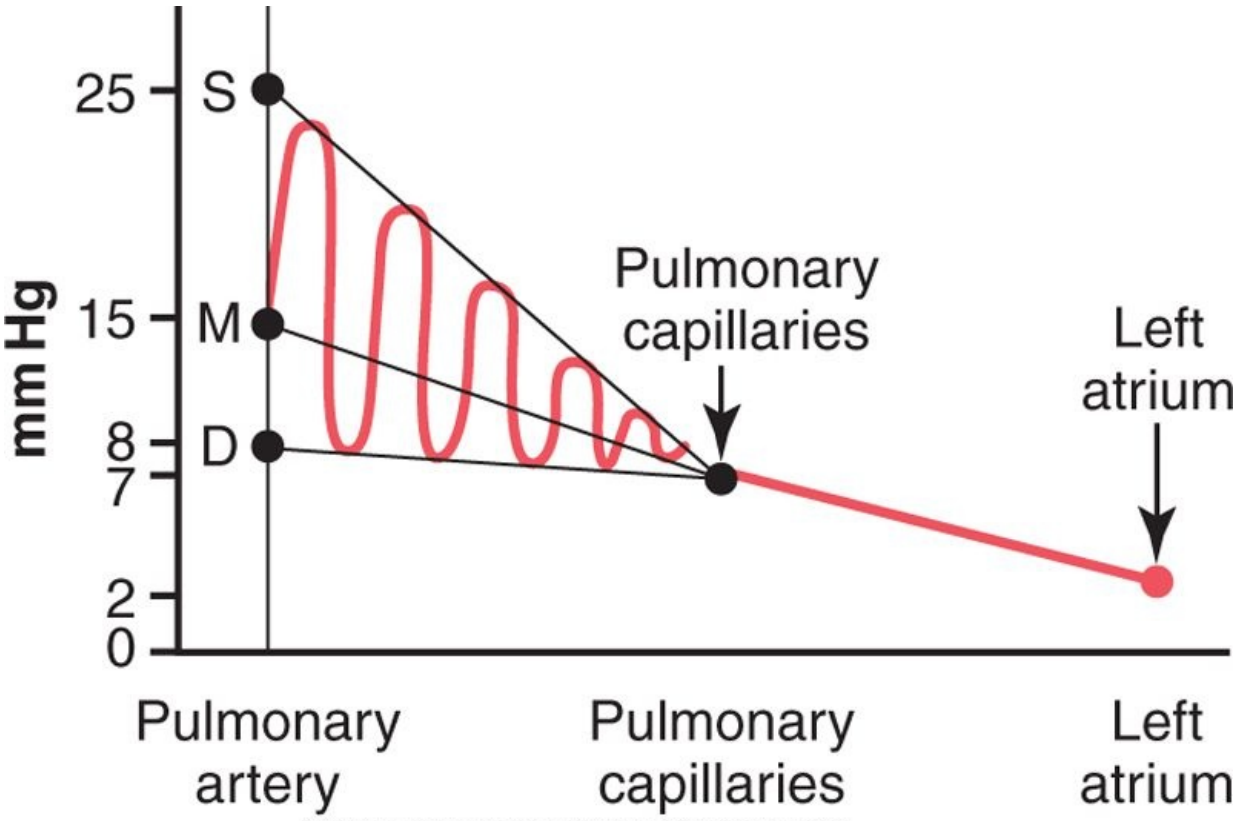


Figure 38-2 Pressures in the different vessels of the lungs. D, diastolic; M, mean; S, systolic; red curve, arterial pulsations.

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.

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

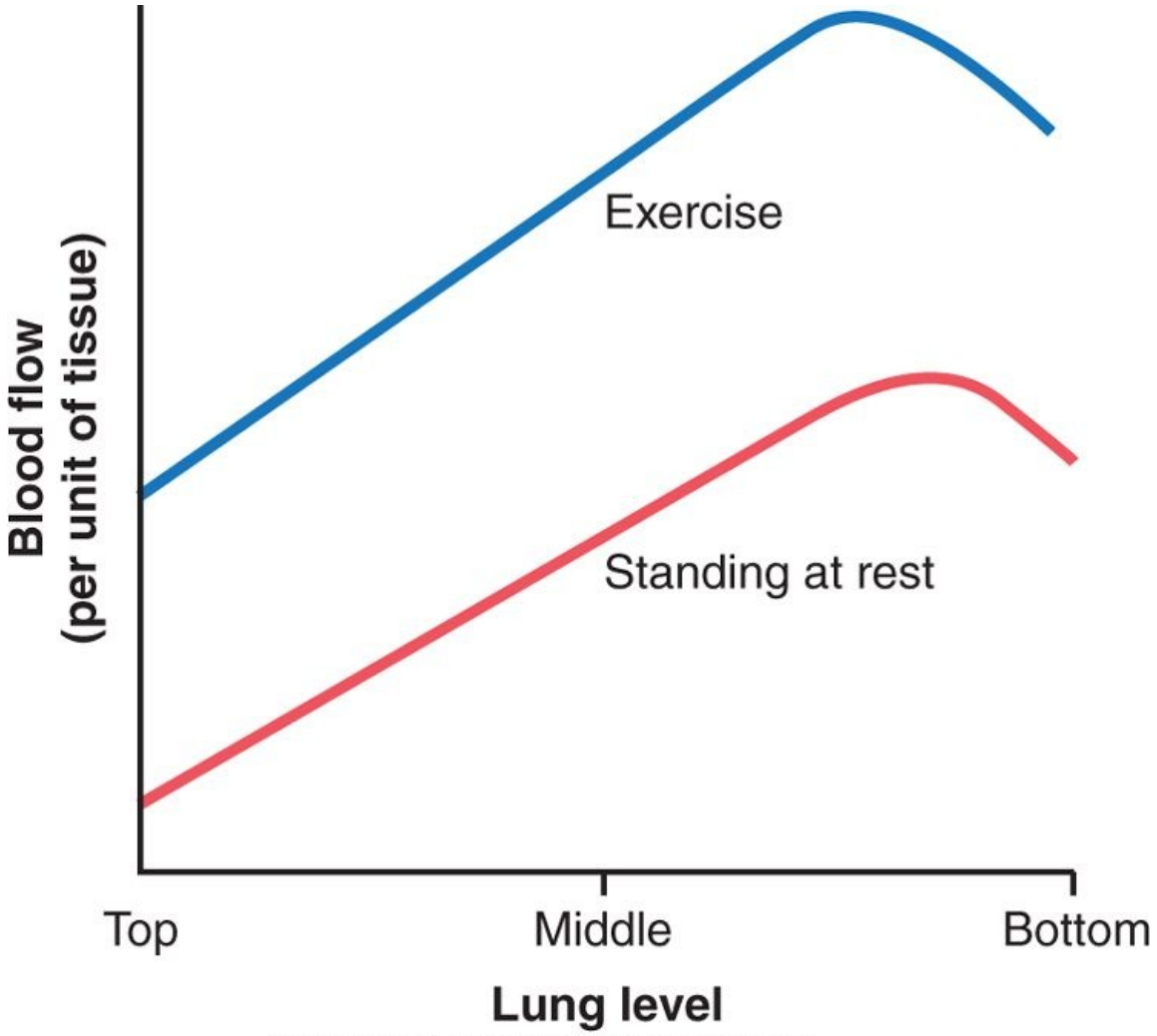


Figure 38-3 Blood flow at different levels in the lung of an upright person *at rest* and *during exercise*. Note that when the person is at rest, the blood flow is very low at the top of the lungs; most of the flow is through the bottom of the lung.

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
- *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

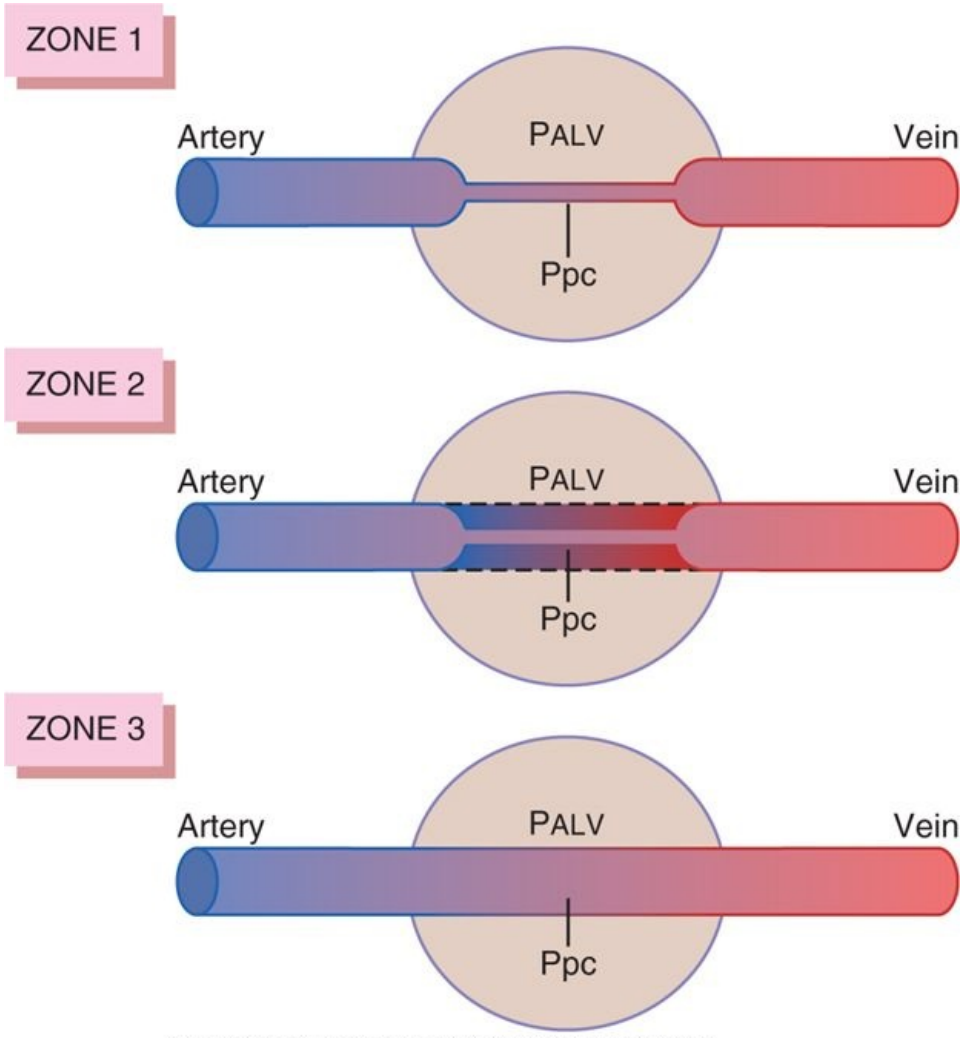


Figure 38-4 Mechanics of blood flow in the three blood flow zones of the lung: *zone 1, no flow*-alveolar air pressure (PALV) is greater than arterial pressure; *zone 2, intermittent flow*-systolic arterial pressure rises higher than alveolar air pressure, but diastolic arterial pressure falls below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

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.

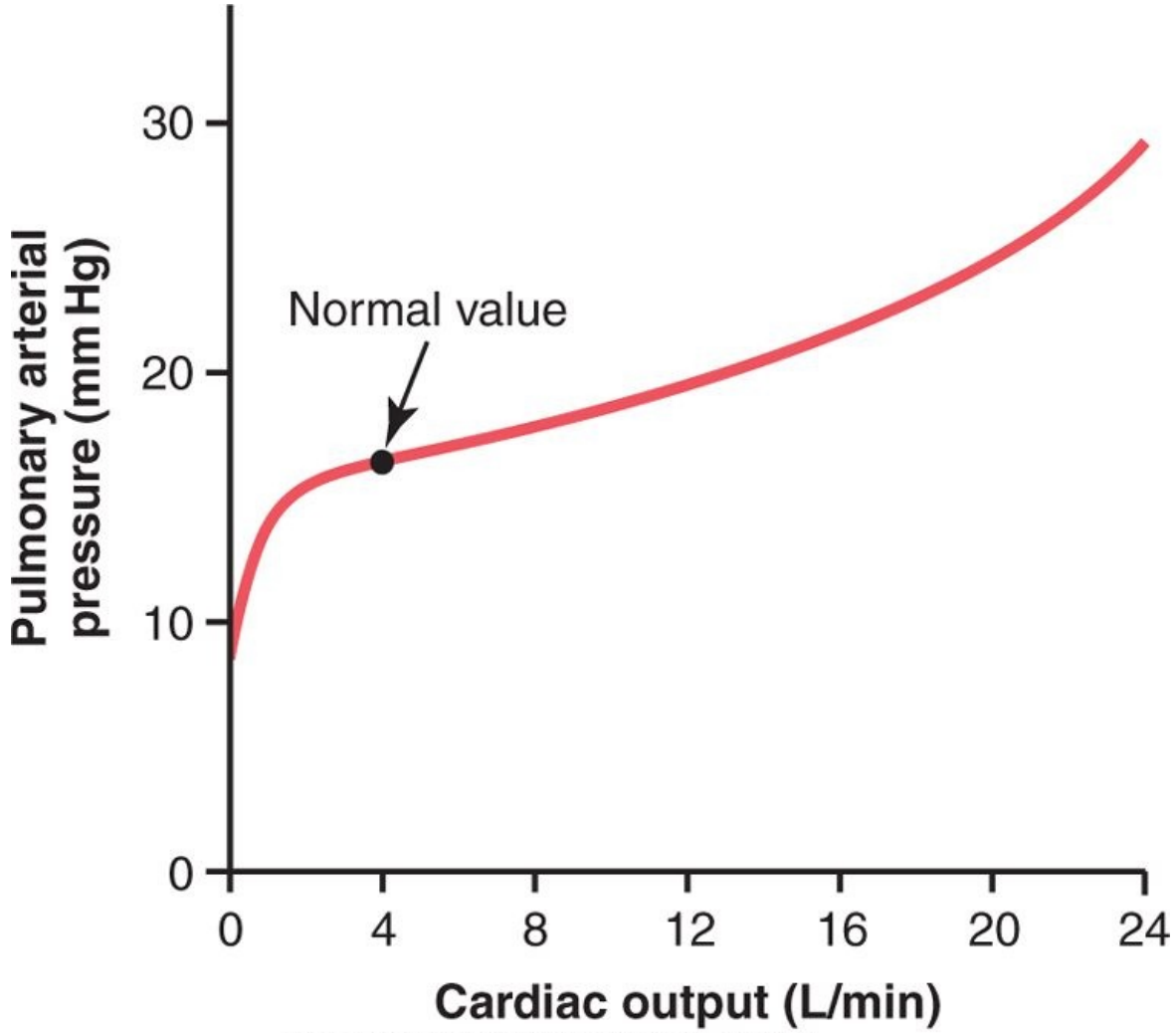


Figure 38-5 Effect on mean pulmonary arterial pressure caused by increasing the cardiac output during exercise.

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

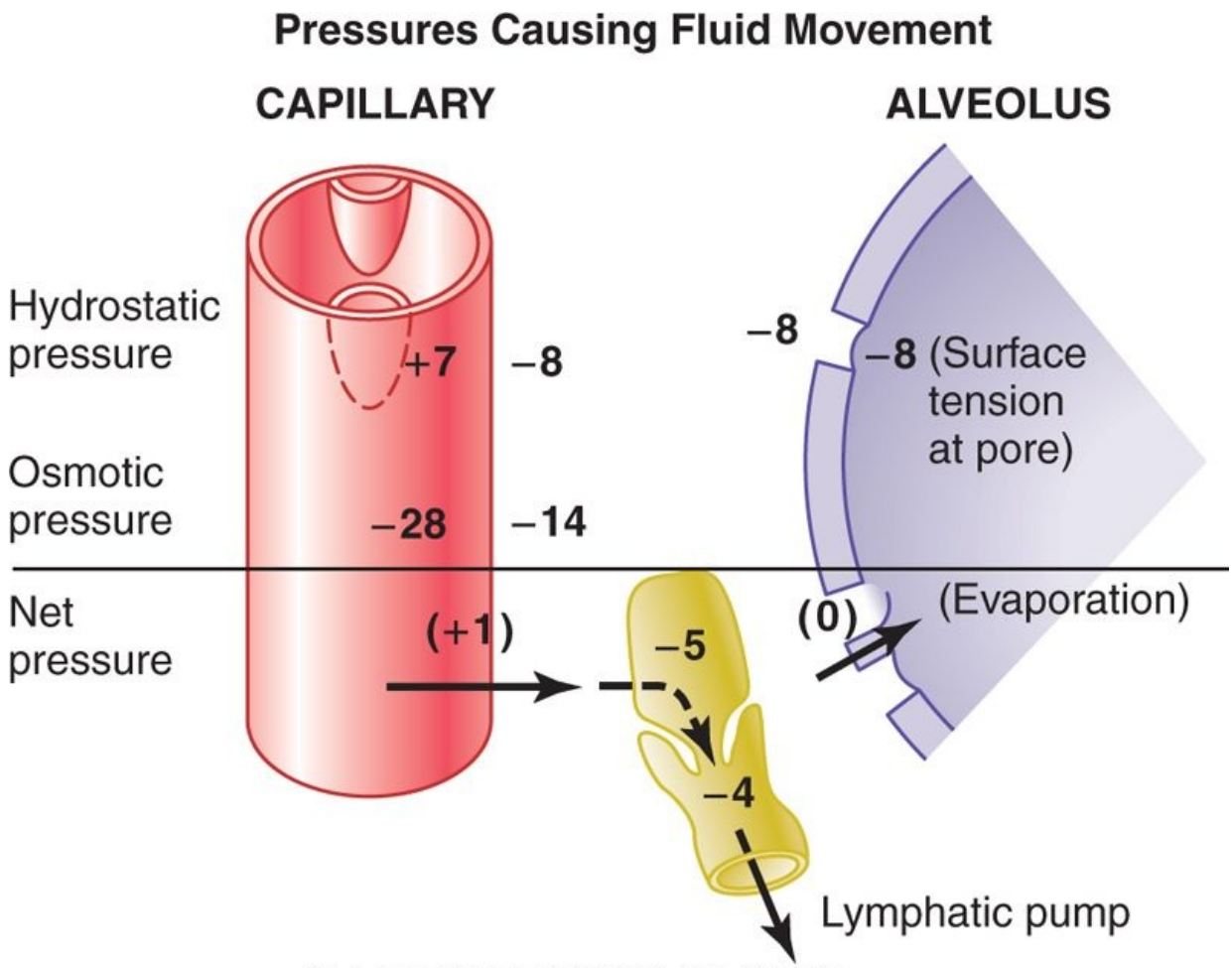


Figure 38-6 Hydrostatic and osmotic forces in mm Hg at the capillary (*left*) and alveolar membrane (*right*) of the lungs. Also shown is the tip end of a lymphatic vessel (*center*) that pumps fluid from the pulmonary interstitial spaces. (Modified from Guyton AC, Taylor AE, Granger HJ: Circulatory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

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:

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

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:

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."

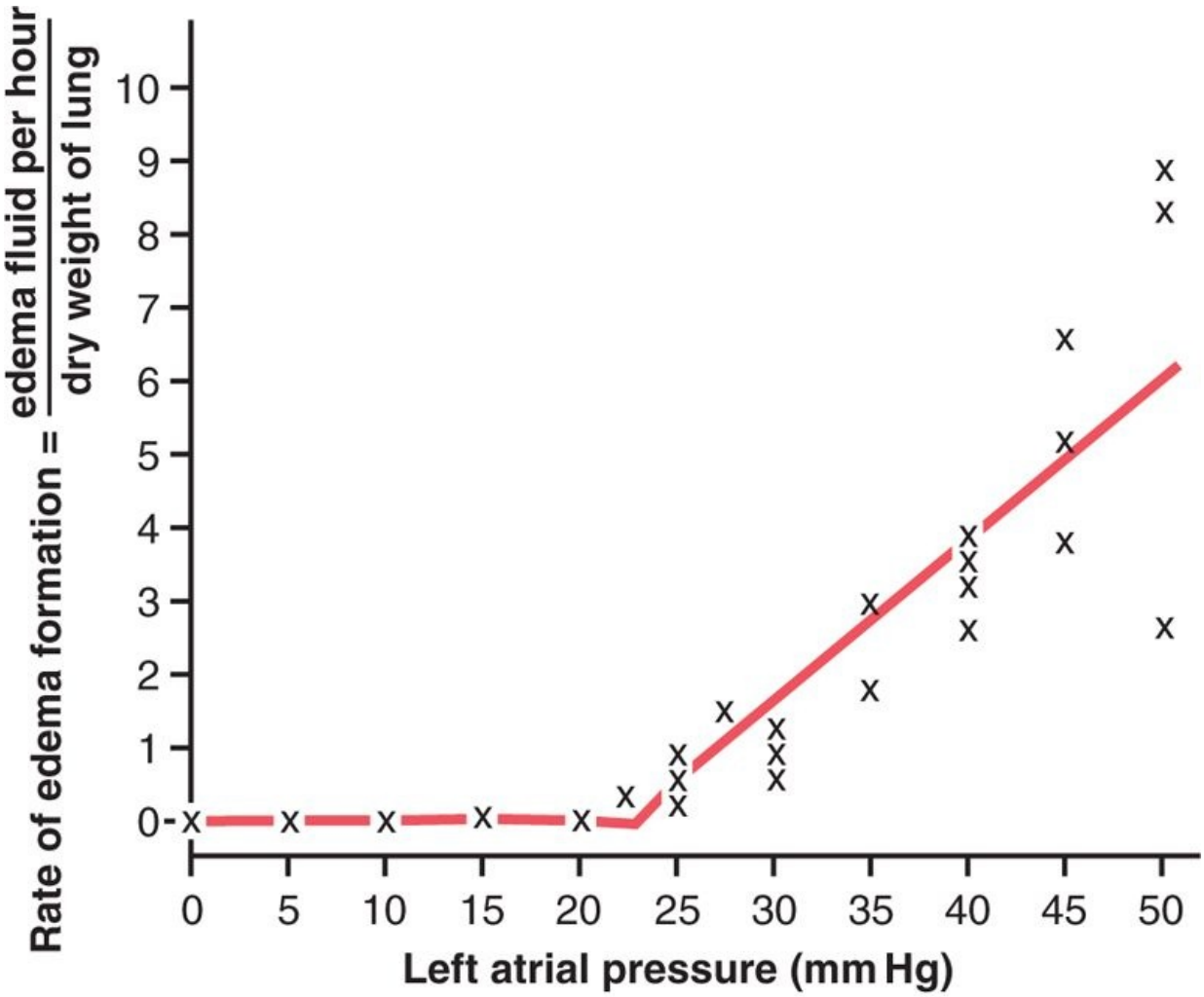


Figure 38-7 Rate of fluid loss into the lung tissues when the left atrial pressure (and pulmonary capillary pressure) is increased. (From Guyton AC, Lindsey AW: Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. Circ Res 7:649, 1959.)

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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 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.

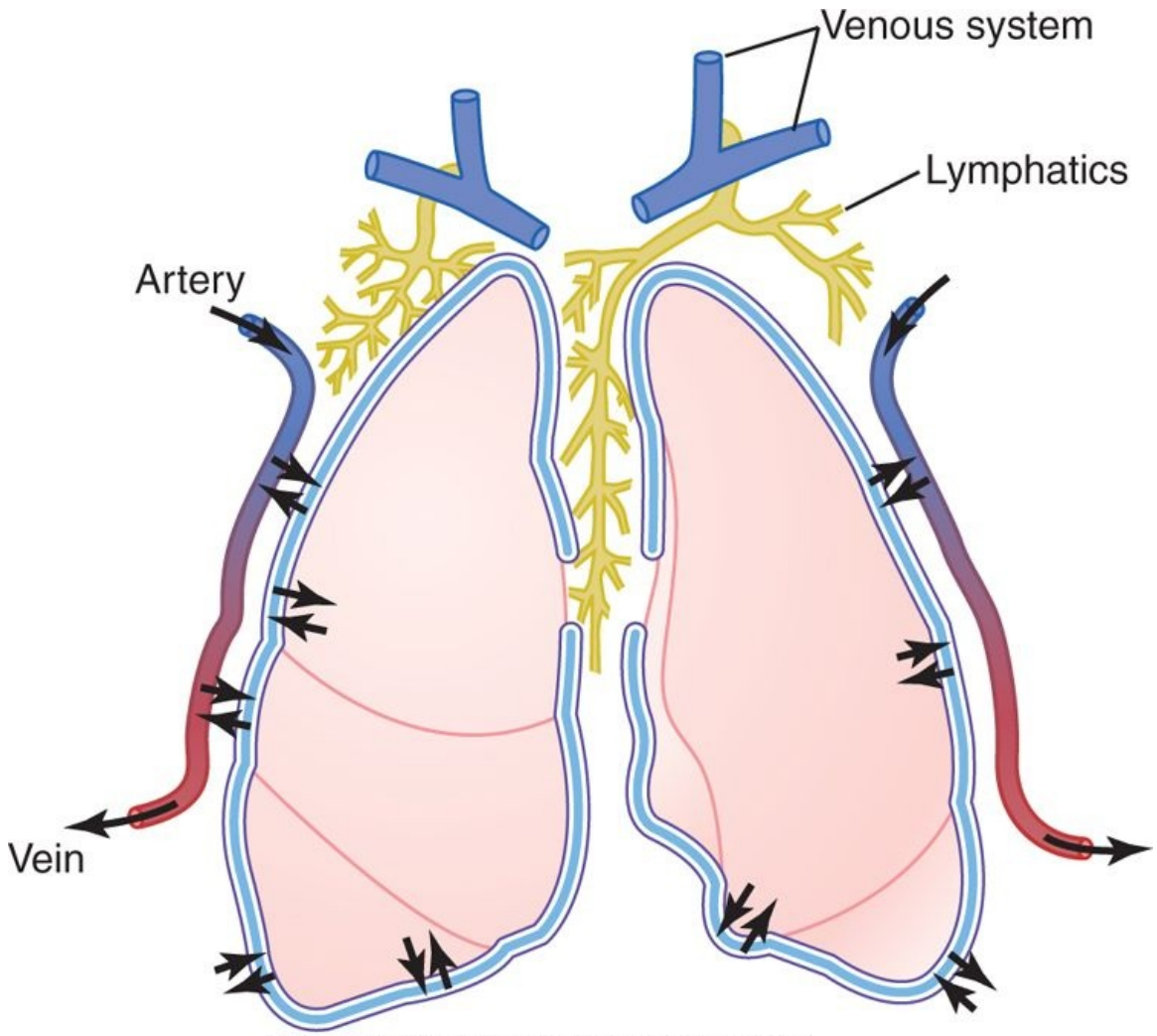

Figure 38-8 Dynamics of fluid exchange in the intrapleural space.

"Negative Pressure" in Pleural Fluid

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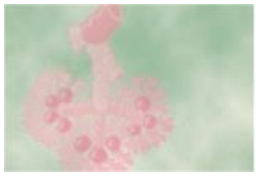
39 Physical Principles of Gas Exchange; Diffusion of Oxygen and Carbon Dioxide Through the Respiratory Membrane



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*.

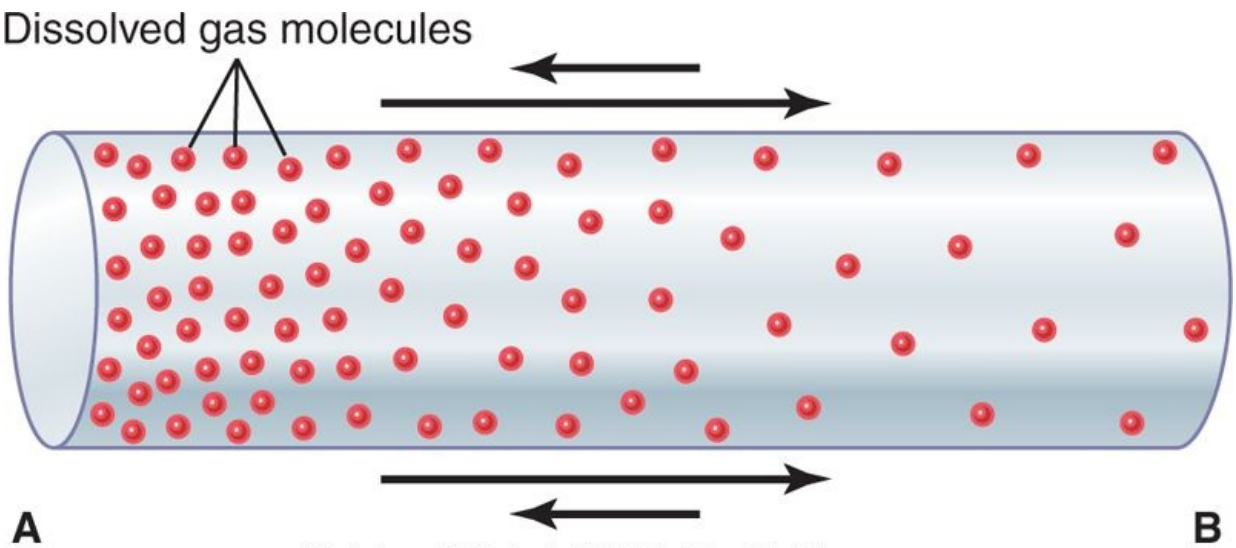
In respiratory physiology, one deals with mixtures of gases, mainly of *oxygen, nitrogen*, and *carbon dioxide*. The rate of diffusion of each of these gases is directly proportional to the pressure caused by that gas alone, which is called the *partial pressure* of that gas. The concept of partial pressure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



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

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*.

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 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*:

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

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:

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.

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

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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: 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.

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

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:

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

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.

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.

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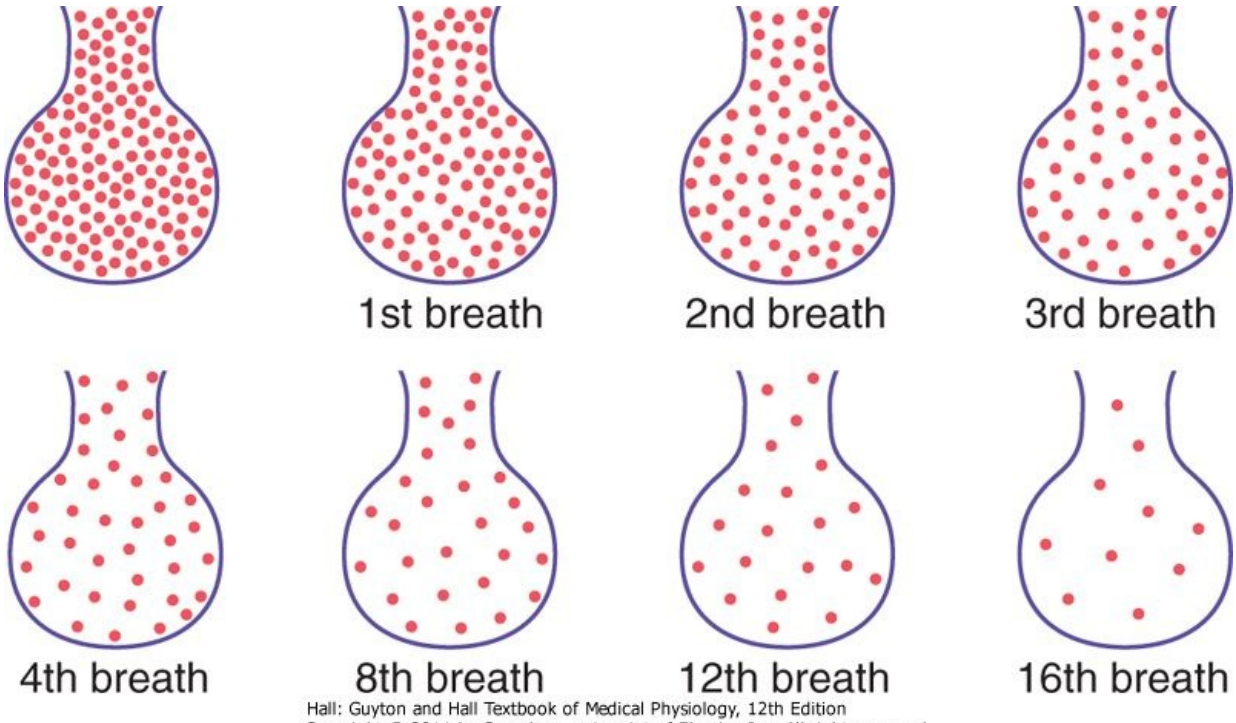

Figure 39-2 Expiration of a gas from an alveolus with successive breaths.

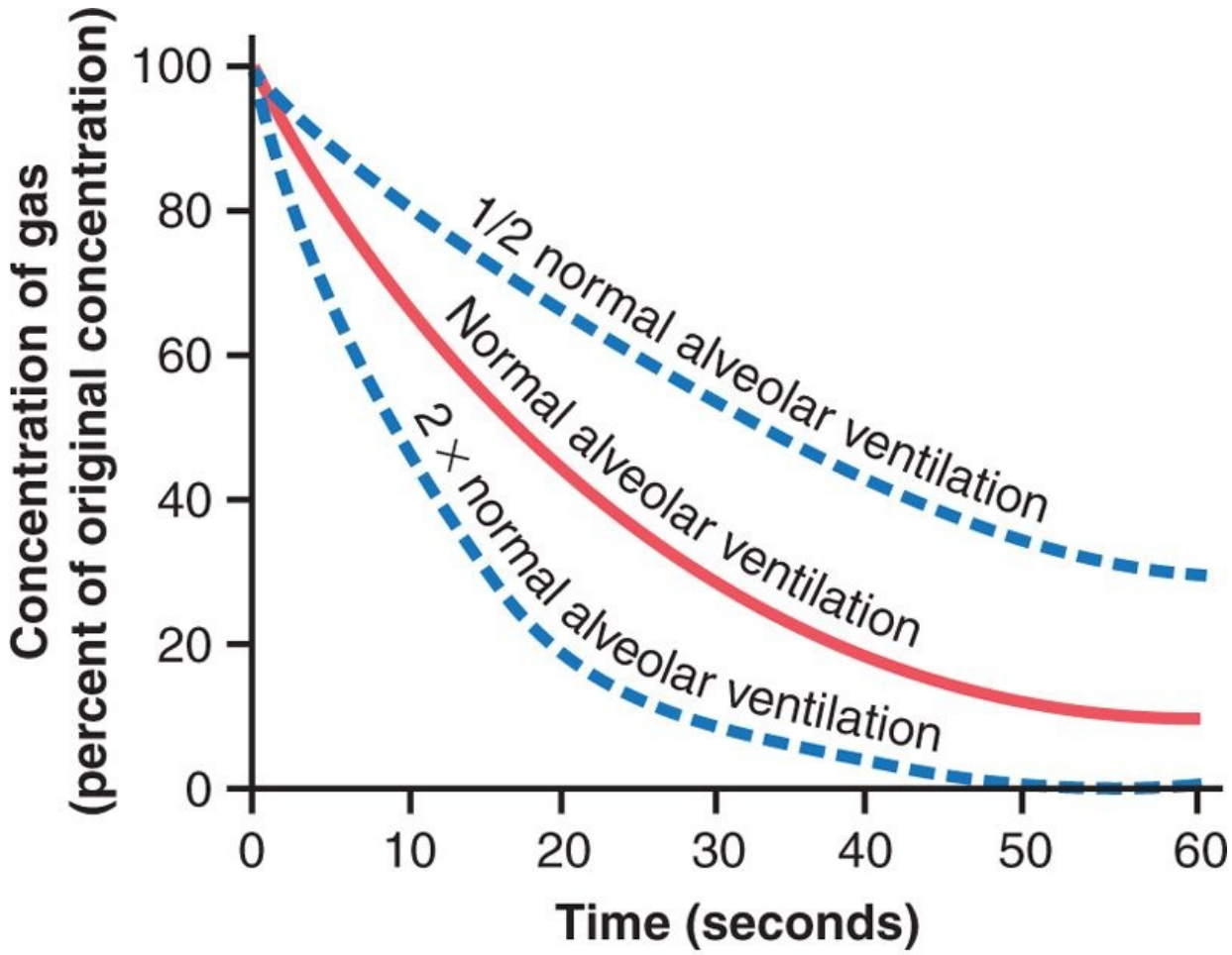

Figure 39-3 Rate of removal of excess gas from alveoli.

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 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.

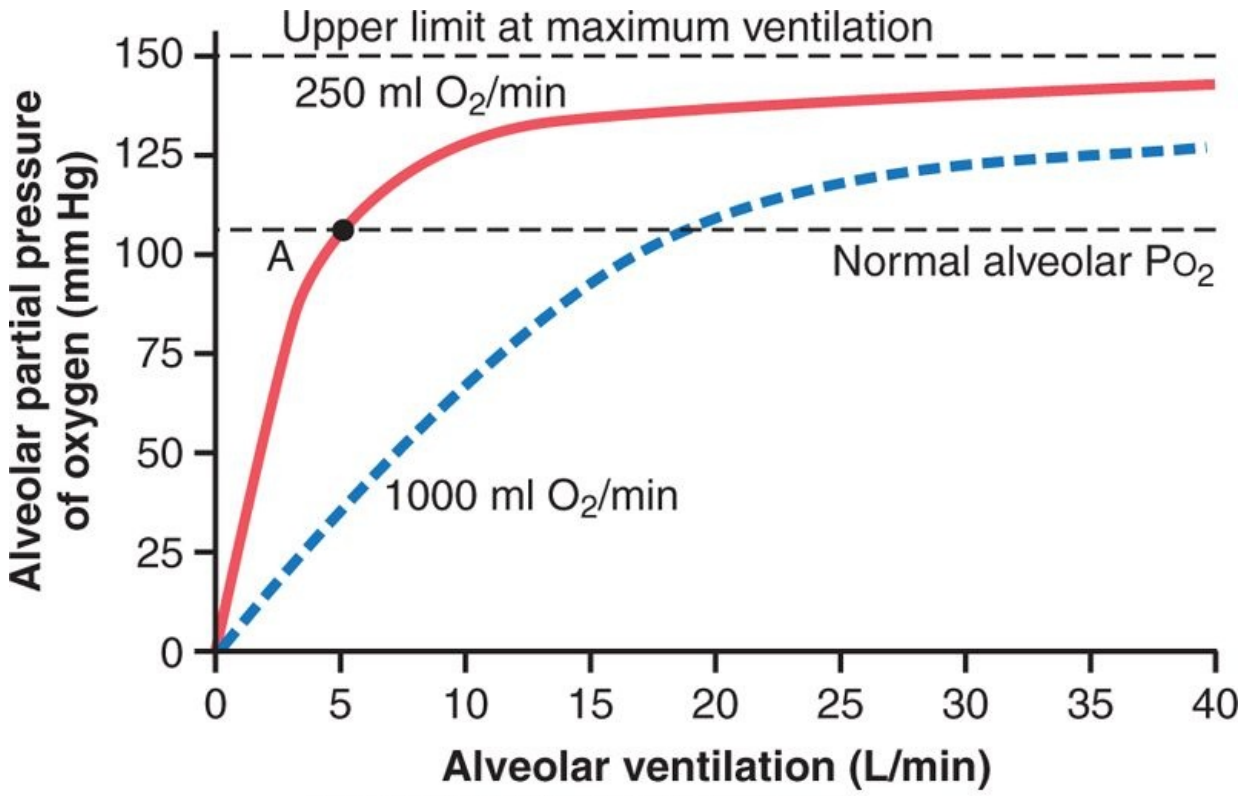

Figure 39-4 Effect of alveolar ventilation on the alveolar P_{O_2} at two rates of oxygen absorption from the alveoli-250 ml/min and 1000 ml/min. *Point A* is the normal operating point.

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).

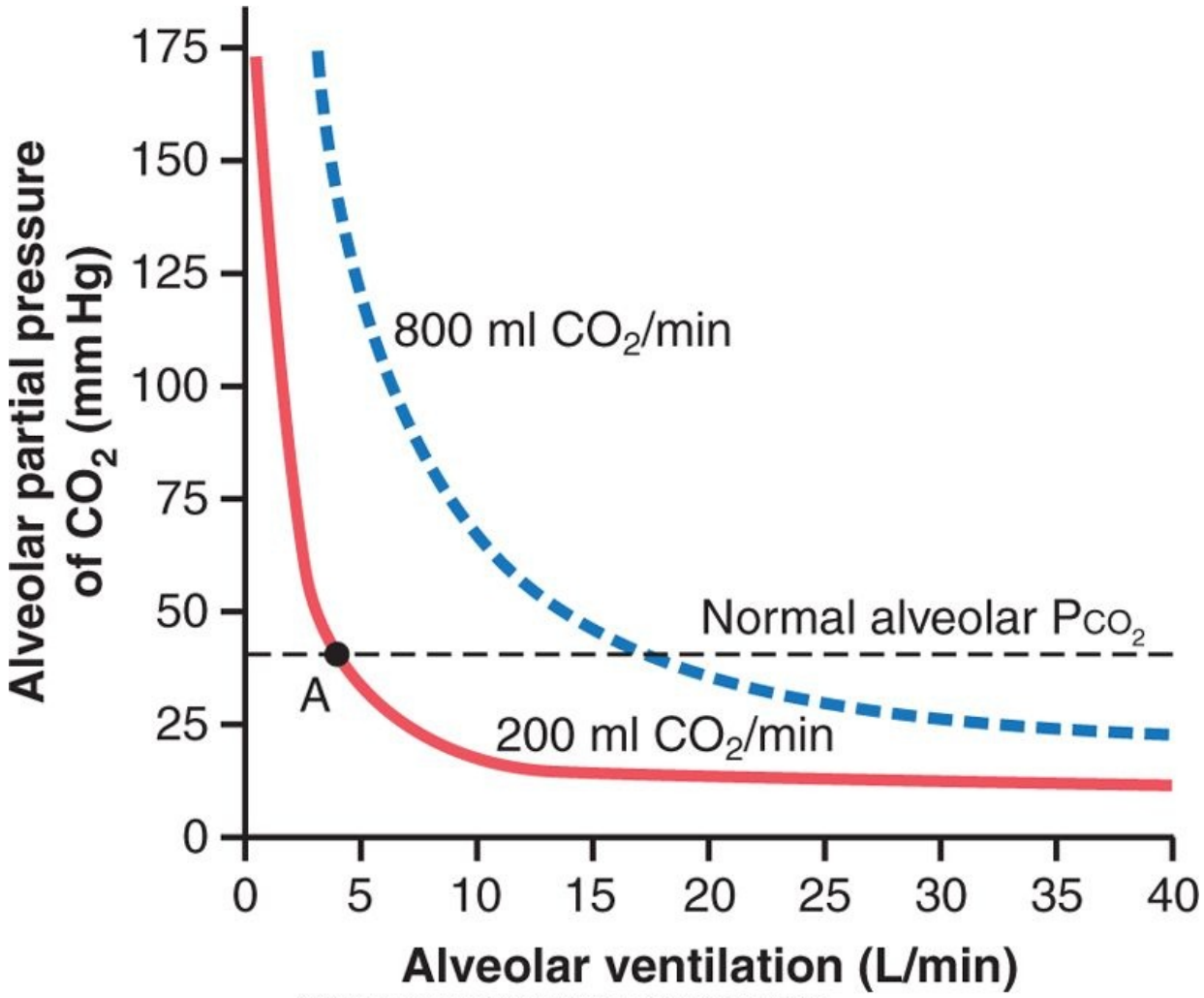

Figure 39-5 Effect of alveolar ventilation on the alveolar P_{CO_2} at two rates of carbon dioxide excretion from the blood-800 ml/min and 200 ml/min. *Point A* is the normal operating point.

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*. 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.

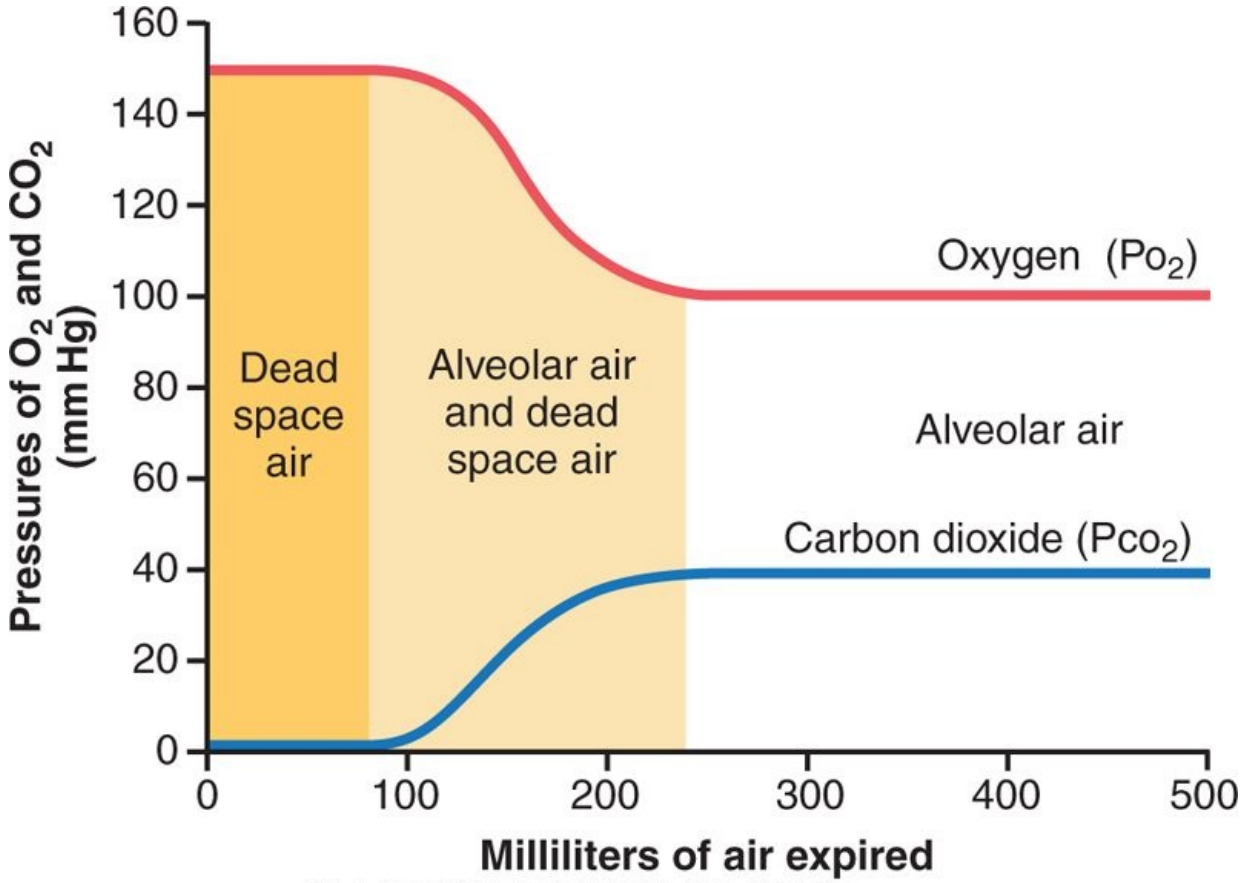

Figure 39-6 Oxygen and carbon dioxide partial pressures in the various portions of normal expired air.

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).

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

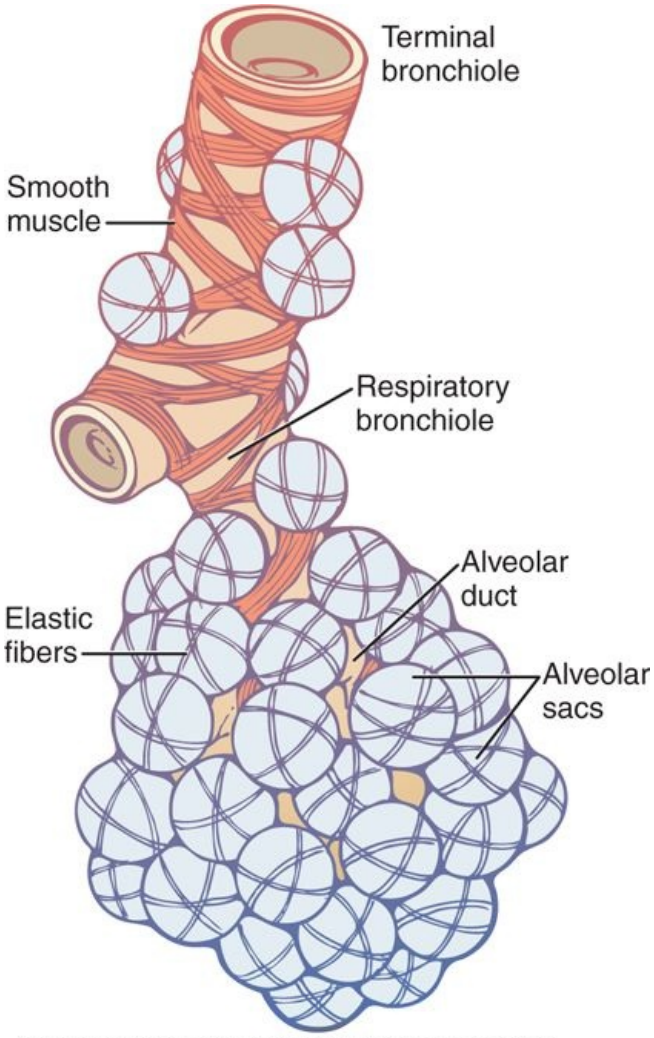

Figure 39-7 Respiratory unit.

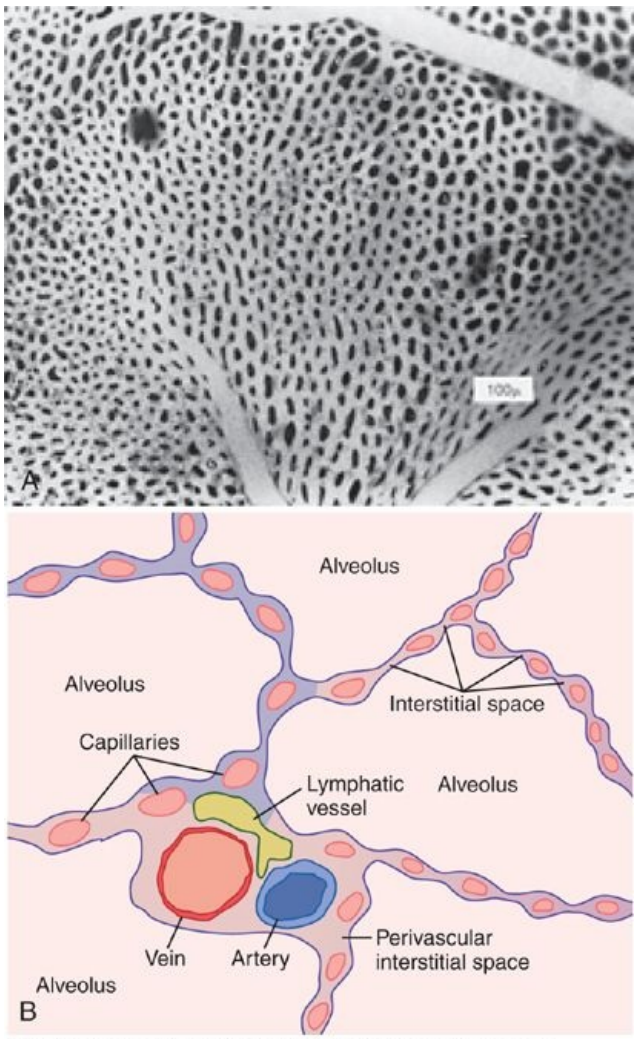

Figure 39-8 *A*, Surface view of capillaries in an alveolar wall. *B*, Cross-sectional view of alveolar walls and their vascular supply. (*A*, From Maloney JE, Castle BL: Pressure-diameter relations of capillaries and small blood vessels in frog lung. Respir Physiol 7:150, 1969. Reproduced by permission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

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 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

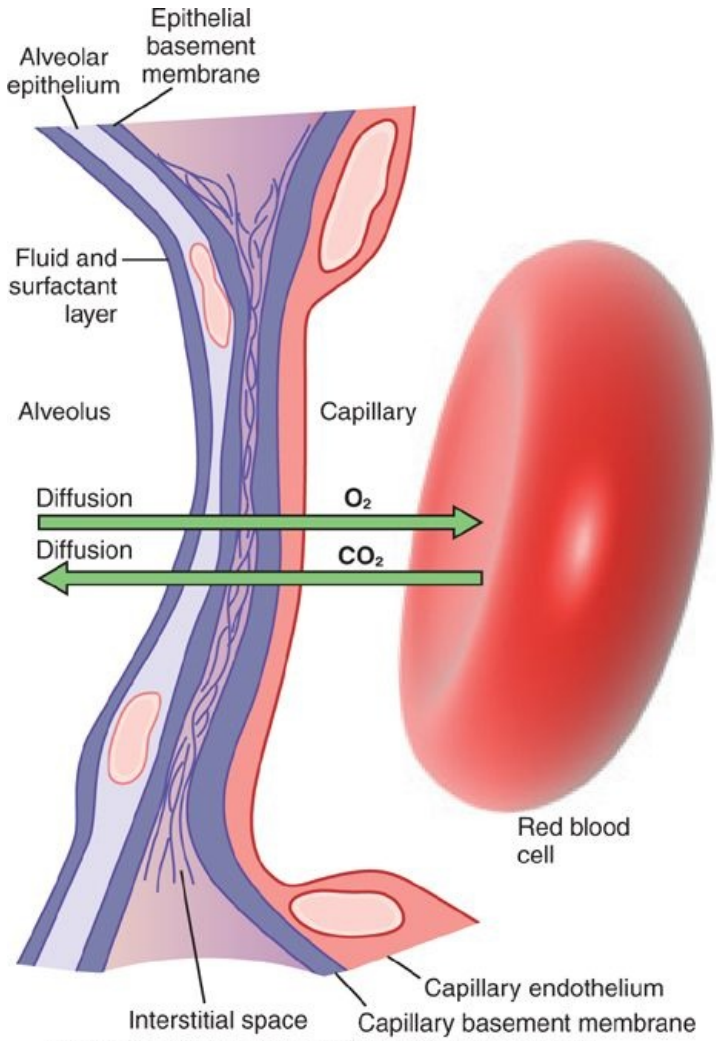

Figure 39-9 Ultrastructure of the alveolar respiratory membrane, shown in cross section.

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 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

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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.

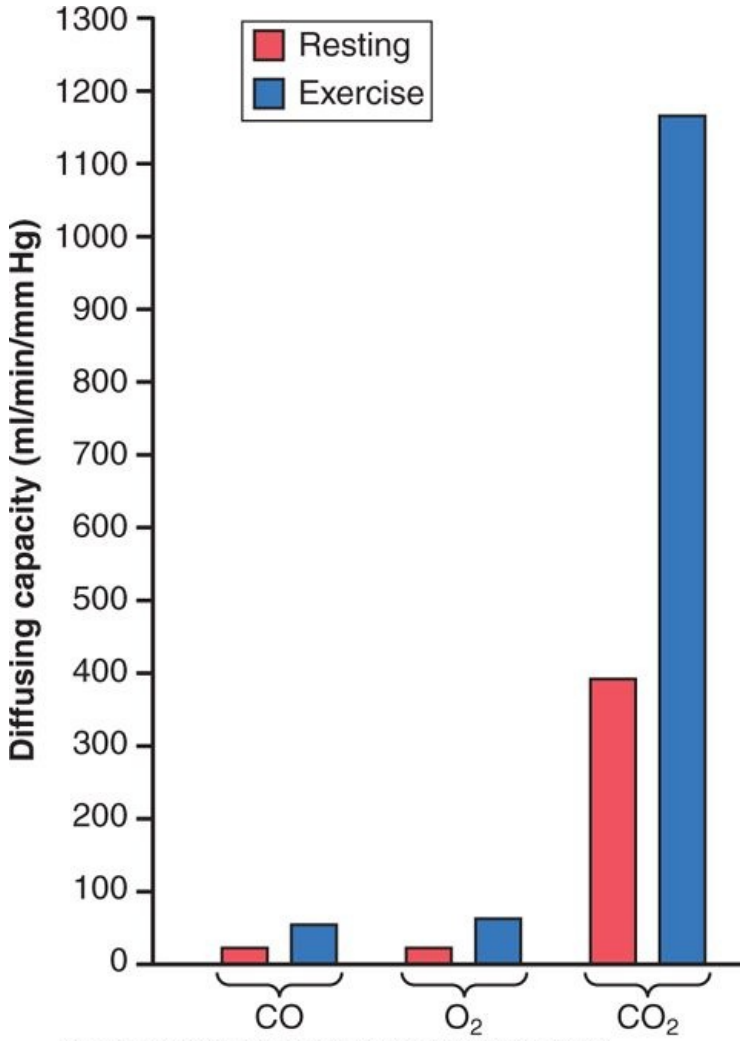

Figure 39-10 *Diffusing capacities* for carbon monoxide, oxygen, and carbon dioxide in the normal lungs under resting conditions and during exercise.

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 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 V_A/Q. When V_A (alveolar ventilation) is normal for a given alveolus and Q (blood flow) is also normal for the same alveolus, the ventilation-perfusion ratio (V_A/Q) is also said to be normal. When the ventilation (V_A) is zero, yet there is still perfusion (Q) of the alveolus, the V_A/Q is zero. Or, at the other extreme, when there is adequate ventilation (V_A) but zero perfusion (Q), the ratio V_A/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 V_A/Q Equals Zero

When V_A/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 (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 V_A/Q Equals Infinity

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The effect on the alveolar gas partial pressures when V_A/Q equals infinity is entirely different from the effect when V_A/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 V_A/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}, V_A/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}, V_A/Q diagram. The curve in the diagram represents all possible P_{O_2} and P_{CO_2} combinations between the limits of V_A/Q equals zero and V_A/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 v is the plot of P_{O_2} and P_{CO_2} when V_A/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 V_A/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 V_A/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 V_A/Q Is Below Normal)

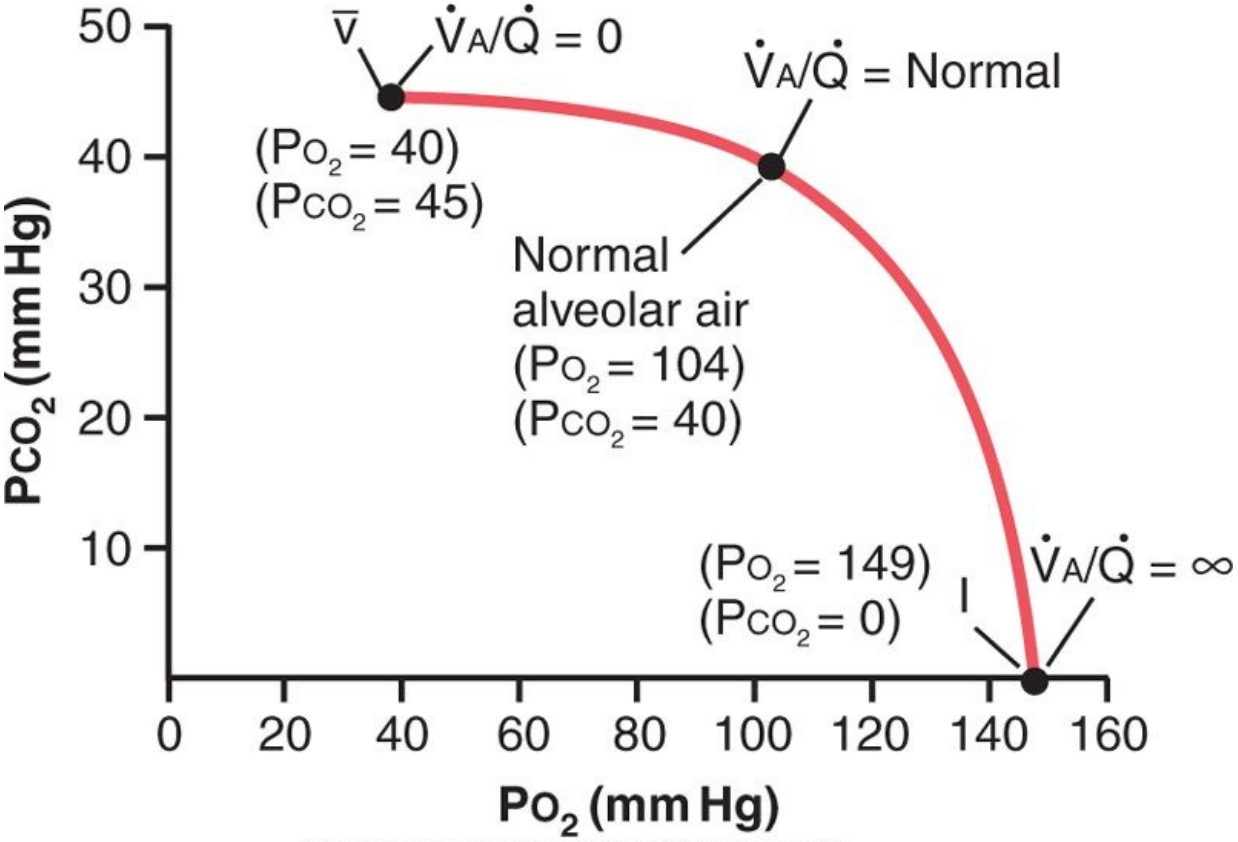

Figure 39-11 Normal P_{O_2}-P_{CO_2}, V_A/Q diagram.

Whenever V_A/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.

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

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: in which Q_{PS} is the physiologic shunt blood flow per minute, 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 Cv_{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 V_A/Q Is Greater Than Normal)

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

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: in which $V_{D_{phys}}$ is the physiologic dead space, V_T is the tidal volume, Pa_{CO_2} is the partial pressure of carbon dioxide in the arterial blood, and $P[emacr]_{CO_2}$ 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 V_A/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, V_A/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 V_A/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*.

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 V_A/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 V_A/Q. First, because many of the small bronchioles are obstructed, the alveoli beyond the obstructions are unventilated, causing a V_A/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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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.

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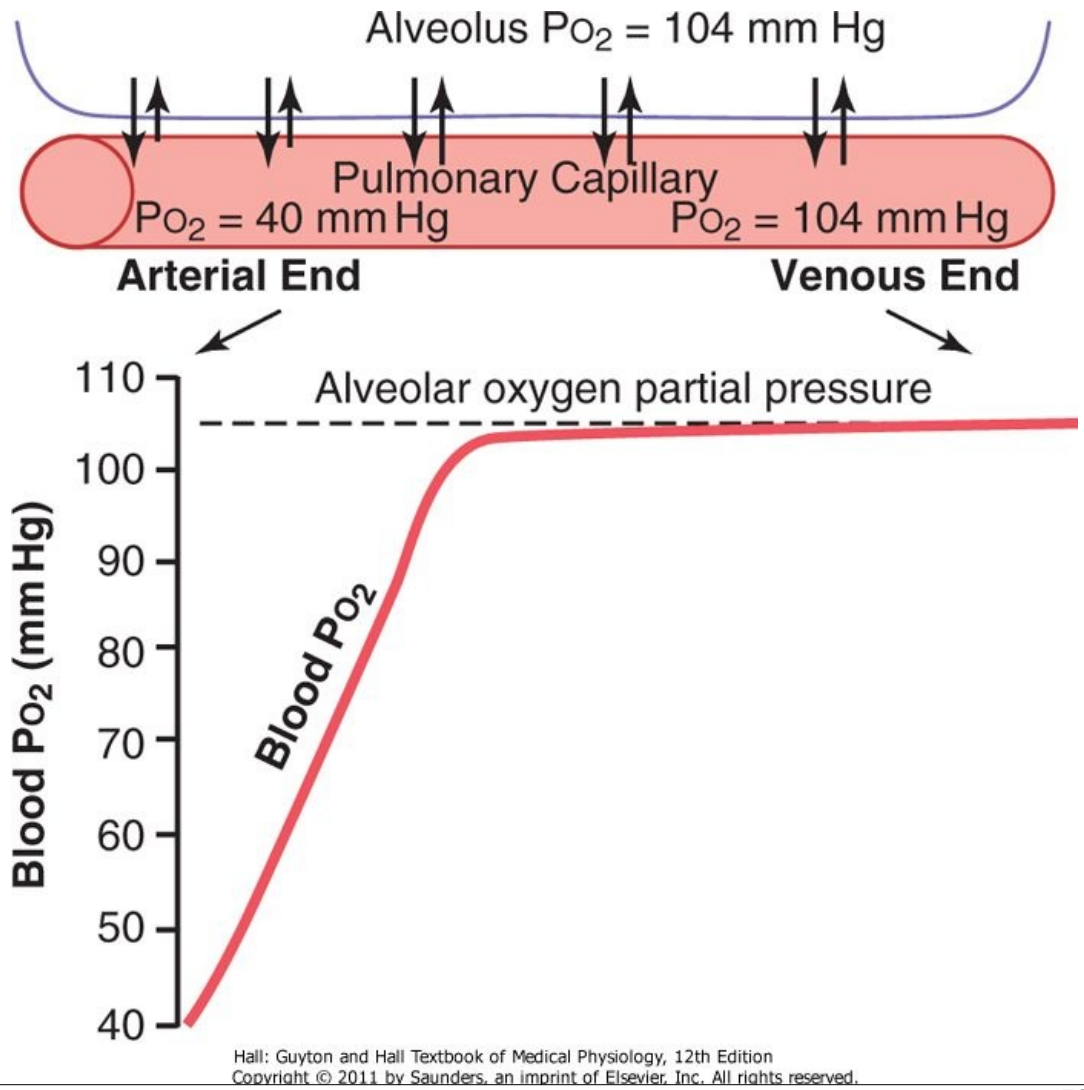

Hall: Guyton and Hall Textbook of Medical Physiology, 12th Edition

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.)

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 oxygenated 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

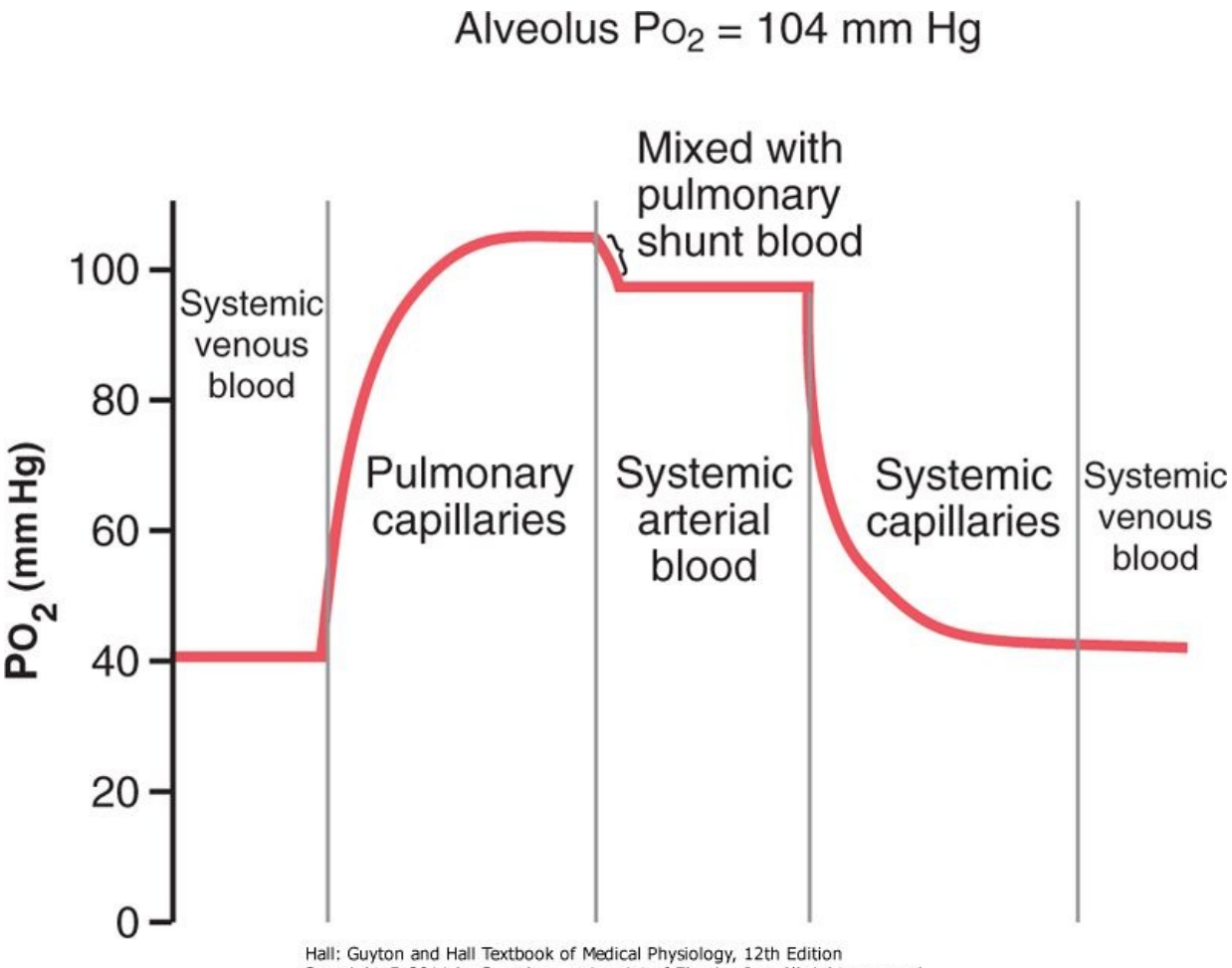

Figure 40-2 Changes in P_{O_2} in the pulmonary capillary blood, systemic arterial blood, and systemic capillary blood, demonstrating the effect of "venous admixture."

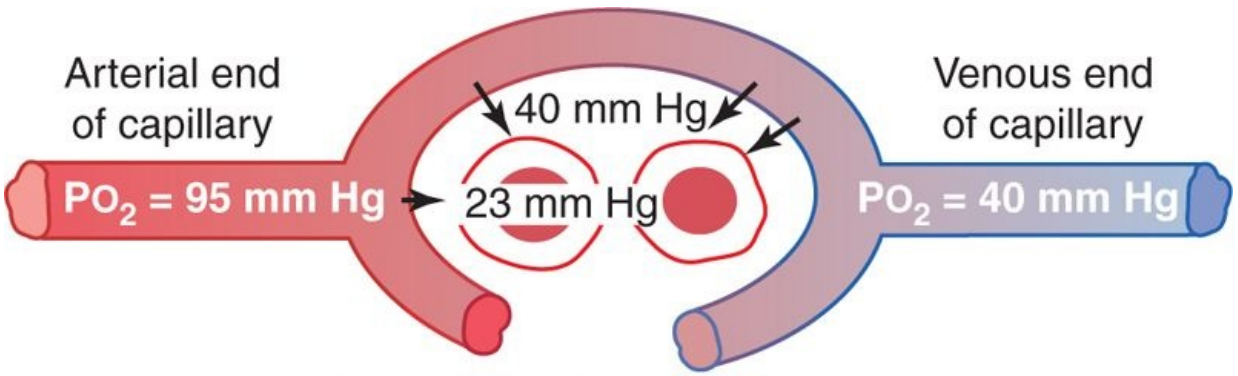

Figure 40-3 Diffusion of oxygen from a peripheral tissue capillary to the cells. (P_{O_2} in interstitial fluid = 40 mm Hg, and in tissue cells = 23 mm Hg.)

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}

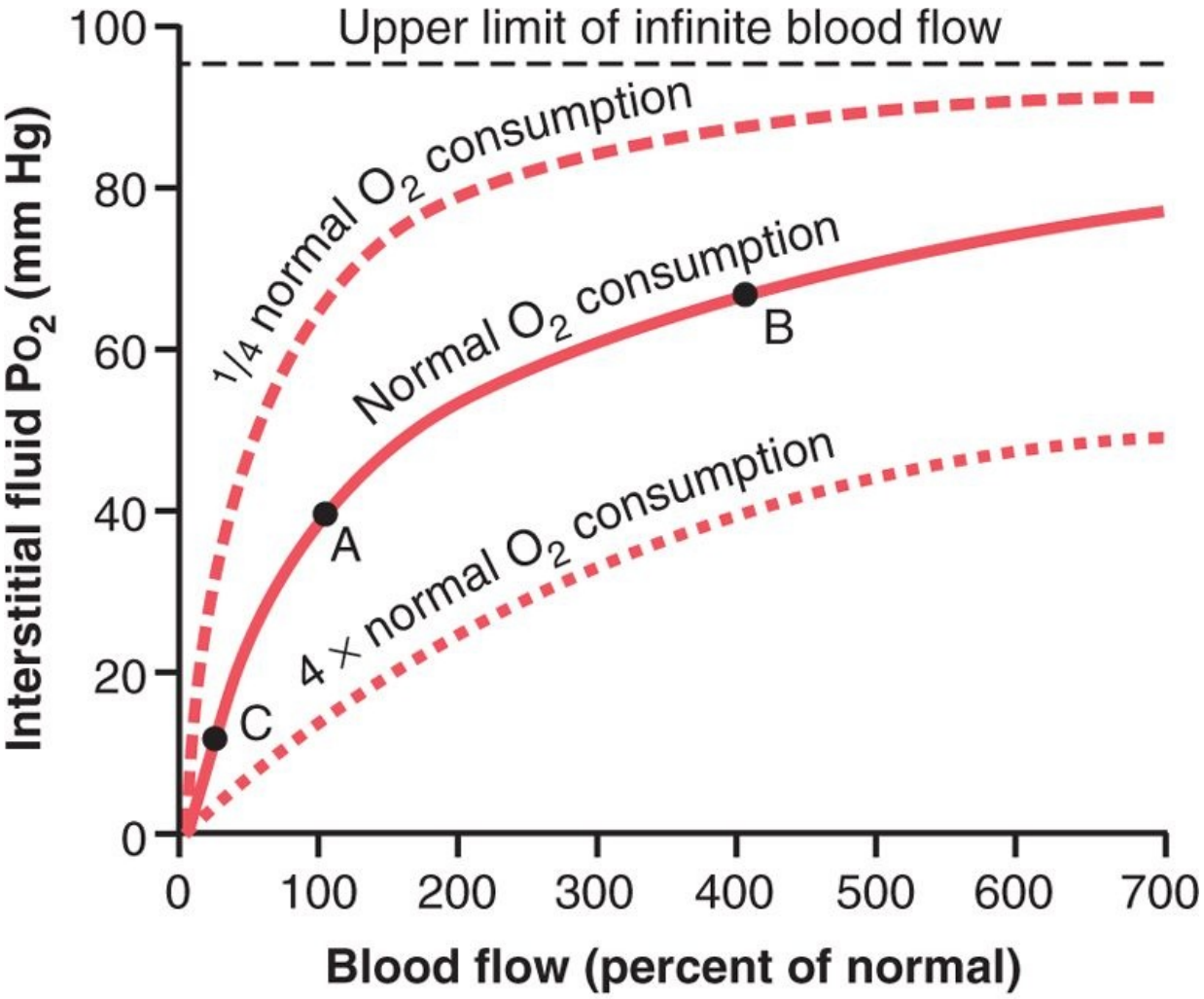

Figure 40-4 Effect of blood flow and rate of oxygen consumption on tissue P_{O_2}.

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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 capillaries. 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.

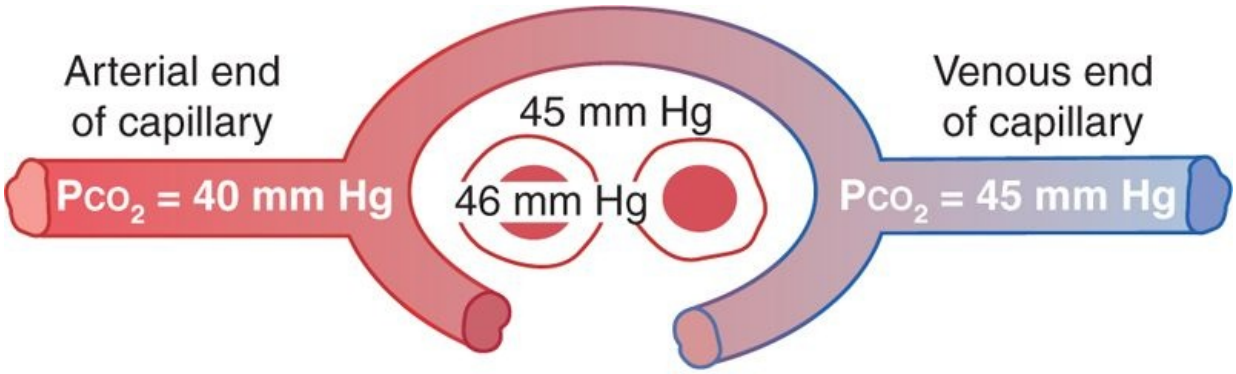

Figure 40-5 Uptake of carbon dioxide by the blood in the tissue capillaries. (P_{CO_2} in tissue cells = 46 mm Hg, and in interstitial fluid = 45 mm Hg.)

Effect of Rate of Tissue Metabolism and Tissue Blood Flow on Interstitial P_{CO_2}

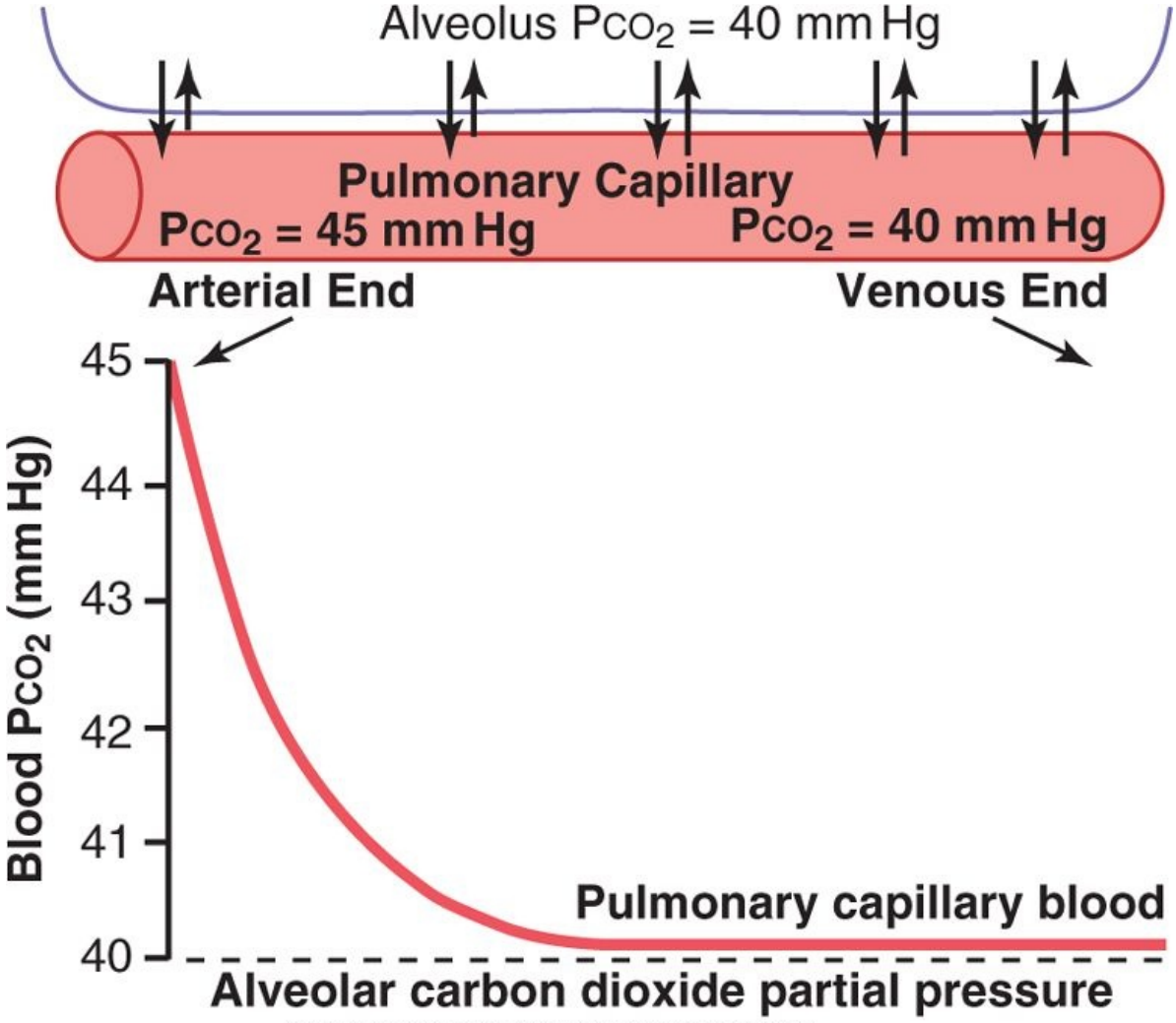

Figure 40-6 Diffusion of carbon dioxide from the pulmonary blood into the alveolus. (This curve was constructed from data in Milhorn HT Jr, Pulley PE Jr: A theoretical study of pulmonary capillary gas exchange and venous admixture. Biophys J 8:337, 1968.)

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 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.

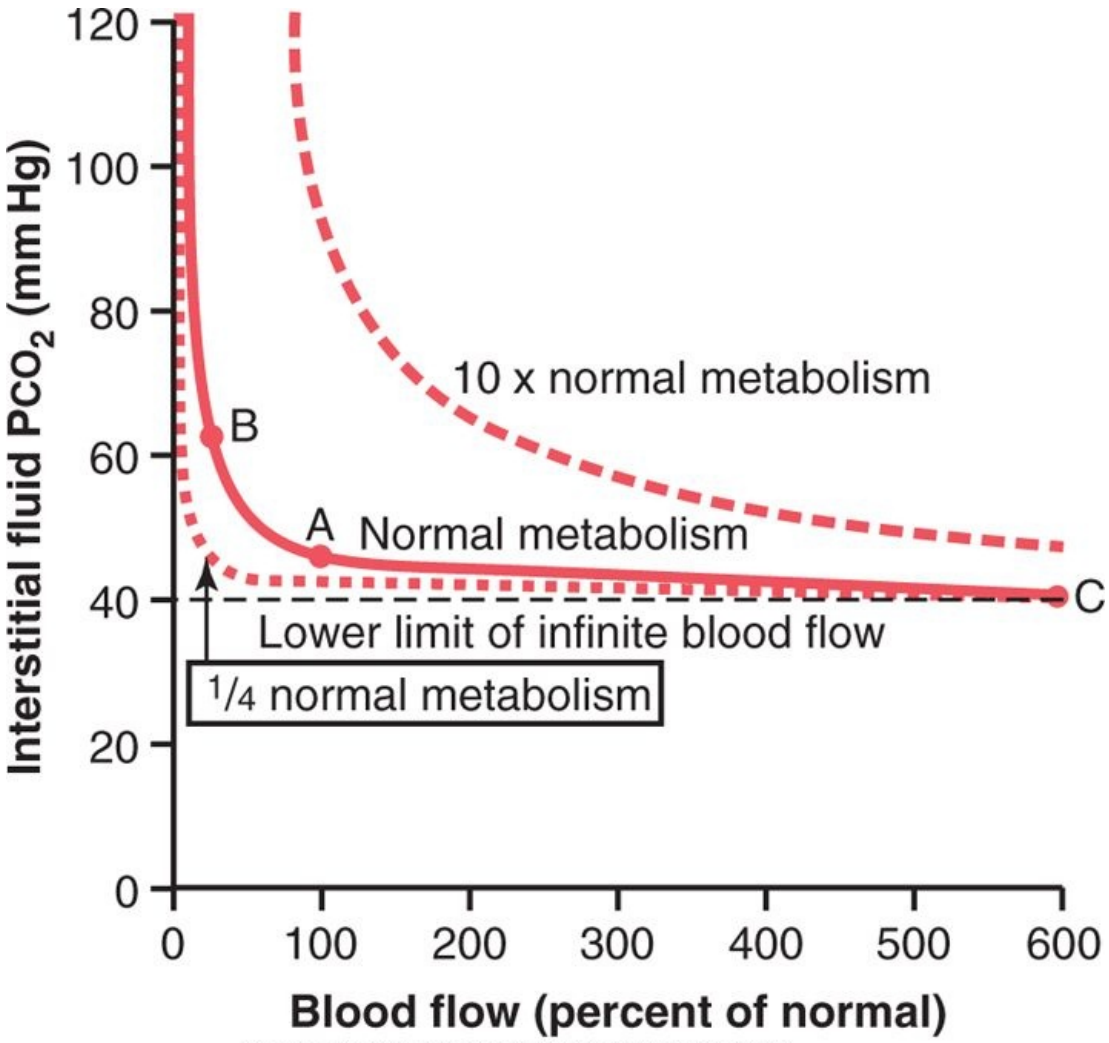

Figure 40-7 Effect of blood flow and metabolic rate on peripheral tissue P_{CO_2}.

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 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*.

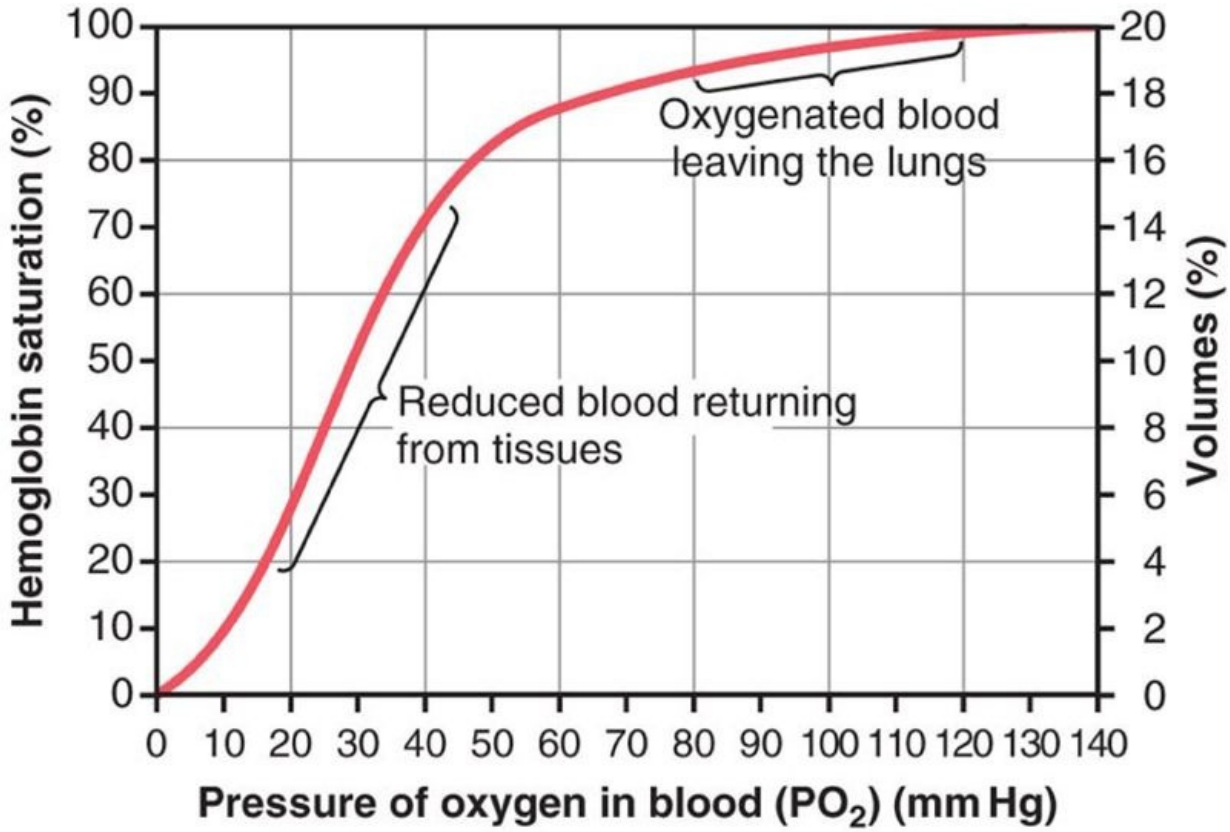

Figure 40-8 Oxygen-hemoglobin dissociation curve.

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

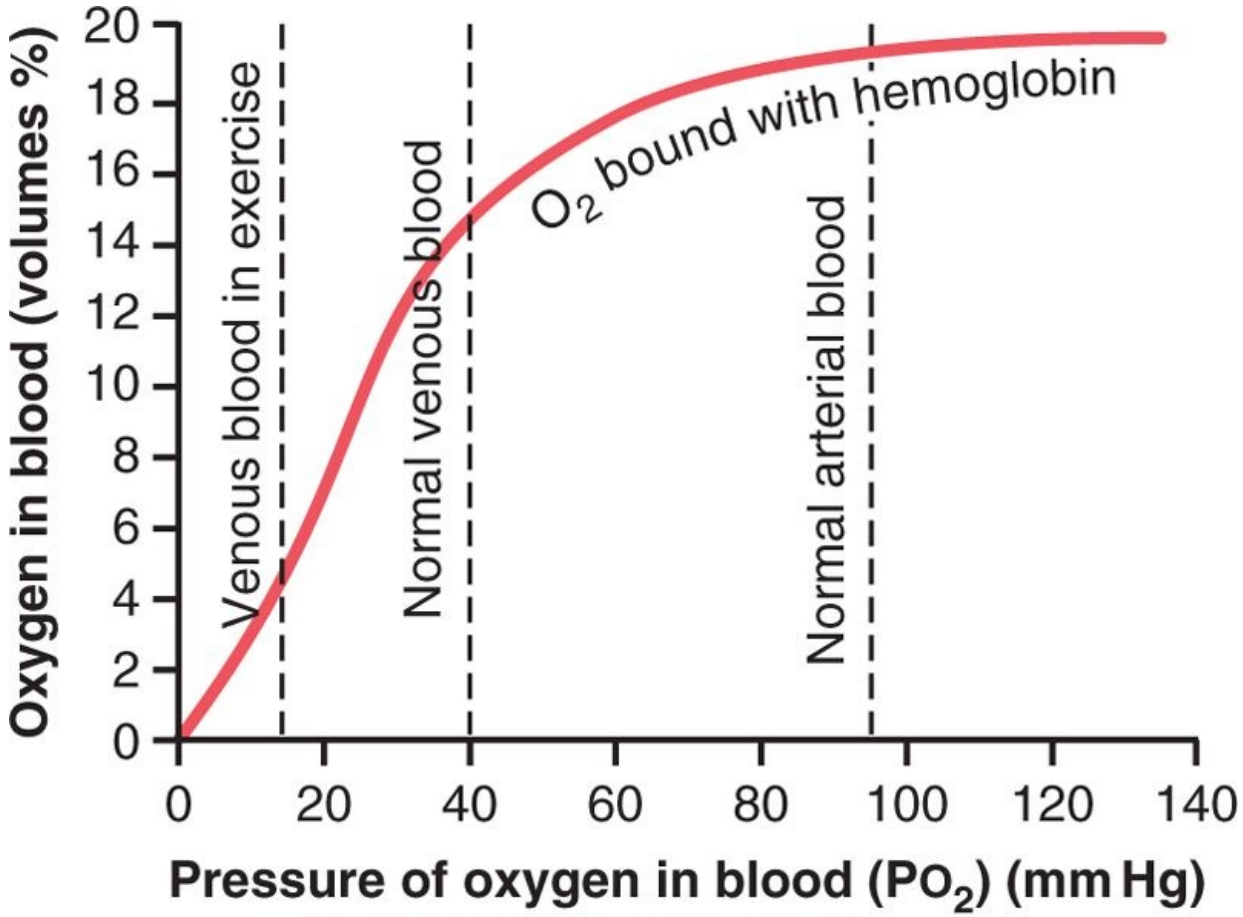

Figure 40-9 Effect of blood PO_2 on the quantity of oxygen bound with hemoglobin in each 100 milliliters of blood.

During heavy exercise, 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, 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

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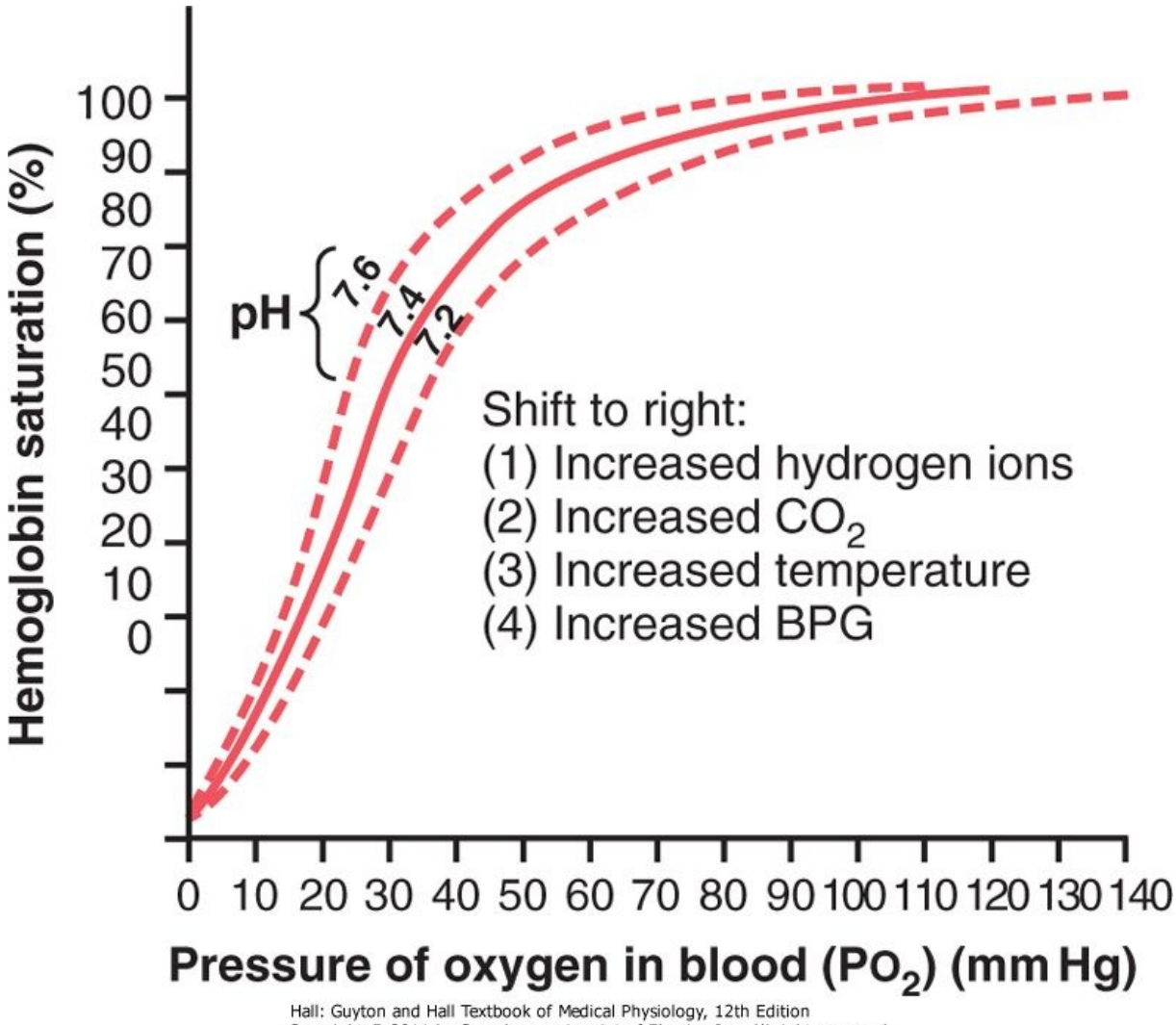

Figure 40-10 Shift of the oxygen-hemoglobin dissociation curve to the right caused by an increase in hydrogen ion concentration (decrease in pH). BPG, 2,3-biphosphoglycerate.

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 mechanism 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.

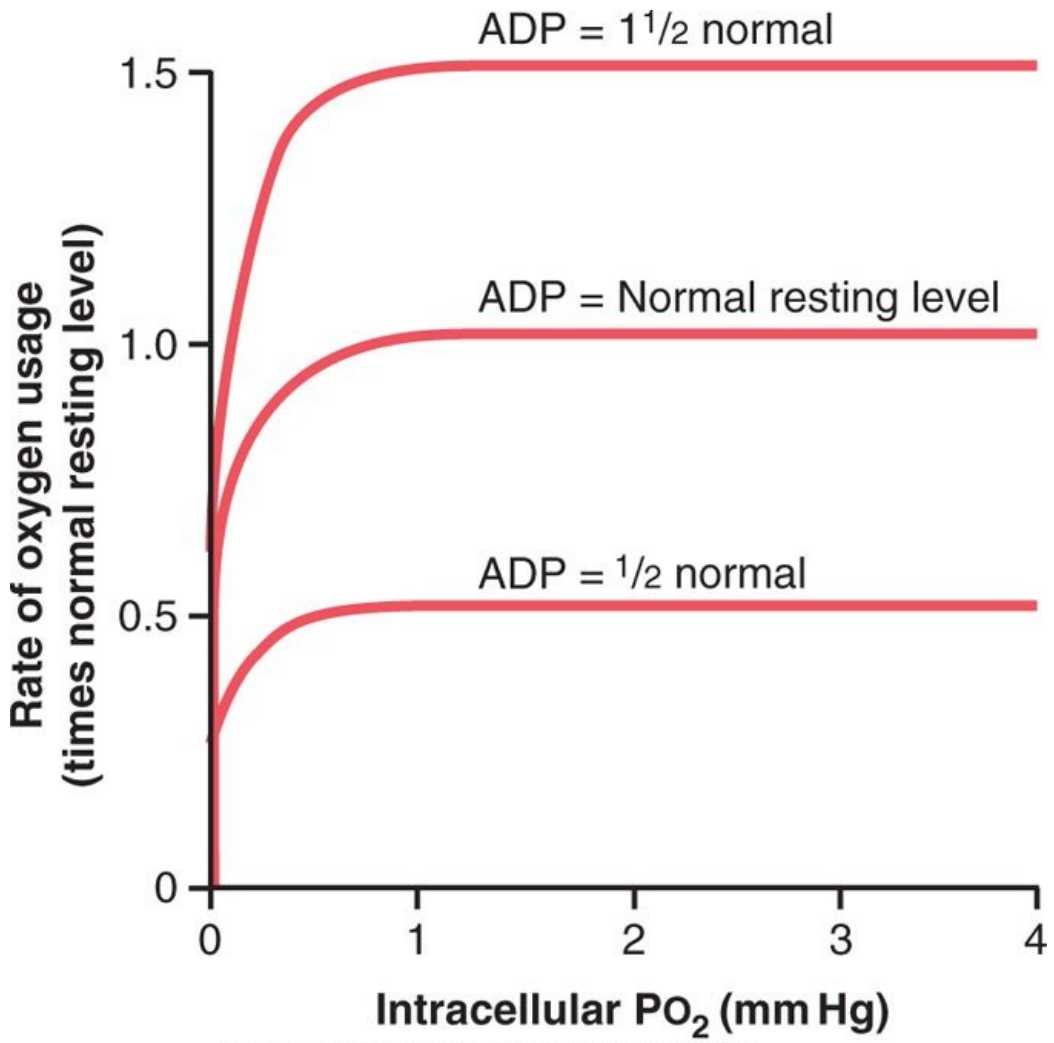

Figure 40-11 Effect of intracellular adenosine diphosphate (ADP) and P_{O_2} on rate of oxygen usage by the cells. Note that as long as the intracellular P_{O_2} remains above 1 mm Hg, the controlling factor for the rate of oxygen usage is the intracellular concentration of ADP.

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 breathing of oxygen among deep-sea divers.

Combination of Hemoglobin with Carbon Monoxide-Displacement of Oxygen

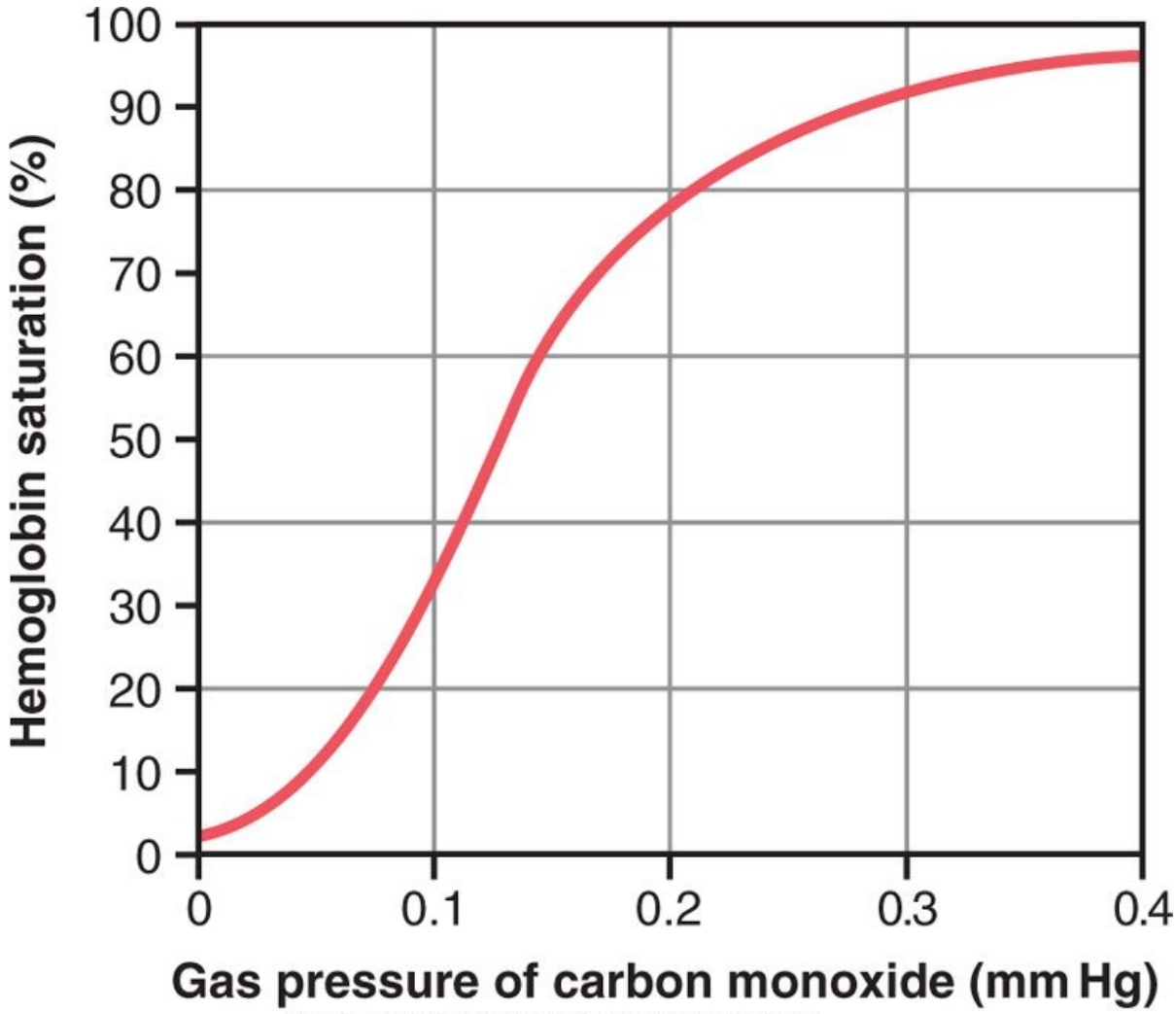

Figure 40-12 Carbon monoxide-hemoglobin dissociation curve. Note the extremely low carbon monoxide pressures at which carbon monoxide combines with hemoglobin.

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page 502

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 1/250 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, 1/250 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

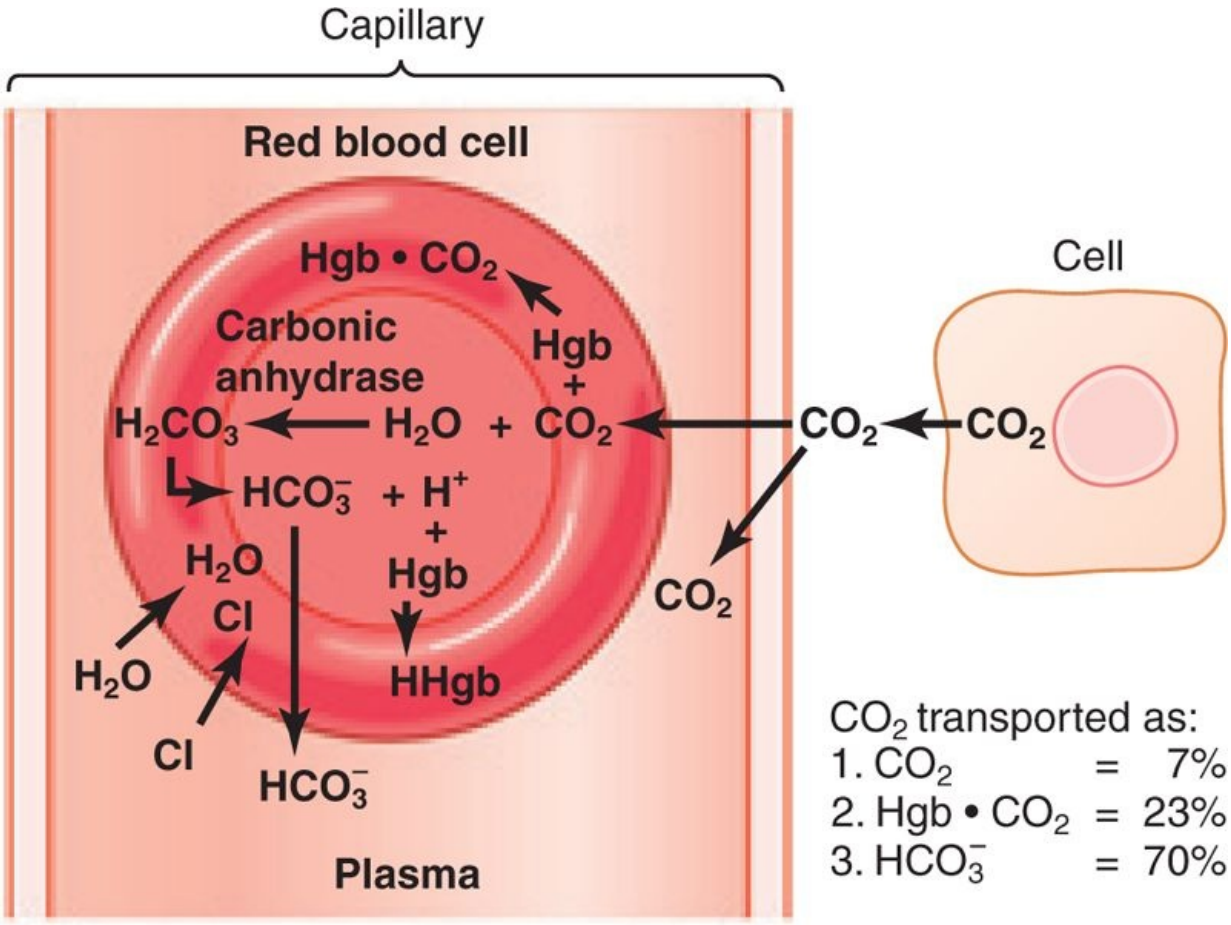

Figure 40-13 Transport of carbon dioxide in the blood.

Asmall 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 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.

Asmall 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 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.

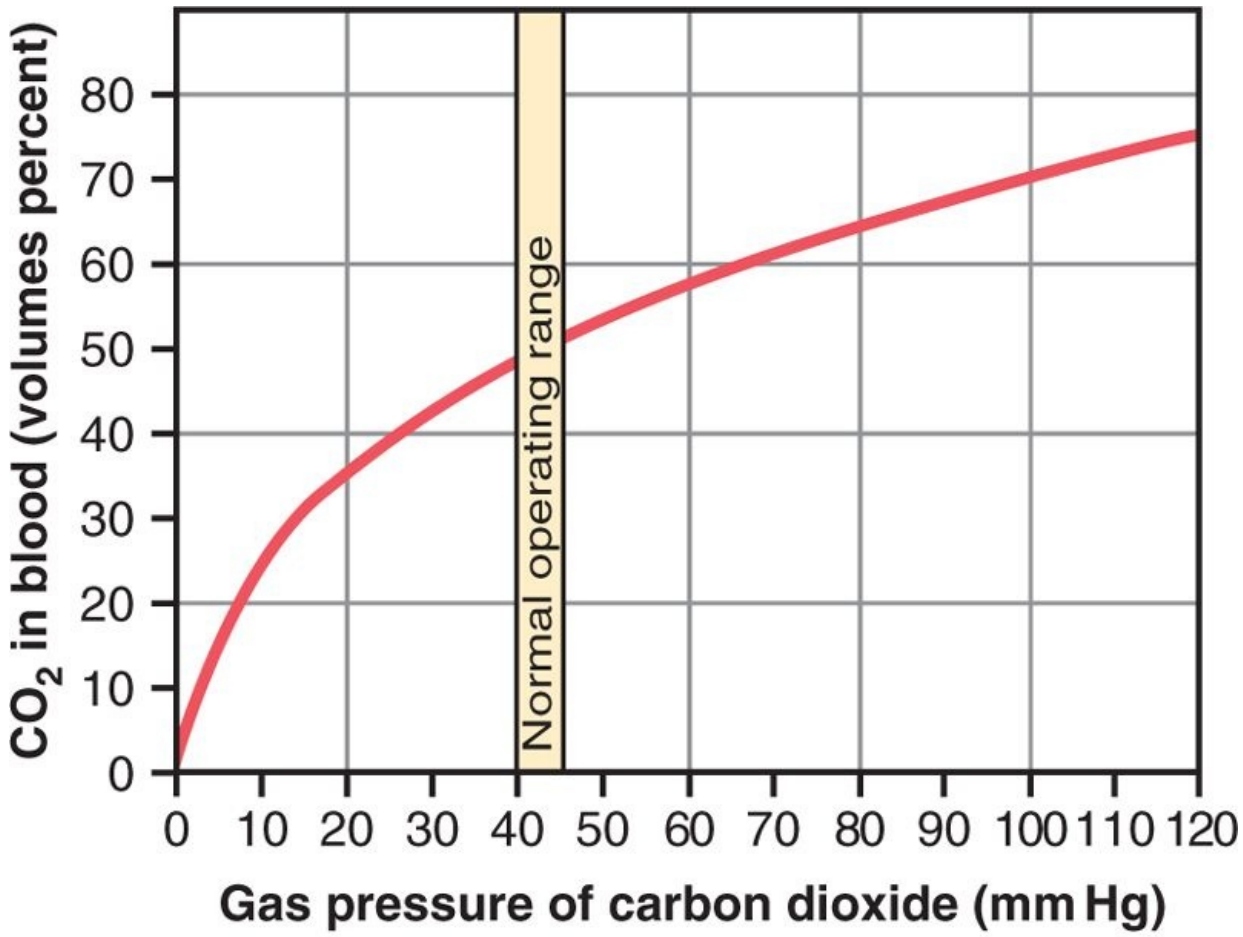

Figure 40-14 Carbon dioxide dissociation curve.

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.

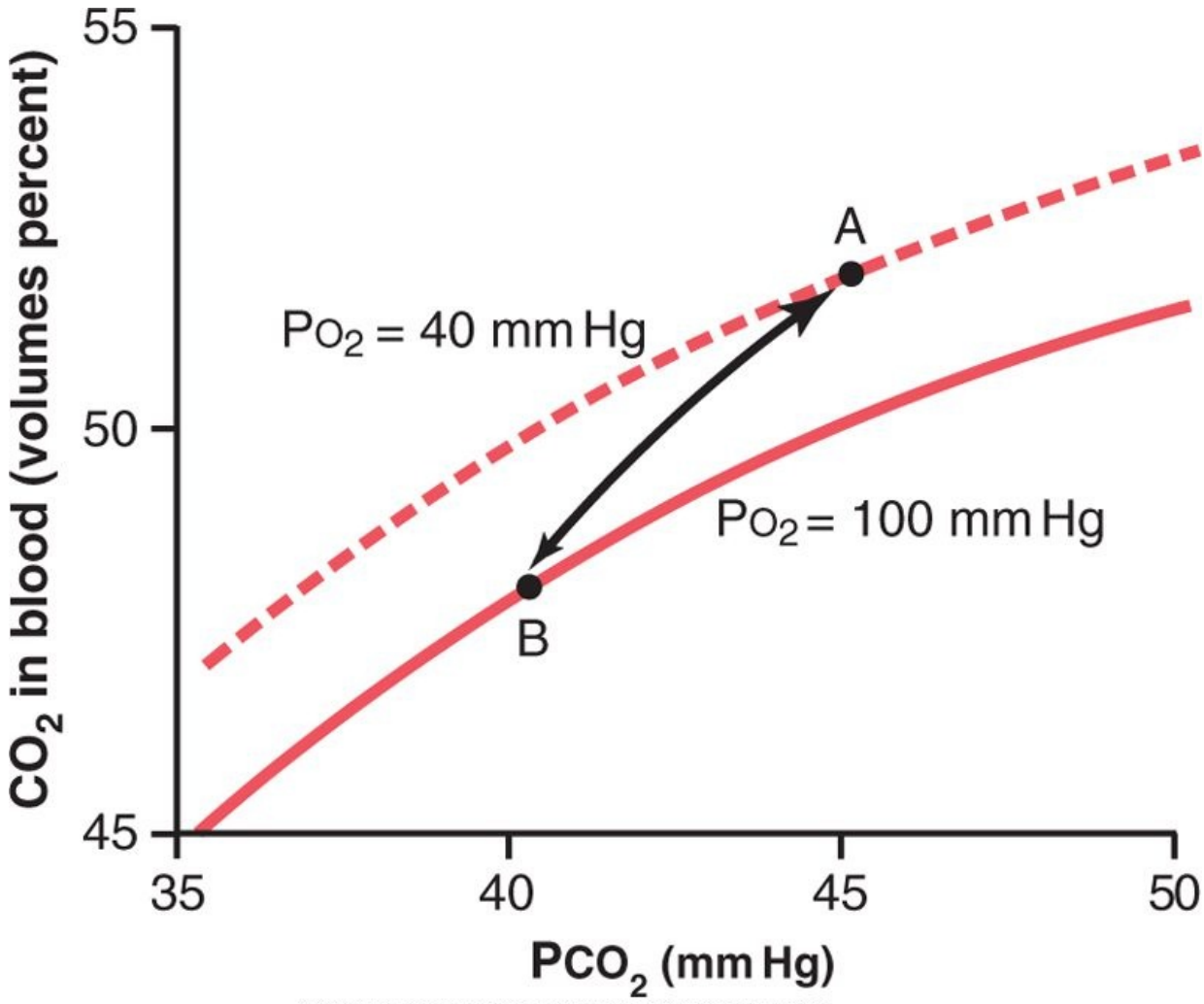

Figure 40-15 Portions of the carbon dioxide dissociation curve when the P_{O_2} is 100 mm Hg or 40 mm Hg. The arrow represents the Haldane effect on the transport of carbon dioxide, as discussed in the text.

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

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

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,

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.) 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.

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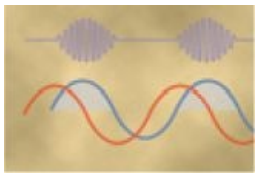
41 Regulation of Respiration



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

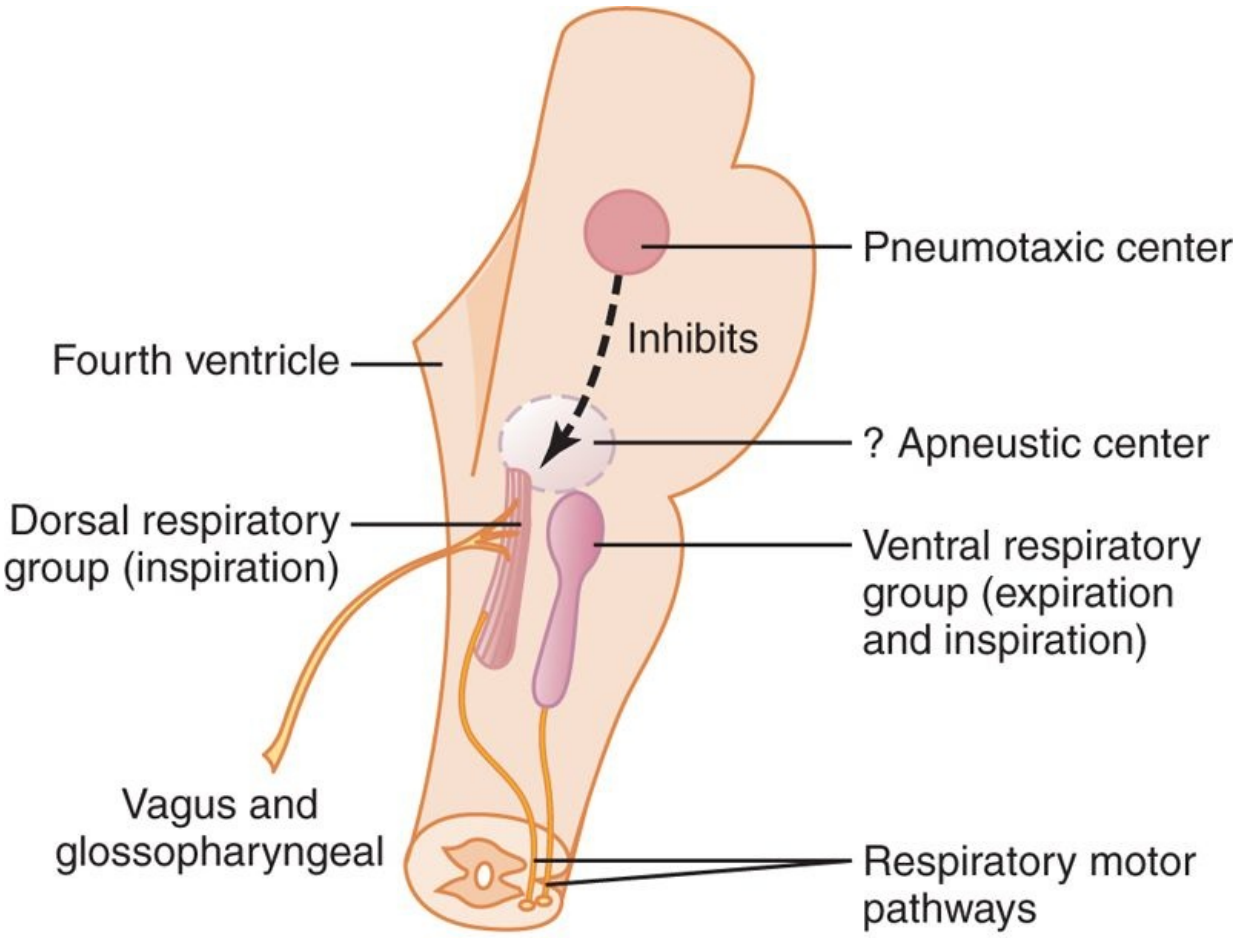


Figure 41-1 Organization of the respiratory center.

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

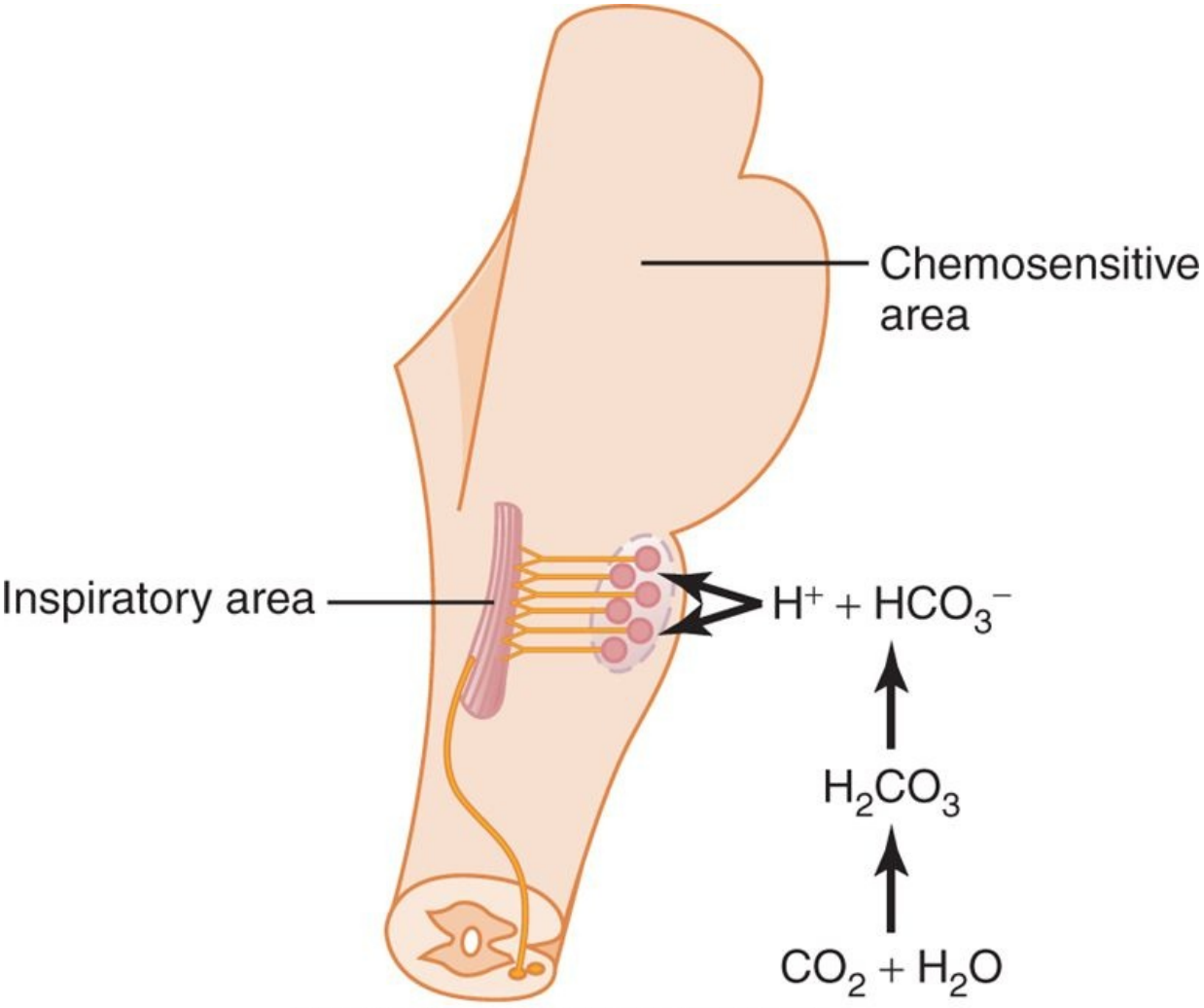


Figure 41-2 Stimulation of the *brain stem inspiratory* area by signals from the *chemosensitive area* located bilaterally in the medulla, lying only a fraction of a millimeter beneath the ventral medullary surface. Note also that hydrogen ions stimulate the chemosensitive area, but carbon dioxide in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

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.

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).

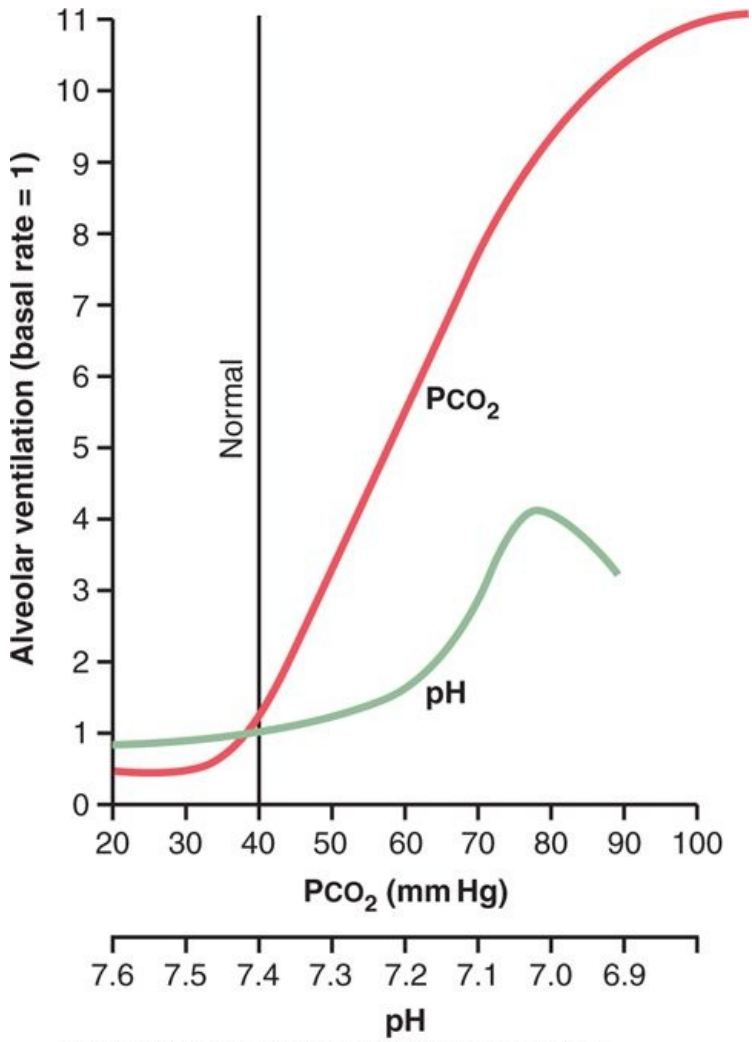


Figure 41-3 Effects of increased arterial blood P_{CO_2} and decreased arterial pH (increased hydrogen ion concentration) on the rate of alveolar ventilation.

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.

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.

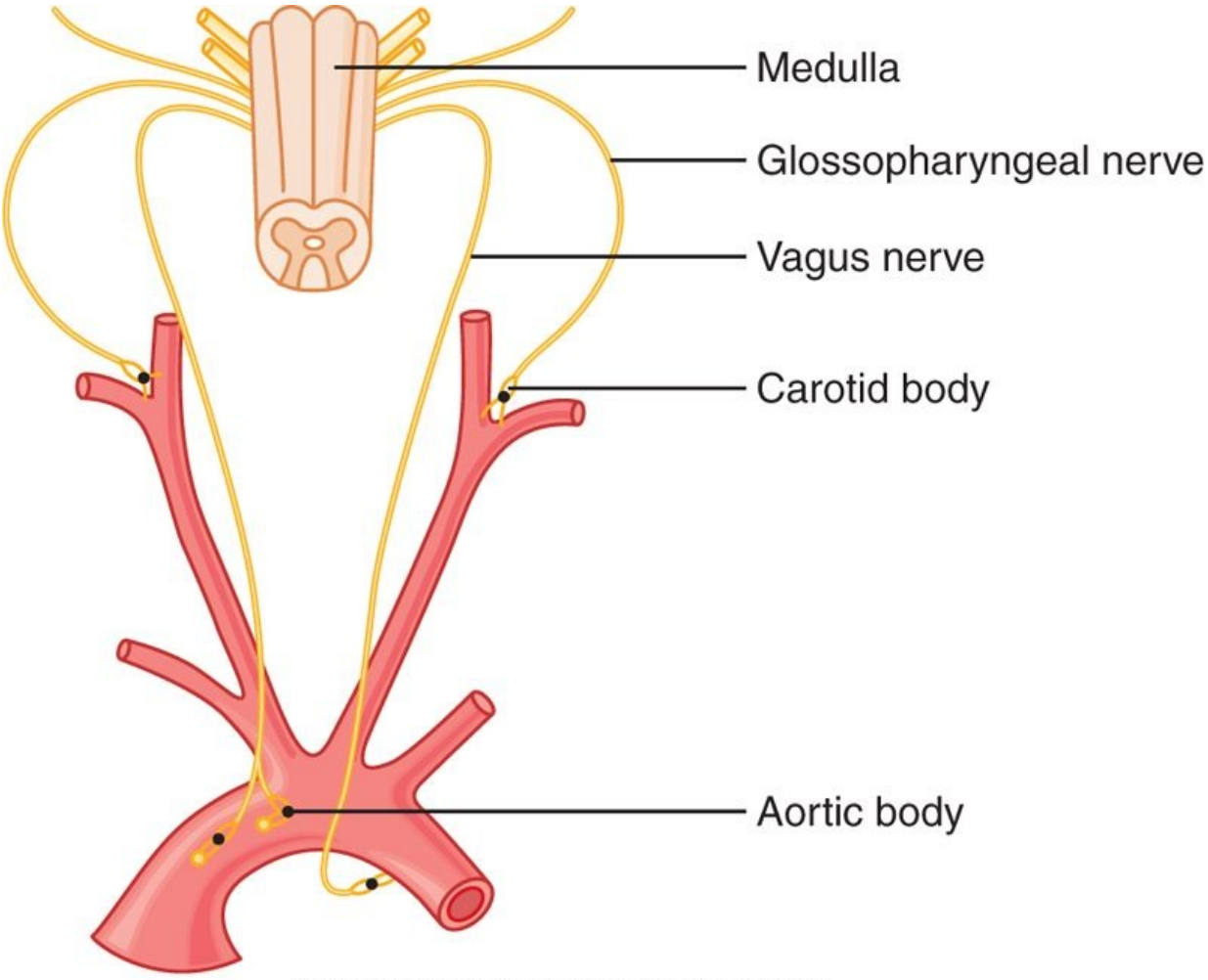


Figure 41-4 Respiratory control by peripheral chemoreceptors in the carotid and aortic bodies.

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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.

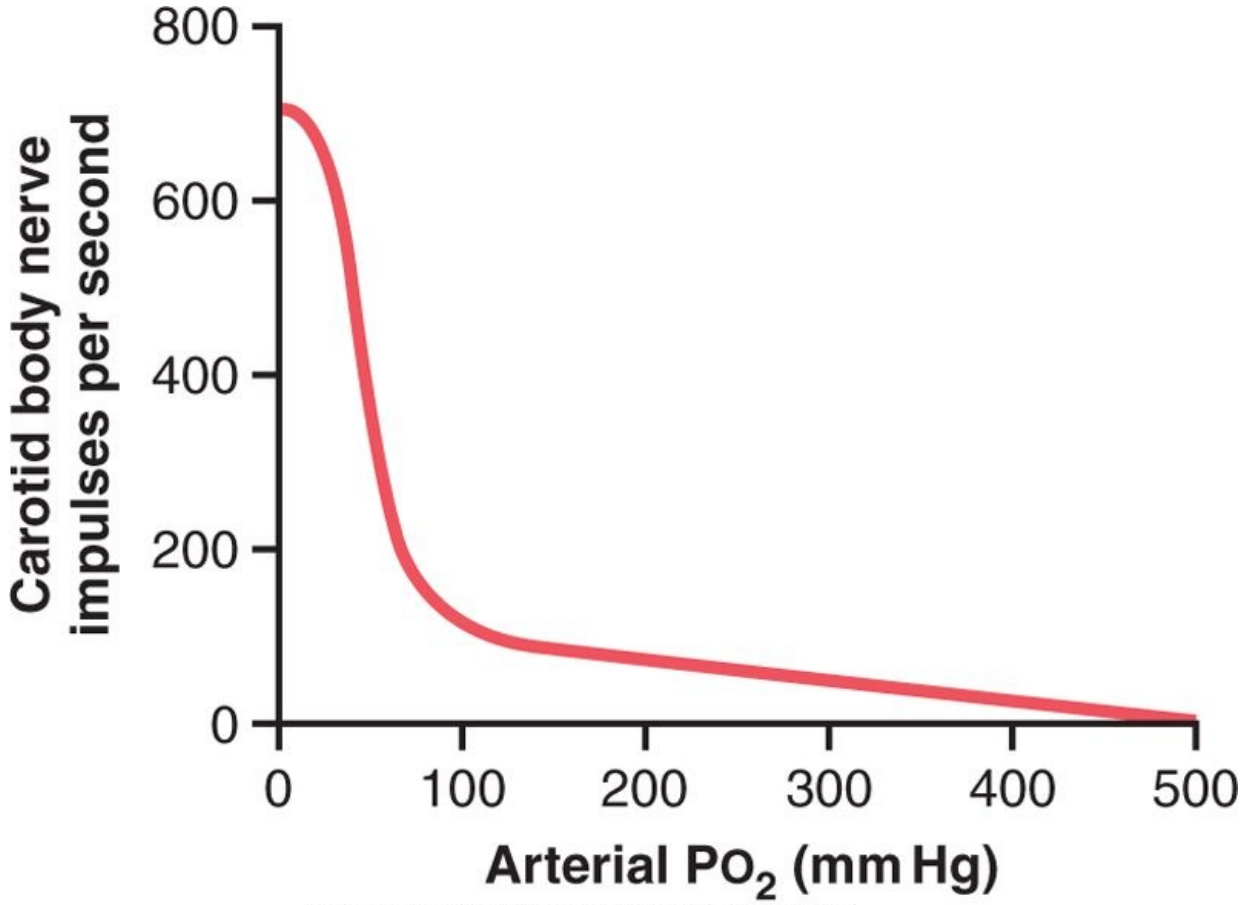

Figure 41-5 Effect of arterial P_{O_2} on impulse rate from the carotid body.

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.

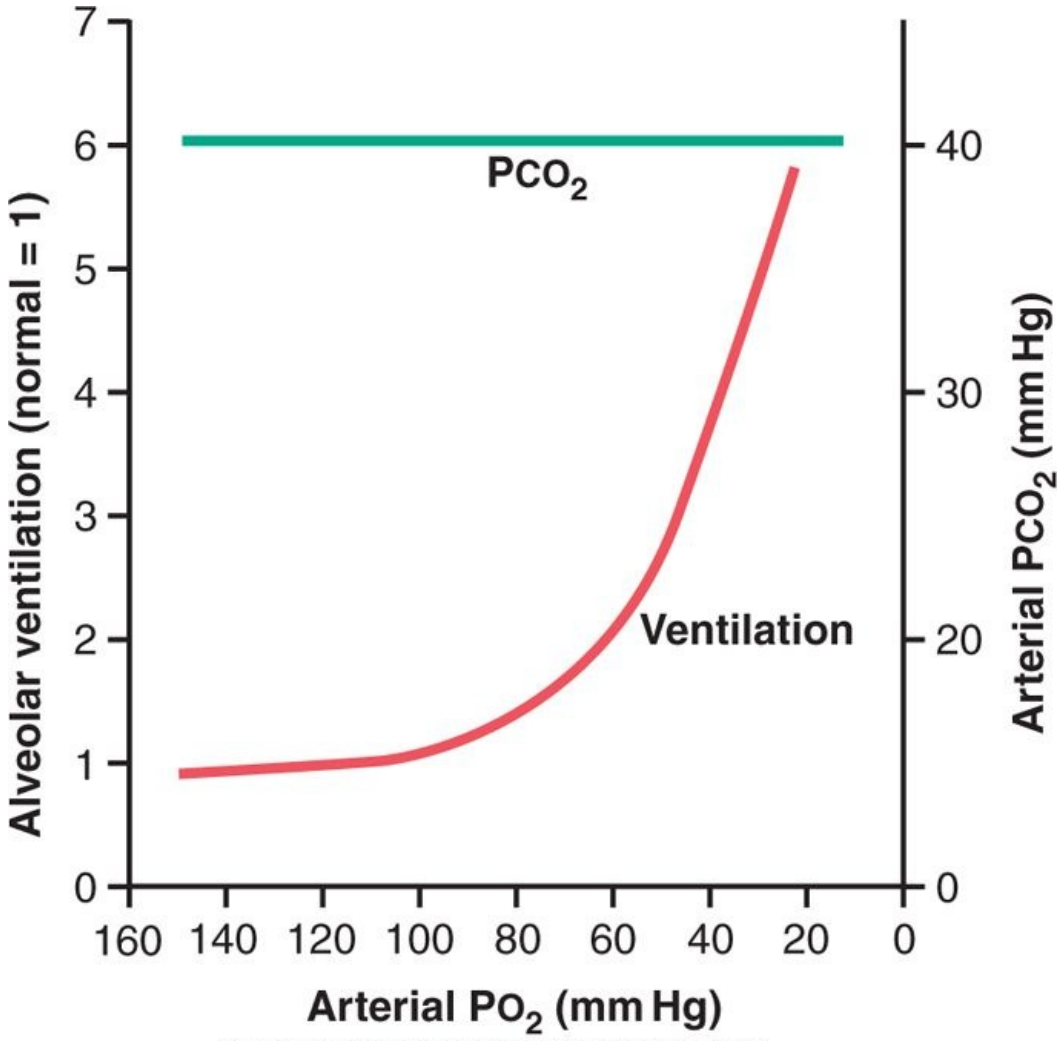

Figure 41-6 The lower curve demonstrates the effect of different levels of arterial P_{O_2} on alveolar ventilation, showing a sixfold increase in ventilation as the P_{O_2} decreases from the normal level of 100 mm Hg to 20 mm Hg. The upper line shows that the arterial P_{CO_2} was kept at a constant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

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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.

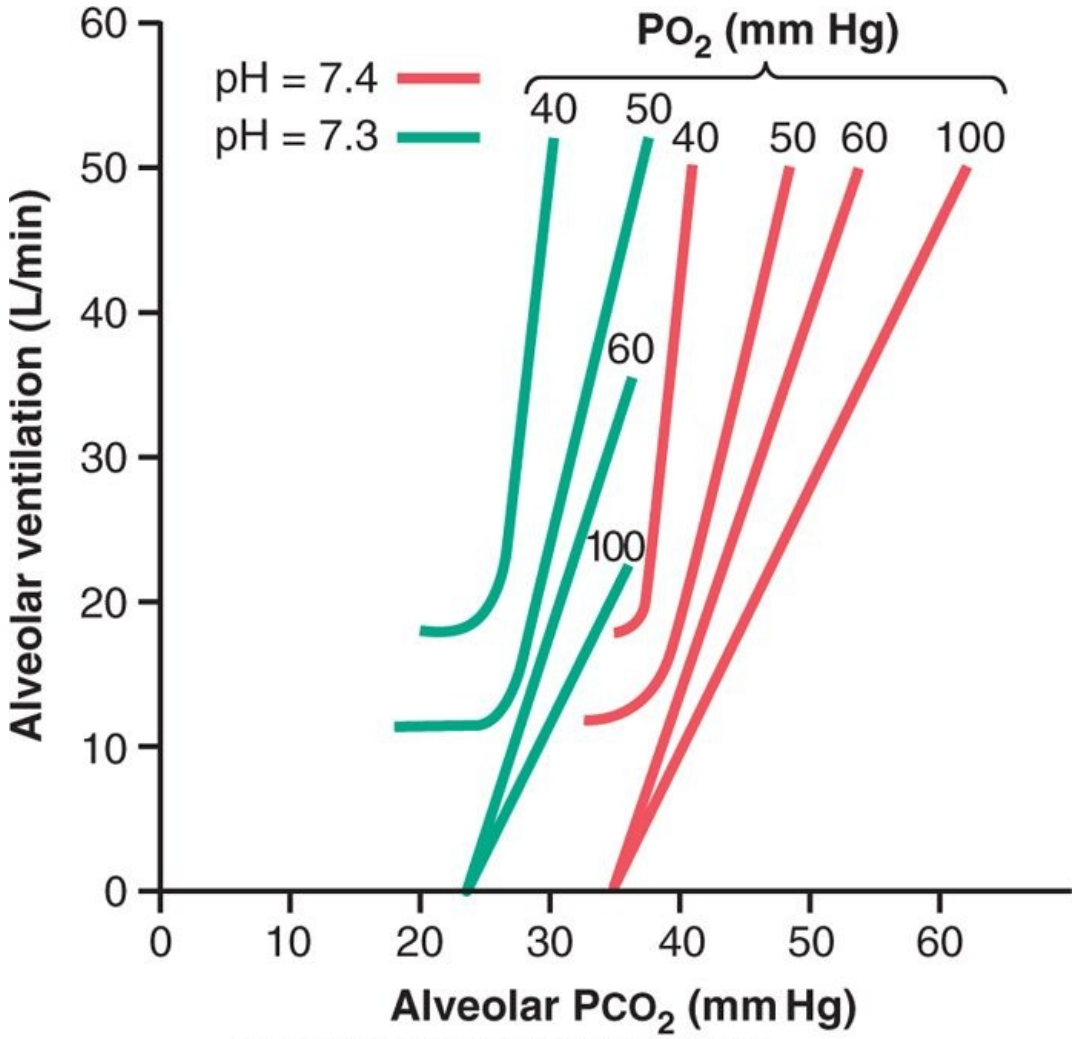

Figure 41-7 Composite diagram showing the interrelated effects of P_{CO_2}, P_{O_2}, and pH on alveolar ventilation. (Drawn from data in Cunningham DJC, Lloyd BB: The Regulation of Human Respiration. Oxford: Blackwell Scientific Publications, 1963.)

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.

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9 Cardiac Muscle; The Heart as a Pump and Function of the Heart Valves

With this chapter we begin discussion of the heart and circulatory system. The heart, shown in Figure 9-1, is actually two separate pumps: a *right heart* that pumps blood through the lungs, and a *left heart* that pumps blood through the peripheral organs. In turn, each of these hearts is a pulsatile two-chamber pump composed of an *atrium* and a *ventricle.* Each atrium is a weak primer pump for the ventricle, helping to move blood into the ventricle. The ventricles then supply the main pumping force that propels the blood either (1) through the pulmonary circulation by the right ventricle or (2) through the peripheral circulation by the left ventricle.

Special mechanisms in the heart cause a continuing succession of heart contractions called *cardiac rhythmicity,* transmitting action potentials throughout the cardiac muscle to cause the heart's rhythmical beat. This rhythmical control system is explained in Chapter 10. In this chapter, we explain how the heart operates as a pump, beginning with the special features of cardiac muscle itself.

Physiology of Cardiac Muscle

The heart is composed of three major types of cardiac muscle: *atrial muscle, ventricular muscle,* and specialized *excitatory* and *conductive muscle* fibers. The atrial and ventricular types of muscle contract in much the same way as skeletal muscle, except that the duration of contraction is much longer. The specialized excitatory and conductive fibers, however, contract only feebly because they contain few contractile fibrils; instead, they exhibit either automatic rhythmical electrical discharge in the form of action potentials or conduction of the action potentials through the heart, providing an excitatory system that controls the rhythmical beating of the heart.

Physiologic Anatomy of Cardiac Muscle

Figure 9-2 shows the histology of cardiac muscle, demonstrating cardiac muscle fibers arranged in a latticework, with the fibers dividing, recombining, and then spreading again. One also notes immediately from this figure that cardiac muscle is *striated* in the same manner as in skeletal muscle. Further, cardiac muscle has typical myofibrils that contain *actin* and *myosin filaments* almost identical to those found in skeletal muscle; these filaments lie side by side and slide along one another during contraction in the same manner as occurs in skeletal muscle (see Chapter 6). But in other ways, cardiac muscle is quite different from skeletal muscle, as we shall see.

Cardiac Muscle as a Syncytium

The dark areas crossing the cardiac muscle fibers in Figure 9-2 are called *intercalated discs;* they are actually cell membranes that separate individual cardiac muscle cells from one another. That is, cardiac muscle fibers are made up of many individual cells connected in series and in parallel with one another.

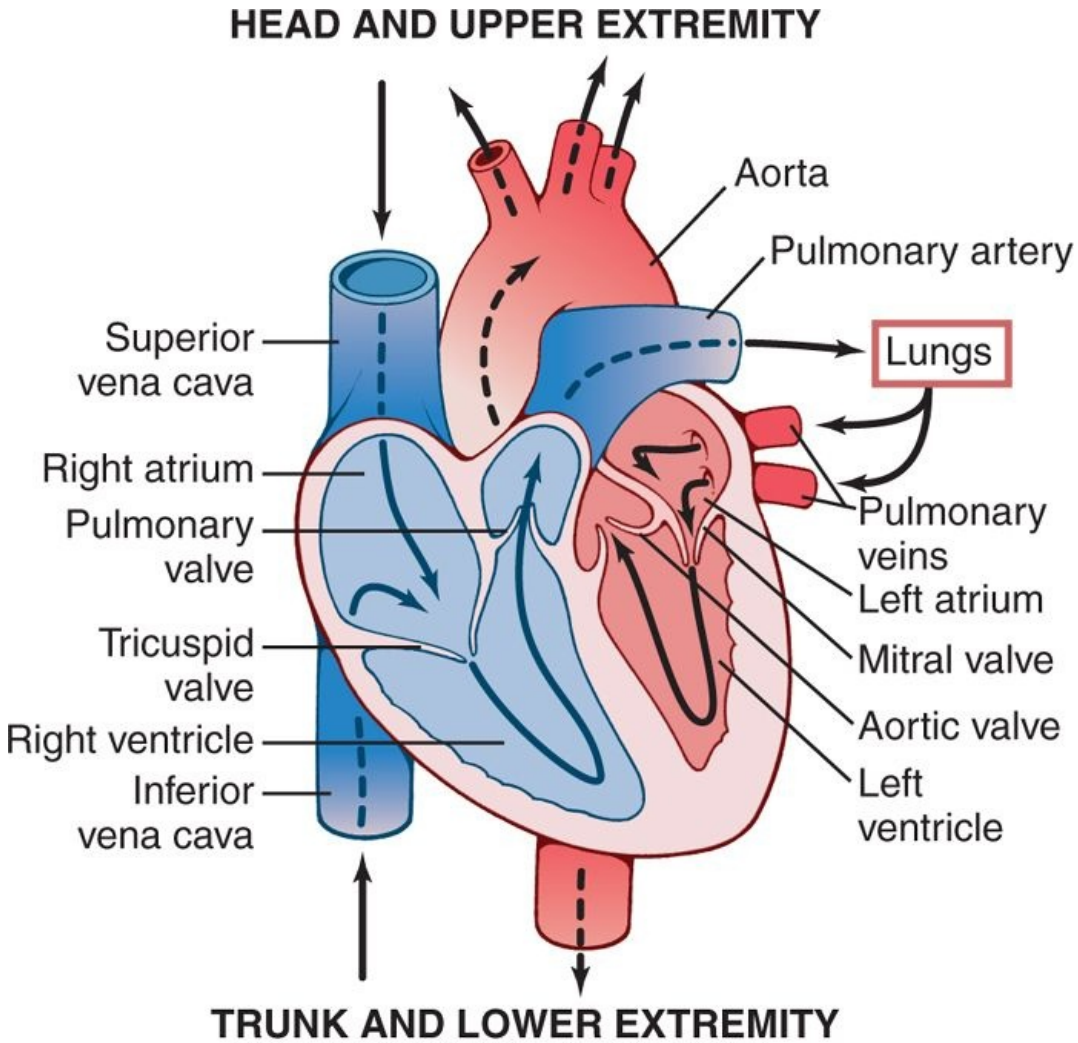

Figure 9-1 Structure of the heart, and course of blood flow through the heart chambers and heart valves.

Figure 9-2 "Syncytial," interconnecting nature of cardiac muscle fibers.

At each intercalated disc the cell membranes fuse with one another in such a way that they form permeable "communicating" junctions (gap junctions) that allow rapid diffusion of ions. Therefore, from a functional point of view, ions move with ease in the intracellular fluid along the longitudinal axes of the cardiac muscle fibers so that action potentials travel easily from one cardiac muscle cell to the next, past the intercalated discs. Thus, cardiac muscle is a *syncytium* of many heart muscle cells in which the cardiac cells are so interconnected that when one of these cells becomes excited, the action potential spreads to all of them, from cell to cell throughout the latticework interconnections.

The heart actually is composed of two syncytiums: the *atrial syncytium,* which constitutes the walls of the two atria, and the *ventricular syncytium,* which constitutes the walls of the two ventricles. The atria are separated from the ventricles by fibrous tissue that surrounds the atrioventricular (A-V) valvular openings between the atria and ventricles. Normally, potentials are not conducted from the atrial syncytium into the ventricular syncytium directly through this fibrous tissue. Instead, they are conducted only by way of a specialized conductive system called the *A-V bundle,* a bundle of conductive fibers several millimeters in diameter that is discussed in detail in Chapter 10.

This division of the muscle of the heart into two functional syncytiums allows the atria to contract a short time ahead of ventricular contraction, which is important for effectiveness of heart pumping.

Action Potentials in Cardiac Muscle

The *action potential* recorded in a ventricular muscle fiber, shown in Figure 9-3, averages about 105 millivolts, which means that the intracellular potential rises from a very negative value, about -85 millivolts, between beats to a slightly positive value, about +20 millivolts, during each beat. After the initial *spike,* the membrane remains depolarized for about 0.2 second, exhibiting a *plateau* as shown in the figure, followed at the end of the plateau by abrupt repolarization. The presence of this plateau in the action potential causes ventricular contraction to last as much as 15 times as long in cardiac muscle as in skeletal muscle.

What Causes the Long Action Potential and the Plateau?

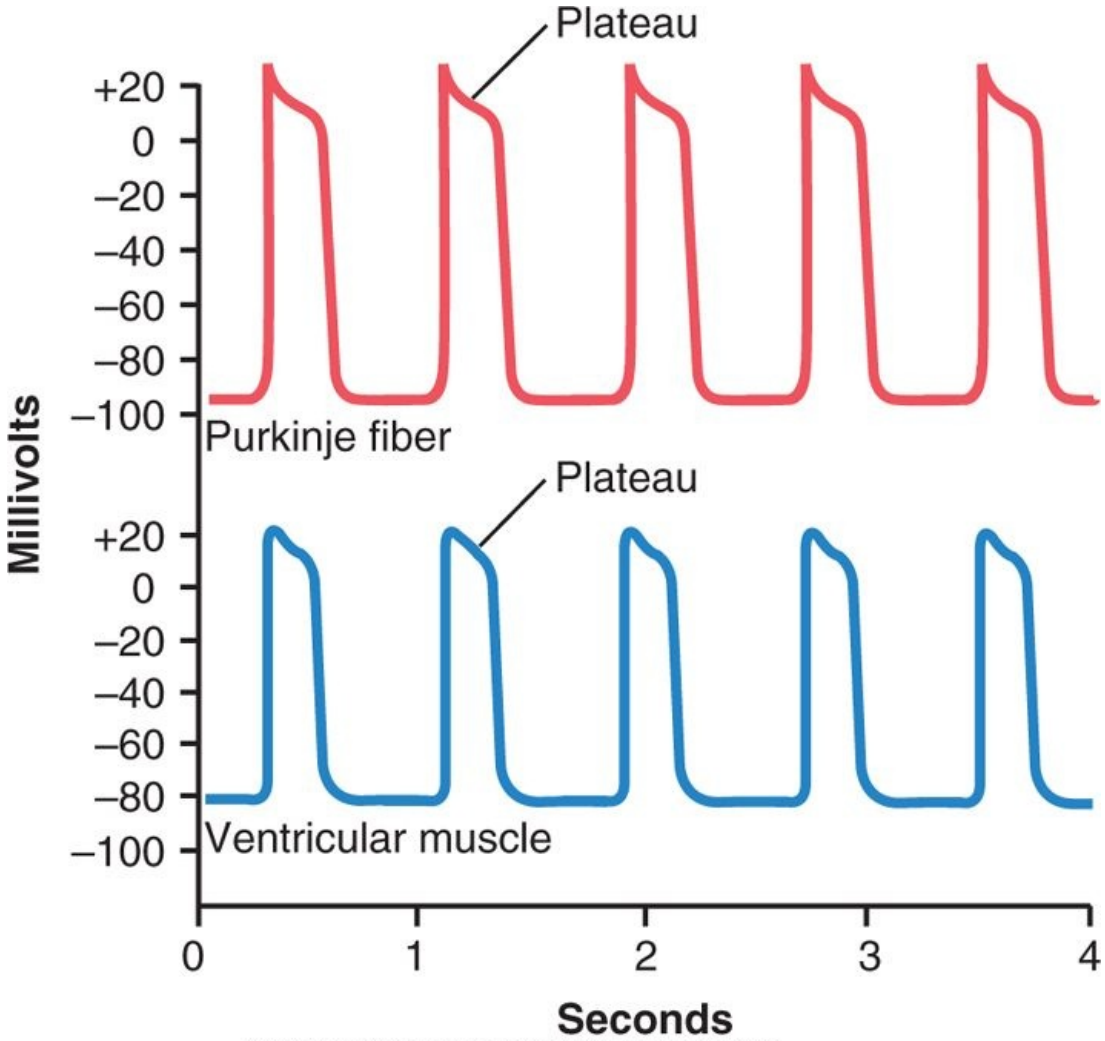

Figure 9-3 Rhythmical action potentials (in millivolts) from a Purkinje fiber and from a ventricular muscle fiber, recorded by means of microelectrodes.

At this point, we address the questions: Why is the action potential of cardiac muscle so long and why does it have a plateau, whereas that of skeletal muscle does not? The basic biophysical answers to these questions were presented in Chapter 5, but they merit summarizing here as well.

At least two major differences between the membrane properties of cardiac and skeletal muscle account for the prolonged action potential and the plateau in cardiac muscle. First, the *action potential of skeletal muscle* is caused almost entirely by sudden opening of large numbers of so-called *fast sodium channels* that allow tremendous numbers of sodium ions to enter the skeletal muscle fiber from the extracellular fluid. These channels are called "fast" channels because they remain open for only a few thousandths of a second and then abruptly close. At the end of this closure, repolarization occurs, and the action potential is over within another thousandth of a second or so.

In *cardiac muscle, the action potential* is caused by opening of two types of channels: (1) the same *fast sodium channels* as those in skeletal muscle and (2) another entirely different population of *slow calcium channels,* which are also called *calcium-sodium channels*. This second population of channels differs from the fast sodium channels in that they are slower to open and, even more important, remain open for several tenths of a second. During this time, a large quantity of both calcium and sodium ions flows through these channels to the interior of the cardiac muscle fiber, and this maintains a prolonged period of depolarization, *causing the plateau* in the action potential. Further, the calcium ions that enter during this plateau phase activate the muscle contractile process, while the calcium ions that cause skeletal muscle contraction are derived from the intracellular sarcoplasmic reticulum.

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The second major functional difference between cardiac muscle and skeletal muscle that helps account for both the prolonged action potential and its plateau is this: Immediately after the onset of the action potential, the permeability of the cardiac muscle membrane for potassium ions *decreases* about fivefold, an effect that does not occur in skeletal muscle. This decreased potassium permeability may result from the excess calcium influx through the calcium channels just noted. Regardless of the cause, the decreased potassium permeability greatly decreases the outflux of positively charged potassium ions during the action potential plateau and thereby prevents early return of the action potential voltage to its resting level. When the slow calcium-sodium channels do close at the end of 0.2 to 0.3 second and the influx of calcium and sodium ions ceases, the membrane permeability for potassium ions also increases rapidly, this rapid loss of potassium from the fiber immediately returns the membrane potential to its resting level, thus ending the action potential.

Integration link: Calcium channel blockers

Taken from Clinical Pharmacology 10E

Velocity of Signal Conduction in Cardiac Muscle

The velocity of conduction of the excitatory action potential signal along both *atrial and ventricular muscle fibers* is about 0.3 to 0.5 m/sec, or about 1/250 the velocity in very large nerve fibers and about 1/10 the velocity in skeletal muscle fibers. The velocity of conduction in the specialized heart conductive system-in the *Purkinje fibers*-is as great as 4 m/sec in most parts of the system, which allows reasonably rapid conduction of the excitatory signal to the different parts of the heart, as explained in Chapter 10.

Refractory Period of Cardiac Muscle

Cardiac muscle, like all excitable tissue, is refractory to restimulation during the action potential. Therefore, the refractory period of the heart is the interval of time, as shown to the left in Figure 9-4, during which a normal cardiac impulse cannot re-excite an already excited area of cardiac muscle. The normal refractory period of the ventricle is 0.25 to 0.30 second, which is about the duration of the prolonged plateau action potential. There is an additional *relative refractory period* of about 0.05 second during which the muscle is more difficult than normal to excite but nevertheless can be excited by a very strong excitatory signal, as demonstrated by the early "premature" contraction in the second example of Figure 9-4. The refractory period of atrial muscle is much shorter than that for the ventricles (about 0.15 second for the atria compared with 0.25 to 0.30 second for the ventricles).

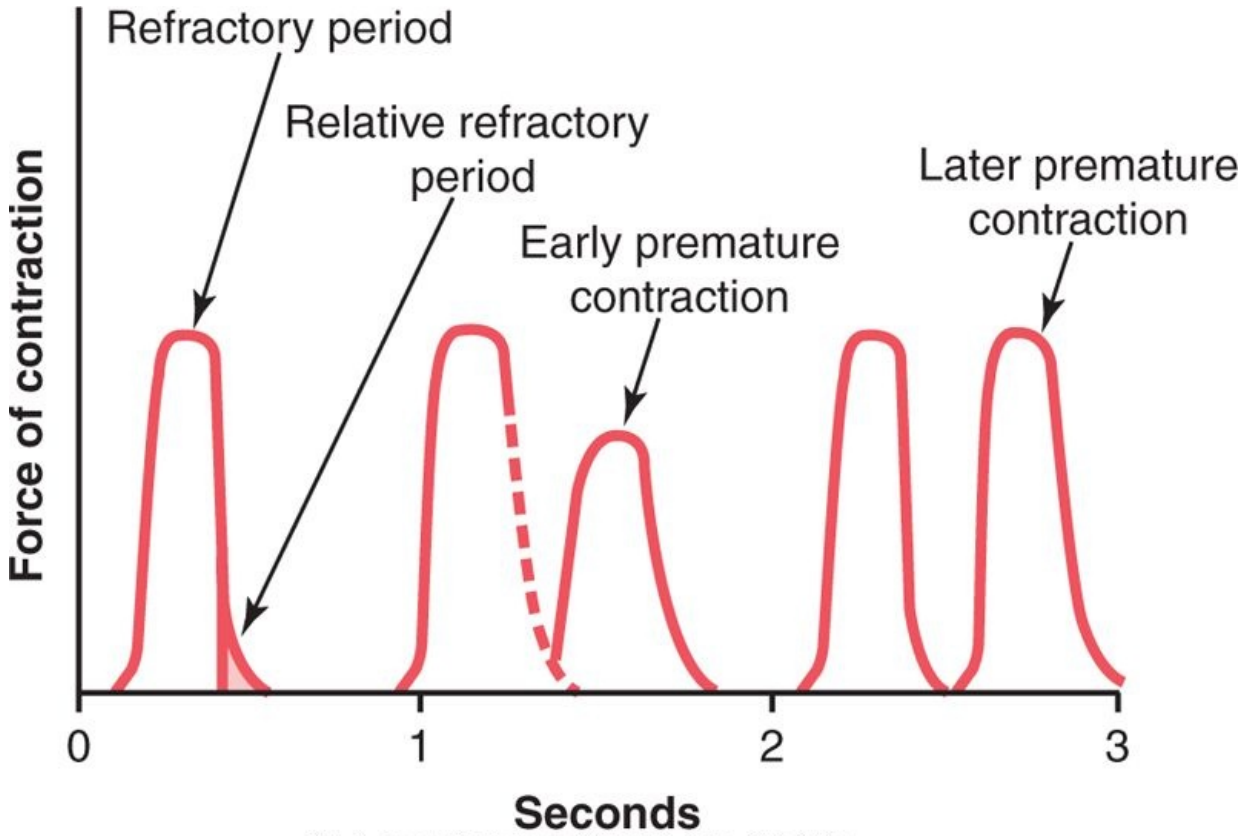

Figure 9-4 Force of ventricular heart muscle contraction, showing also duration of the refractory period and relative refractory period, plus the effect of premature contraction. Note that premature contractions do not cause wave summation, as occurs in skeletal muscle.

Excitation-Contraction Coupling-Function of Calcium Ions and the *Transverse Tubules*

The term "excitation-contraction coupling" refers to the mechanism by which the action potential causes the myofibrils of muscle to contract. This was discussed for skeletal muscle in Chapter 7. Once again, there are differences in this mechanism in cardiac muscle that have important effects on the characteristics of heart muscle contraction.

As is true for skeletal muscle, when an action potential passes over the cardiac muscle membrane, the action potential spreads to the interior of the cardiac muscle fiber along the membranes of the transverse (T) tubules. The T tubule action potentials in turn act on the membranes of the *longitudinal sarcoplasmic tubules* to cause release of calcium ions into the muscle sarcoplasm from the sarcoplasmic reticulum. In another few thousandths of a second, these calcium ions diffuse into the myofibrils and catalyze the chemical reactions that promote sliding of the actin and myosin filaments along one another; this produces the muscle contraction.

Thus far, this mechanism of excitation-contraction coupling is the same as that for skeletal muscle, but there is a second effect that is quite different. In addition to the calcium ions that are released into the sarcoplasm from the cisternae of the sarcoplasmic reticulum, calcium ions also diffuse into the sarcoplasm from the T tubules themselves at the time of the action potential, which opens voltage-dependent calcium channels in the membrane of the T tubule (Figure 9-5). Calcium entering the cell then activates *calcium release channels,* also called *ryanodine receptor channels,* in the sarcoplasmic reticulum membrane, triggering the release of calcium into the sarcoplasm. Calcium ions in the sarcoplasm then interact with troponin to initiate cross-bridge formation and contraction by the same basic mechanism as described for skeletal muscle in Chapter 6.

Without the calcium from the T tubules, the strength of cardiac muscle contraction would be reduced considerably because the sarcoplasmic reticulum of cardiac muscle is less well developed than that of skeletal muscle and does not store enough calcium to provide full contraction. The T tubules of cardiac muscle, however, have a diameter 5 times as great as that of the skeletal muscle tubules, which means a volume 25 times as great. Also, inside the T tubules is a large quantity of mucopolysaccharides that are electronegatively charged and bind an abundant store of calcium ions, keeping these always available for diffusion to the interior of the cardiac muscle fiber when a T tubule action potential appears.

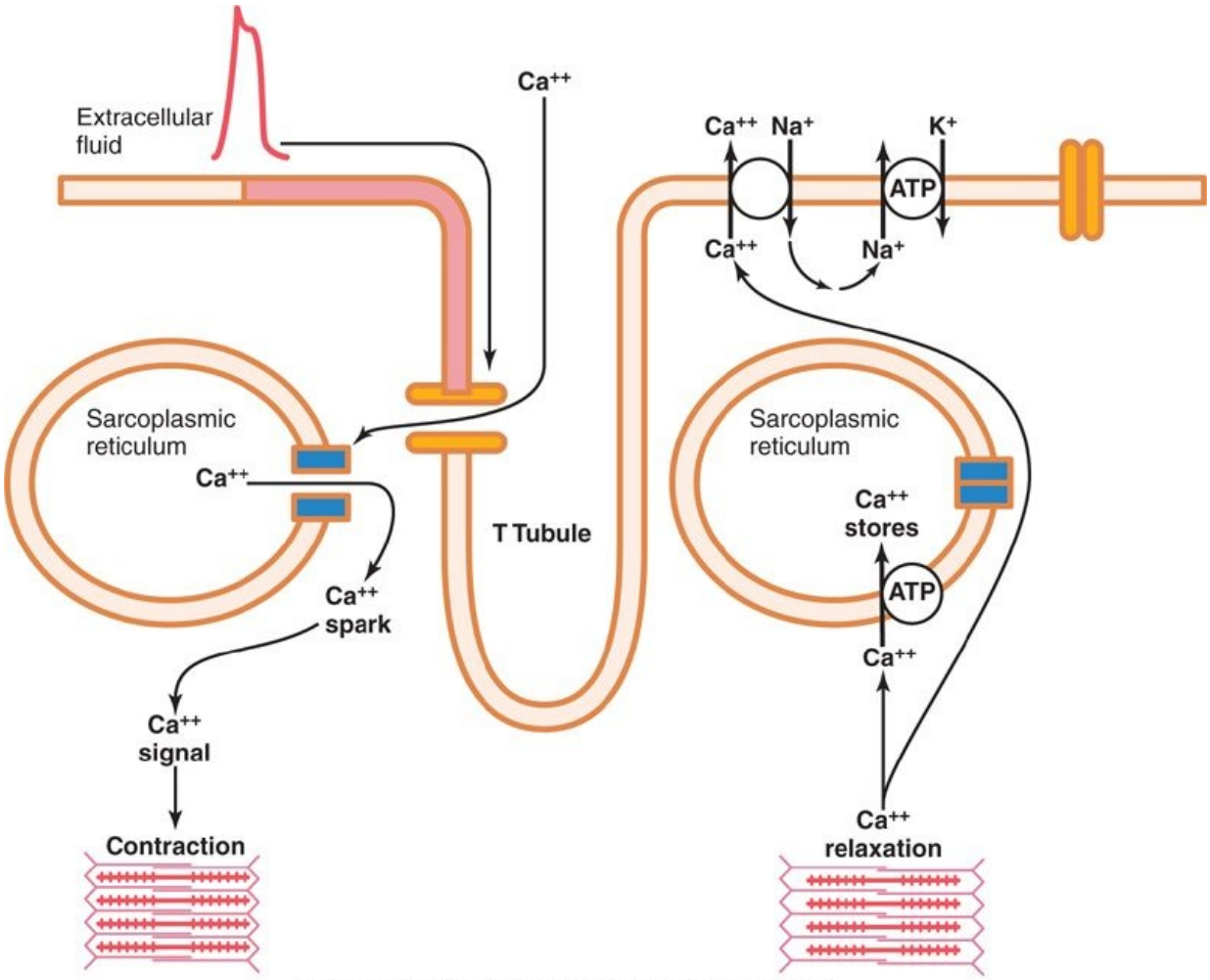

Figure 9-5 Mechanisms of excitation-contraction coupling and relaxation in cardiac muscle.

The strength of contraction of cardiac muscle depends to a great extent on the concentration of calcium ions in the extracellular fluids. In fact, a heart placed in a calcium-free solution will quickly stop beating. The reason for this is that the openings of the T tubules pass directly through the cardiac muscle cell membrane into the extracellular spaces surrounding the cells, allowing the same extracellular fluid that is in the cardiac muscle interstitium to percolate through the T tubules as well. Consequently, the quantity of calcium ions in the T tubule system (i.e., the availability of calcium ions to cause cardiac muscle contraction) depends to a great extent on the extracellular fluid calcium ion concentration.

In contrast, the strength of skeletal muscle contraction is hardly affected by moderate changes in extracellular fluid calcium concentration because skeletal muscle contraction is caused almost entirely by calcium ions released from the sarcoplasmic reticulum *inside* the skeletal muscle fiber.

At the end of the plateau of the cardiac action potential, the influx of calcium ions to the interior of the muscle fiber is suddenly cut off, and the calcium ions in the sarcoplasm are rapidly pumped back out of the muscle fibers into both the sarcoplasmic reticulum and the T tubule-extracellular fluid space. Transport of calcium back into the sarcoplasmic reticulum is achieved with the help of a calcium-ATPase pump (see Figure 9-5). Calcium ions are also removed from the cell by a sodium-calcium exchanger. The sodium that enters the cell during this exchange is then transported out of the cell by the sodium-potassium ATPase pump. As a result, the contraction ceases until a new action potential comes along.

Duration of Contraction

Cardiac muscle begins to contract a few milliseconds after the action potential begins and continues to contract until a few milliseconds after the action potential ends. Therefore, the duration of contraction of cardiac muscle is mainly a function of the duration of the action potential, *including the plateau*-about 0.2 second in atrial muscle and 0.3 second in ventricular muscle.

Cardiac Cycle

The cardiac events that occur from the beginning of one heartbeat to the beginning of the next are called the *cardiac cycle*. Each cycle is initiated by spontaneous generation of an action potential in the *sinus node,* as explained in Chapter 10. This node is located in the superior lateral wall of the right atrium near the opening of the superior vena cava, and the action potential travels from here rapidly through both atria and then through the A-V bundle into the ventricles. Because of this special arrangement of the conducting system from the atria into the ventricles, there is a delay of more than 0.1 second during passage of the cardiac impulse from the atria into the ventricles. This allows the atria to contract ahead of ventricular contraction, thereby pumping blood into the ventricles before the strong ventricular contraction begins. Thus, the atria act as *primer pumps* for the ventricles, and the ventricles in turn provide the major source of power for moving blood through the body's vascular system.

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Diastole and Systole

The cardiac cycle consists of a period of relaxation called *diastole,* during which the heart fills with blood, followed by a period of contraction called *systole.*

The total *duration of the cardiac cycle,* including systole and diastole, is the reciprocal of the heart rate. For example, if heart rate is 72 beats/min, the duration of the cardiac cycle is 1/72 beats/min-about 0.0139 minutes per beat, or 0.833 second per beat.

Figure 9-6 shows the different events during the cardiac cycle for the left side of the heart. The top three curves show the pressure changes in the aorta, left ventricle, and left atrium, respectively. The fourth curve depicts the changes in left ventricular volume, the fifth the electrocardiogram, and the sixth a phonocardiogram, which is a recording of the sounds produced by the heart-mainly by the heart valves-as it pumps. It is especially important that the reader study in detail this figure and understand the causes of all the events shown.

Effect of Heart Rate on Duration of Cardiac Cycle

When heart rate increases, the duration of each cardiac cycle decreases, including the contraction and relaxation phases. The duration of the action potential and the period of contraction (systole) also decrease, but not by as great a percentage as does the relaxation phase (diastole). At a normal heart rate of 72 beats/min, systole comprises about 0.4 of the entire cardiac cycle. At three times the normal heart rate, systole is about 0.65 of the entire cardiac cycle. This means that the heart beating at a very fast rate does not remain relaxed long enough to allow complete filling of the cardiac chambers before the next contraction.

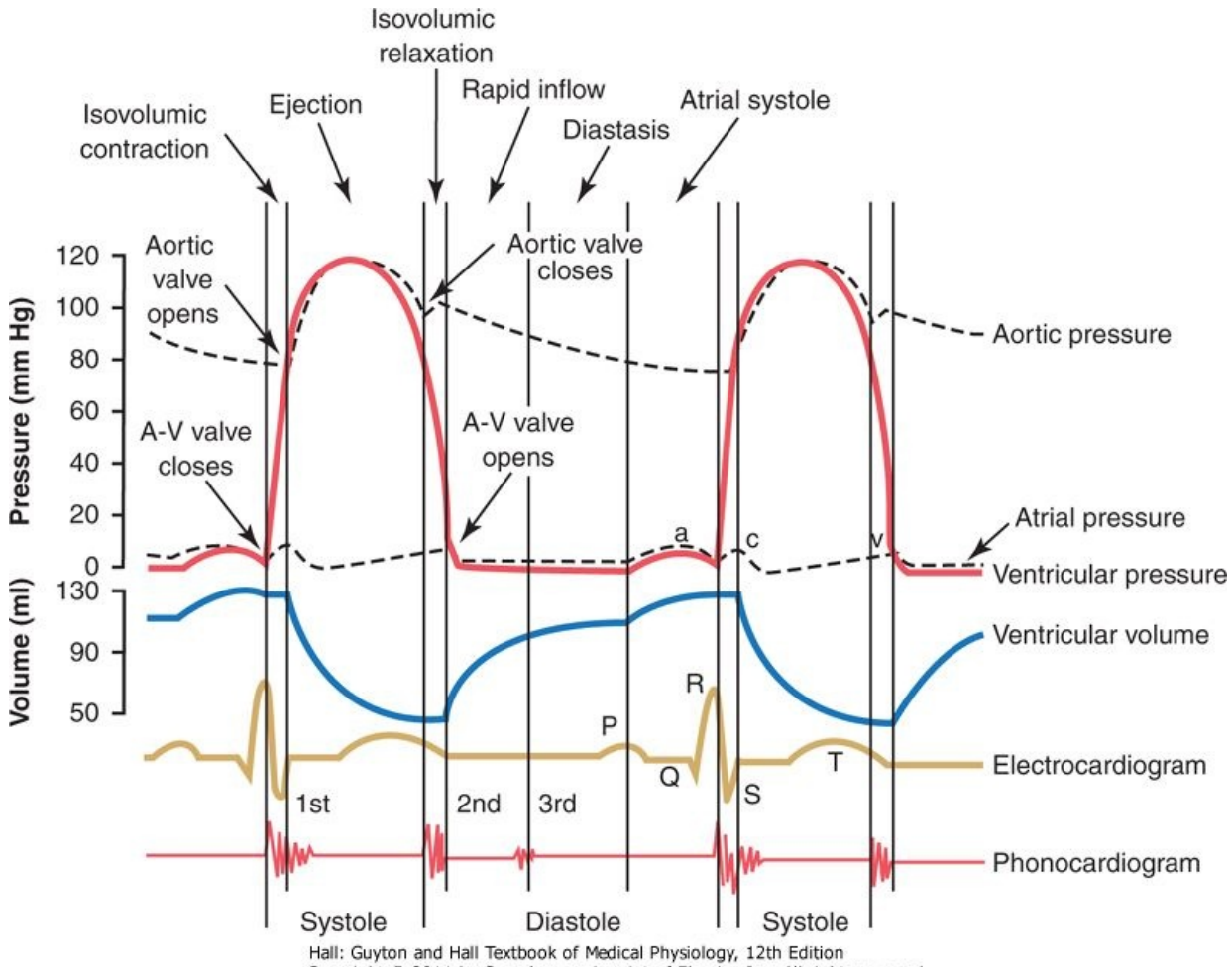

Figure 9-6 Events of the cardiac cycle for left ventricular function, showing changes in left atrial pressure, left ventricular pressure, aortic pressure, ventricular volume, the electrocardiogram, and the phonocardiogram.

Relationship of the Electrocardiogram to the Cardiac Cycle

The electrocardiogram in Figure 9-6 shows the *P, Q, R, S,* and *T waves,* which are discussed in Chapters 11, 12, and 13. They are electrical voltages generated by the heart and recorded by the electrocardiograph from the surface of the body.

The *P wave* is caused by *spread of depolarization* through the atria, and this is followed by atrial contraction, which causes a slight rise in the atrial pressure curve immediately after the electrocardiographic P wave.

About 0.16 second after the onset of the P wave, the *QRS waves* appear as a result of electrical depolarization of the ventricles, which initiates contraction of the ventricles and causes the ventricular pressure to begin rising, as also shown in the figure. Therefore, the QRS complex begins slightly before the onset of ventricular systole.

Finally, one observes the *ventricular T wave* in the electrocardiogram. This represents the stage of repolarization of the ventricles when the ventricular muscle fibers begin to relax. Therefore, the T wave occurs slightly before the end of ventricular contraction.

Function of the Atria as Primer Pumps

Blood normally flows continually from the great veins into the atria; about 80 percent of the blood flows directly through the atria into the ventricles even before the atria contract. Then, atrial contraction usually causes an additional 20 percent filling of the ventricles. Therefore, the atria simply function as primer pumps that increase the ventricular pumping effectiveness as much as 20 percent. However, the heart can continue to operate under most conditions even without this extra 20 percent effectiveness because it normally has the capability of pumping 300 to 400 percent more blood than is required by the resting body. Therefore, when the atria fail to function, the difference is unlikely to be noticed unless a person exercises; then acute signs of heart failure occasionally develop, especially shortness of breath.

Pressure Changes in the Atria-a, c, and v Waves

In the atrial pressure curve of Figure 9-6, three minor pressure elevations, called the *a, c,* and *v atrial pressure waves,* are noted.

The *a wave* is caused by atrial contraction. Ordinarily, the *right* atrial pressure increases 4 to 6 mm Hg during atrial contraction, and the *left* atrial pressure increases about 7 to 8 mm Hg.

The *c wave* occurs when the ventricles begin to contract; it is caused partly by slight backflow of blood into the atria at the onset of ventricular contraction but mainly by bulging of the A-V valves backward toward the atria because of increasing pressure in the ventricles.

The *v wave* occurs toward the end of ventricular contraction; it results from slow flow of blood into the atria from the veins while the A-V valves are closed during ventricular contraction. Then, when ventricular contraction is over, the A-V valves open, allowing this stored atrial blood to flow rapidly into the ventricles and causing the v wave to disappear.

Function of the Ventricles as Pumps

Filling of the Ventricles During Diastole

During ventricular systole, large amounts of blood accumulate in the right and left atria because of the closed A-V valves. Therefore, as soon as systole is over and the ventricular pressures fall again to their low diastolic values, the moderately increased pressures that have developed in the atria during ventricular systole immediately push the A-V valves open and allow blood to flow rapidly into the ventricles, as shown by the rise of the left *ventricular volume curve* in Figure 9-6. This is called the *period of rapid filling of the ventricles.*

The period of rapid filling lasts for about the first third of diastole. During the middle third of diastole, only a small amount of blood normally flows into the ventricles; this is blood that continues to empty into the atria from the veins and passes through the atria directly into the ventricles.

During the last third of diastole, the atria contract and give an additional thrust to the inflow of blood into the ventricles; this accounts for about 20 percent of the filling of the ventricles during each heart cycle.

Emptying of the Ventricles During Systole

Period of Isovolumic (Isometric) Contraction

Immediately after ventricular contraction begins, the ventricular pressure rises abruptly, as shown in Figure 9-6, causing the A-V valves to close. Then an additional 0.02 to 0.03 second is required for the ventricle to build up sufficient pressure to push the semilunar (aortic and pulmonary) valves open against the pressures in the aorta and pulmonary artery. Therefore, during this period, contraction is occurring in the ventricles, but there is no emptying. This is called the period of *isovolumic* or *isometric contraction,* meaning that tension is increasing in the muscle but little or no shortening of the muscle fibers is occurring.

Period of Ejection

When the left ventricular pressure rises slightly above 80 mm Hg (and the right ventricular pressure slightly above 8 mm Hg), the ventricular pressures push the semilunar valves open. Immediately, blood begins to pour out of the ventricles, with about 70 percent of the blood emptying occurring during the first third of the period of ejection and the remaining 30 percent emptying during the next two thirds. Therefore, the first third is called the *period of rapid ejection,* and the last two thirds, the *period of slow ejection.*

Period of Isovolumic (Isometric) Relaxation

At the end of systole, ventricular relaxation begins suddenly, allowing both the right and left *intraventricular pressures* to decrease rapidly. The elevated pressures in the distended large arteries that have just been filled with blood from the contracted ventricles immediately push blood back toward the ventricles, which snaps the aortic and pulmonary valves closed. For another 0.03 to 0.06 second, the ventricular muscle continues to relax, even though the ventricular volume does not change, giving rise to the period of *isovolumic* or *isometric relaxation.* During this period, the intraventricular pressures decrease rapidly back to their low diastolic levels. Then the A-V valves open to begin a new cycle of ventricular pumping.

End-Diastolic Volume, End-Systolic Volume, and Stroke Volume Output

During diastole, normal filling of the ventricles increases the volume of each ventricle to about 110 to 120 ml. This volume is called the *end-diastolic volume.* Then, as the ventricles empty during systole, the volume decreases about 70 ml, which is called the *stroke volume output.* The remaining volume in each ventricle, about 40 to 50 ml, is called the *end-systolic volume.* The fraction of the end-diastolic volume that is ejected is called the *ejection fraction*-usually equal to about 60 percent.

When the heart contracts strongly, the end-systolic volume can be decreased to as little as 10 to 20 ml. Conversely, when large amounts of blood flow into the ventricles during diastole, the ventricular end-diastolic volumes can become as great as 150 to 180 ml in the healthy heart. By both increasing the end-diastolic volume and decreasing the end-systolic volume, the stroke volume output can be increased to more than double normal.

Function of the Valves

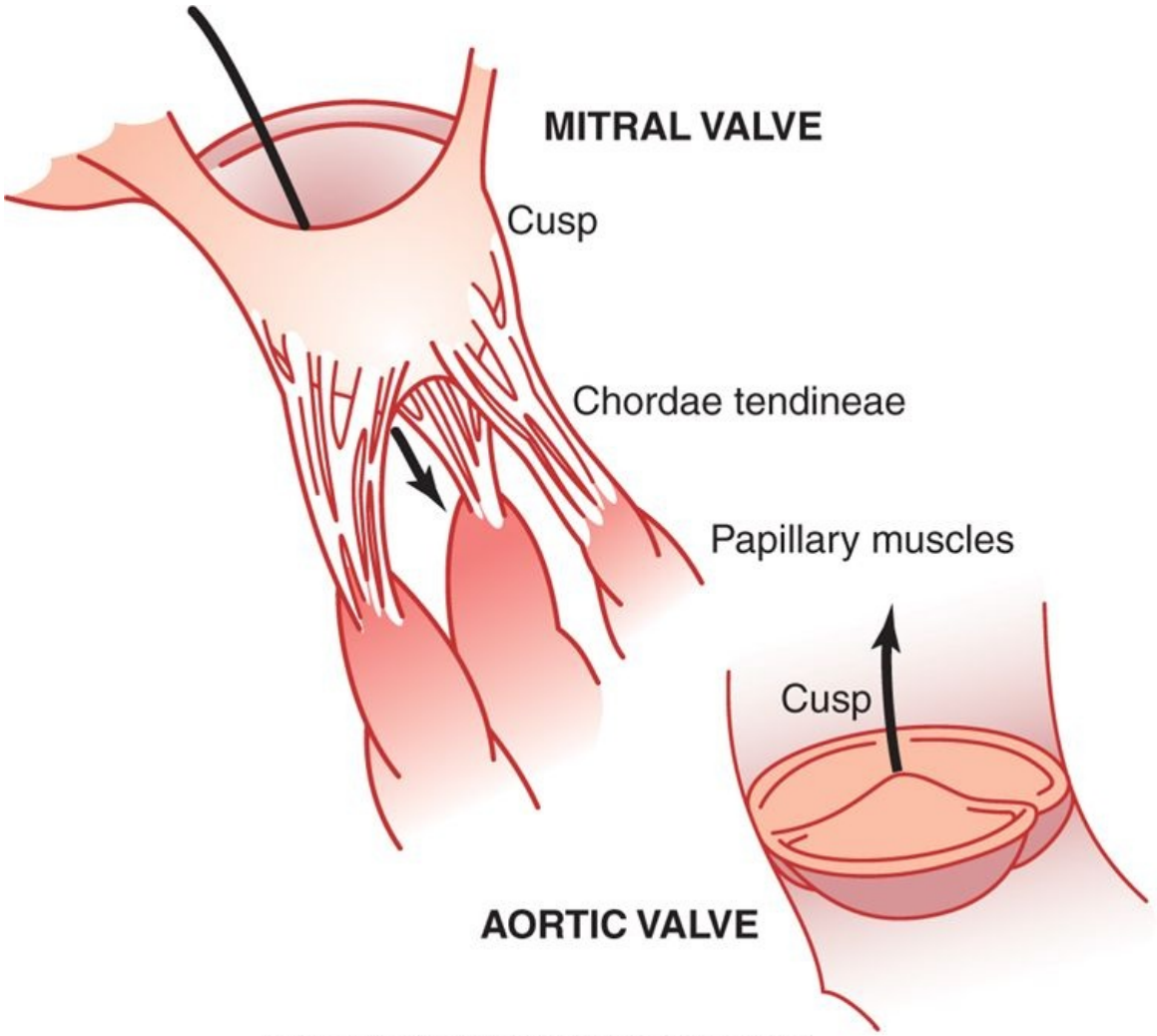

Figure 9-7 Mitral and aortic valves (the left ventricular valves).

The *A-V valves* (the *tricuspid* and *mitral* valves) prevent backflow of blood from the ventricles to the atria during systole, and the *semilunar valves* (the *aortic* and *pulmonary artery* valves) prevent backflow from the aorta and pulmonary arteries into the ventricles during diastole. These valves, shown in Figure 9-7 for the left ventricle, close and open *passively.* That is, they close when a backward pressure gradient pushes blood backward, and they open when a forward pressure gradient forces blood in the forward direction. For anatomical reasons, the thin, filmy A-V valves require almost no backflow to cause closure, whereas the much heavier semilunar valves require rather rapid backflow for a few milliseconds.

Function of the Papillary Muscles

Figure 9-7 also shows papillary muscles that attach to the vanes of the A-V valves by the *chordae tendineae.* The papillary muscles contract when the ventricular walls contract, but contrary to what might be expected, they *do not* help the valves to close. Instead, they pull the vanes of the valves inward toward the ventricles to prevent their bulging too far backward toward the atria during ventricular contraction. If a chorda tendinea becomes ruptured or if one of the papillary muscles becomes paralyzed, the valve bulges far backward during ventricular contraction, sometimes so far that it leaks severely and results in severe or even lethal cardiac incapacity.

Aortic and Pulmonary Artery Valves

The aortic and pulmonary artery semilunar valves function quite differently from the A-V valves. First, the high pressures in the arteries at the end of systole cause the semilunar valves to snap to the closed position, in contrast to the much softer closure of the A-V valves. Second, because of smaller openings, the velocity of blood ejection through the aortic and pulmonary valves is far greater than that through the much larger A-V valves. Also, because of the rapid closure and rapid ejection, the edges of the aortic and pulmonary valves are subjected to much greater mechanical abrasion than are the A-V valves. Finally, the A-V valves are supported by the chordae tendineae, which is not true for the semilunar valves. It is obvious from the anatomy of the aortic and pulmonary valves (as shown for the aortic valve at the bottom of Figure 9-7) that they must be constructed with an especially strong yet very pliable fibrous tissue base to withstand the extra physical stresses.

Aortic Pressure Curve

When the left ventricle contracts, the ventricular pressure increases rapidly until the aortic valve opens. Then, after the valve opens, the pressure in the ventricle rises much less rapidly, as shown in Figure 9-6, because blood immediately flows out of the ventricle into the aorta and then into the systemic distribution arteries.

The entry of blood into the arteries causes the walls of these arteries to stretch and the pressure to increase to about 120 mm Hg.

Next, at the end of systole, after the left ventricle stops ejecting blood and the aortic valve closes, the elastic walls of the arteries maintain a high pressure in the arteries, even during diastole.

Aso-called *incisura* occurs in the aortic pressure curve when the aortic valve closes. This is caused by a short period of backward flow of blood immediately before closure of the valve, followed by sudden cessation of the backflow.

After the aortic valve has closed, the pressure in the aorta decreases slowly throughout diastole because the blood stored in the distended elastic arteries flows continually through the peripheral vessels back to the veins. Before the ventricle contracts again, the aortic pressure usually has fallen to about 80 mm Hg (diastolic pressure), which is two thirds the maximal pressure of 120 mm Hg (systolic pressure) that occurs in the aorta during ventricular contraction.

The pressure curves in the *right ventricle* and *pulmonary artery* are similar to those in the aorta, except that the pressures are only about one sixth as great, as discussed in Chapter 14.

Relationship of the Heart Sounds to Heart Pumping

When listening to the heart with a stethoscope, one does not hear the opening of the valves because this is a relatively slow process that normally makes no noise. However, when the valves close, the vanes of the valves and the surrounding fluids vibrate under the influence of sudden pressure changes, giving off sound that travels in all directions through the chest.

When the ventricles contract, one first hears a sound caused by closure of the A-V valves. The vibration is low in pitch and relatively long-lasting and is known as the *first heart sound.* When the aortic and pulmonary valves close at the end of systole, one hears a rapid snap because these valves close rapidly, and the surroundings vibrate for a short period. This sound is called the *second heart sound.* The precise causes of the heart sounds are discussed more fully in Chapter 23, in relation to listening to the sounds with the stethoscope.

Work Output of the Heart

The *stroke work output* of the heart is the amount of energy that the heart converts to work during each heartbeat while pumping blood into the arteries. *Minute work output* is the total amount of energy converted to work in 1 minute; this is equal to the stroke work output times the heart rate per minute.

Work output of the heart is in two forms. First, by far the major proportion is used to move the blood from the low-pressure veins to the high-pressure arteries. This is called *volume-pressure work* or *external work*. Second, a minor proportion of the energy is used to accelerate the blood to its velocity of ejection through the aortic and pulmonary valves. This is the *kinetic energy of blood flow* component of the work output.

Right ventricular external work output is normally about one sixth the work output of the left ventricle because of the sixfold difference in systolic pressures that the two ventricles pump. The additional work output of each ventricle required to create kinetic energy of blood flow is proportional to the mass of blood ejected times the square of velocity of ejection.

Ordinarily, the work output of the left ventricle required to create kinetic energy of blood flow is only about 1 percent of the total work output of the ventricle and therefore is ignored in the calculation of the total stroke work output. But in certain abnormal conditions, such as aortic stenosis, in which blood flows with great velocity through the stenosed valve, more than 50 percent of the total work output may be required to create kinetic energy of blood flow.

Graphical Analysis of Ventricular Pumping

Figure 9-8 shows a diagram that is especially useful in explaining the pumping mechanics of the *left* ventricle. The most important components of the diagram are the two curves labeled "diastolic pressure" and "systolic pressure." These curves are volume-pressure curves.

The diastolic pressure curve is determined by filling the heart with progressively greater volumes of blood and then measuring the diastolic pressure immediately before ventricular contraction occurs, which is the *end-diastolic pressure* of the ventricle.

The systolic pressure curve is determined by recording the systolic pressure achieved during ventricular contraction at each volume of filling.

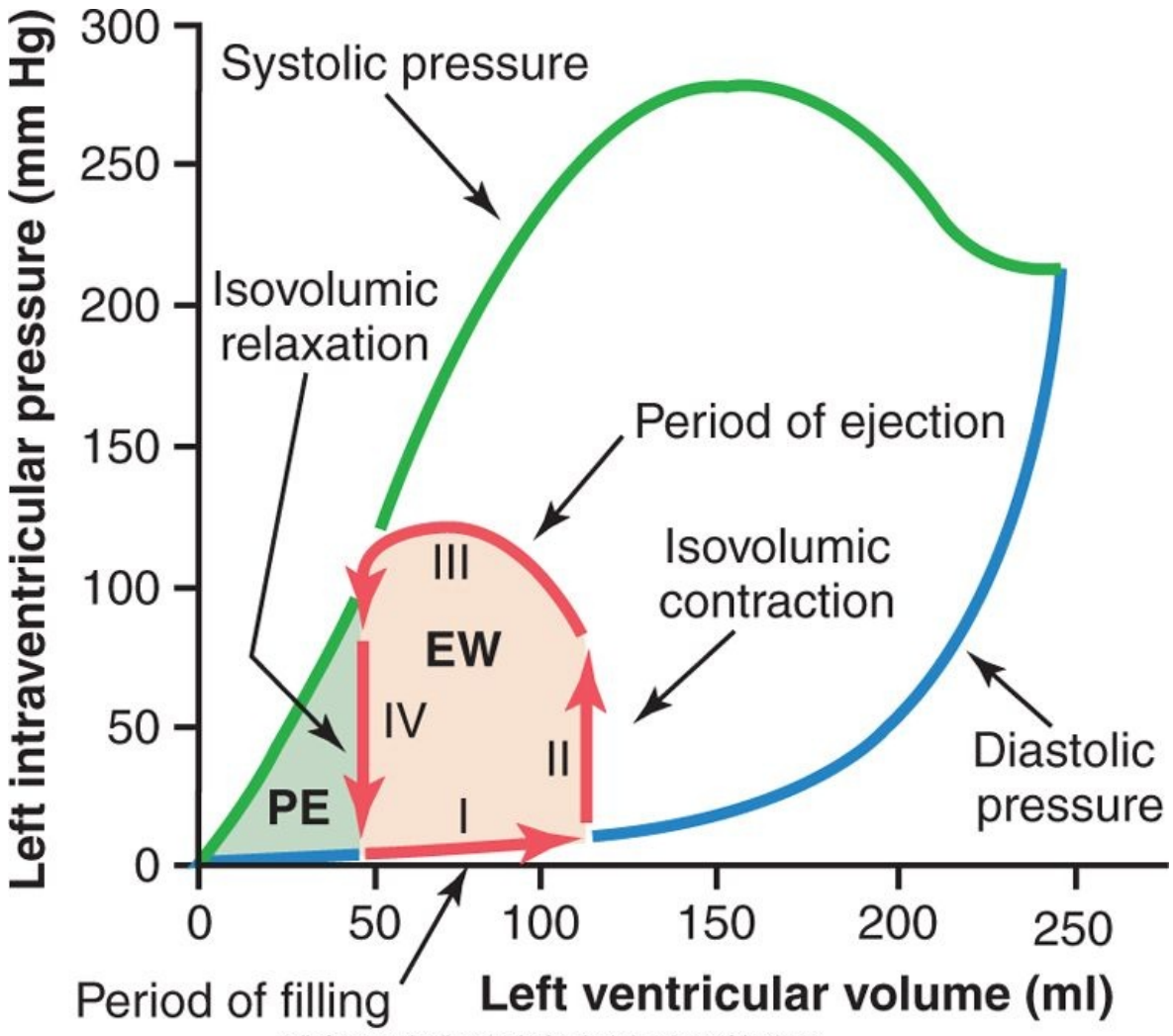

Figure 9-8 Relationship between left ventricular volume and intraventricular pressure during diastole and systole. Also shown by the heavy red lines is the "volume-pressure diagram," demonstrating changes in intraventricular volume and pressure during the normal cardiac cycle. EW, net external work.

Until the volume of the noncontracting ventricle rises above about 150 ml, the "diastolic" pressure does not increase greatly. Therefore, up to this volume, blood can flow easily into the ventricle from the atrium. Above 150 ml, the ventricular diastolic pressure increases rapidly, partly because of

fibrous tissue in the heart that will stretch no more and partly because the pericardium that surrounds the heart becomes filled nearly to its limit.

During ventricular contraction, the "systolic" pressure increases even at low ventricular volumes and reaches a maximum at a ventricular volume of 150 to 170 ml. Then, as the volume increases still further, the systolic pressure actually decreases under some conditions, as demonstrated by the falling systolic pressure curve in Figure 9-8, because at these great volumes, the actin and myosin filaments of the cardiac muscle fibers are pulled apart far enough that the strength of each cardiac fiber contraction becomes less than optimal.

Note especially in the figure that the maximum systolic pressure for the normal *left* ventricle is between 250 and 300 mm Hg, but this varies widely with each person's heart strength and degree of heart stimulation by cardiac nerves. For the normal *right* ventricle, the maximum systolic pressure is between 60 and 80 mm Hg.

"Volume-Pressure Diagram" During the Cardiac Cycle; Cardiac Work Output

The red lines in Figure 9-8 form a loop called the *volume-pressure diagram* of the cardiac cycle for normal function of the *left* ventricle. A more detailed version of this loop is shown in Figure 9-9. It is divided into four phases.

Phase I: *Period of filling.* This phase in the volume-pressure diagram begins at a ventricular volume of about 50 ml and a diastolic pressure of 2 to 3 mm Hg. The amount of blood that remains in the ventricle after the previous heartbeat, 50 ml, is called the *end-systolic volume.* As venous blood flows into the ventricle from the left atrium, the ventricular volume normally increases to about 120 ml, called the *end-diastolic volume,* an increase of 70 ml. Therefore, the volume-pressure diagram during phase I extends along the line labeled "I," from point A to point B, with the volume increasing to 120 ml and the diastolic pressure rising to about 5 to 7 mm Hg.

Phase II: *Period of isovolumic contraction.* During isovolumic contraction, the volume of the ventricle does not change because all valves are closed. However, the pressure inside the ventricle increases to equal the pressure in the aorta, at a pressure value of about 80 mm Hg, as depicted by point C.

Phase III: *Period of ejection.* During ejection, the systolic pressure rises even higher because of still more contraction of the ventricle. At the same time, the volume of the ventricle decreases because the aortic valve has now opened and blood flows out of the ventricle into the aorta. Therefore, the curve labeled "III," or "period of ejection," traces the changes in volume and systolic pressure during this period of ejection.

Phase IV. *Period of isovolumic relaxation.* At the end of the period of ejection (point D), the aortic valve closes, and the ventricular pressure falls back to the diastolic pressure level. The line labeled "IV" traces this decrease in intraventricular pressure without any change in volume. Thus, the ventricle returns to its starting point, with about 50 ml of blood left in the ventricle and at an atrial pressure of 2 to 3 mm Hg.

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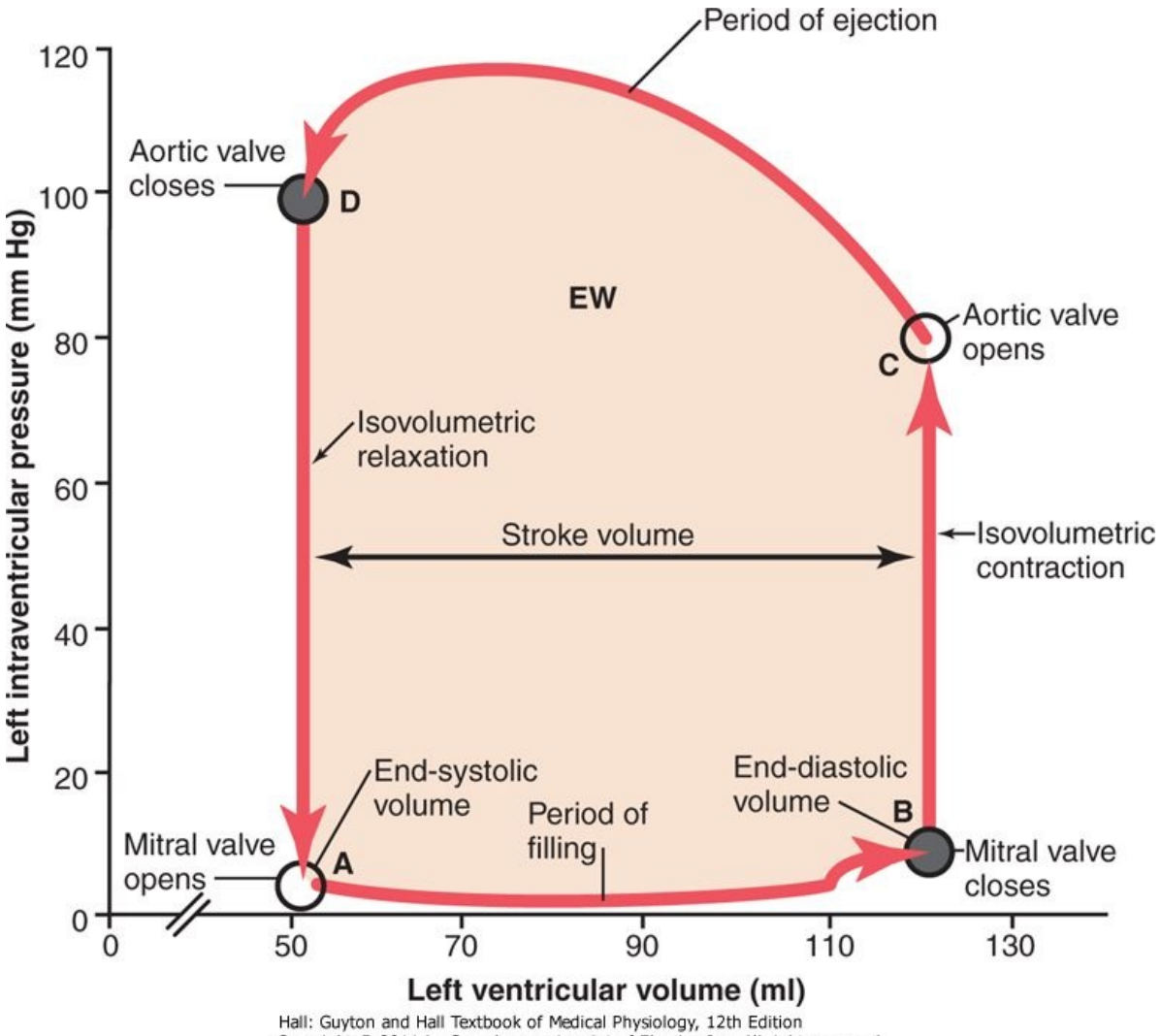

Figure 9-9 The "volume-pressure diagram" demonstrating changes in intraventricular volume and pressure during a single cardiac cycle (*red line*). The tan shaded area represents the net external work (*EW*) output by the left ventricle during the cardiac cycle.

Readers well trained in the basic principles of physics will recognize that the area subtended by this functional volume-pressure diagram (the tan shaded area, labeled EW) represents the *net external work output* of the ventricle during its contraction cycle. In experimental studies of cardiac contraction, this diagram is used for calculating cardiac work output.

When the heart pumps large quantities of blood, the area of the work diagram becomes much larger. That is, it extends far to the right because the ventricle fills with more blood during diastole, it rises much higher because the ventricle contracts with greater pressure, and it usually extends farther to the left because the ventricle contracts to a smaller volume-especially if the ventricle is stimulated to increased activity by the sympathetic nervous system.

Concepts of Preload and Afterload

In assessing the contractile properties of muscle, it is important to specify the degree of tension on the muscle when it begins to contract, which is called the *preload,* and to specify the load against which the muscle exerts its contractile force, which is called the *afterload.*

For cardiac contraction, the *preload* is usually considered to be the end-diastolic pressure when the ventricle has become filled.

The *afterload* of the ventricle is the pressure in the aorta leading from the ventricle. In Figure 9-8, this corresponds to the systolic pressure described by the phase III curve of the volume-pressure diagram. (Sometimes the afterload is loosely considered to be the resistance in the circulation rather than the pressure.)

The importance of the concepts of preload and afterload is that in many abnormal functional states of the heart or circulation, the pressure during filling of the ventricle (the preload), the arterial pressure against which the ventricle must contract (the afterload), or both are severely altered from normal.

Chemical Energy Required for Cardiac Contraction: Oxygen Utilization by the Heart

Heart muscle, like skeletal muscle, uses chemical energy to provide the work of contraction. Approximately 70 to 90 percent of this energy is normally derived from oxidative metabolism of fatty acids with about 10 to 30 percent coming from other nutrients, especially lactate and glucose. Therefore, the rate of oxygen consumption by the heart is an excellent measure of the chemical energy liberated while the heart performs its work. The different chemical reactions that liberate this energy are discussed in Chapters 67 and 68.

Experimental studies have shown that oxygen consumption of the heart and the chemical energy expended during contraction are directly related to the total shaded area in Figure 9-8. This shaded portion consists of the *external work* (EW) as explained earlier and an additional portion called the *potential energy,* labeled PE. The potential energy represents additional work that could be accomplished by contraction of the ventricle if the ventricle should empty completely all the blood in its chamber with each contraction.

Oxygen consumption has also been shown to be nearly proportional to the *tension* that occurs in the heart muscle during contraction multiplied by the *duration of time* that the contraction persists, called the *tension-time index*. Because tension is high when systolic pressure is high, correspondingly more oxygen is used. Also, much more chemical energy is expended even at normal systolic pressures when the ventricle is abnormally dilated because the heart muscle tension during contraction is proportional to pressure times the diameter of the ventricle. This becomes especially important in heart failure where the heart ventricle is dilated and, paradoxically, the amount of chemical energy required for a given amount of work output is greater than normal even though the heart is already failing.

Efficiency of Cardiac Contraction

During heart muscle contraction, most of the expended chemical energy is converted into *heat* and a much smaller portion into *work output*. The ratio of work output to total chemical energy expenditure is called the *efficiency of cardiac contraction,* or simply *efficiency of the heart.* Maximum efficiency of the normal heart is between 20 and 25 percent. In heart failure, this can decrease to as low as 5 to 10 percent.

Regulation of Heart Pumping

When a person is at rest, the heart pumps only 4 to 6 liters of blood each minute. During severe exercise, the heart may be required to pump four to seven times this amount. The basic means by which the volume pumped by the heart is regulated are (1) intrinsic cardiac regulation of pumping in response to changes in volume of blood flowing into the heart and (2) control of heart rate and strength of heart pumping by the autonomic nervous system.

Intrinsic Regulation of Heart Pumping-The Frank-Starling Mechanism

In Chapter 20, we will learn that under most conditions, the amount of blood pumped by the heart each minute is normally determined almost entirely by the rate of blood flow into the heart from the veins, which is called *venous return*. That is, each peripheral tissue of the body controls its own local blood flow, and all the local tissue flows combine and return by way of the veins to the right atrium. The heart, in turn, automatically pumps this incoming blood into the arteries so that it can flow around the circuit again.

This intrinsic ability of the heart to adapt to increasing volumes of inflowing blood is called the *Frank-Starling mechanism of the heart,* in honor of Otto Frank and Ernest Starling, two great physiologists of a century ago. Basically, the Frank-Starling mechanism means that the greater the heart muscle is stretched during filling, the greater is the force of contraction and the greater the quantity of blood pumped into the aorta. Or, stated another way: *Within physiologic limits, the heart pumps all the blood that returns to it by the way of the veins.*

What Is the Explanation of the Frank-Starling Mechanism?

When an extra amount of blood flows into the ventricles, the cardiac muscle itself is stretched to greater length. This in turn causes the muscle to contract with increased force because the actin and myosin filaments are brought to a more nearly optimal degree of overlap for force generation. Therefore, the ventricle, because of its increased pumping, automatically pumps the extra blood into the arteries.

This ability of stretched muscle, up to an optimal length, to contract with increased work output is characteristic of all striated muscle, as explained in Chapter 6, and is not simply a characteristic of cardiac muscle.

In addition to the important effect of lengthening the heart muscle, still another factor increases heart pumping when its volume is increased. Stretch of the right atrial wall directly increases the heart rate by 10 to 20 percent; this, too, helps increase the amount of blood pumped each minute, although its contribution is much less than that of the Frank-Starling mechanism.

Ventricular Function Curves

One of the best ways to express the functional ability of the ventricles to pump blood is by *ventricular function curves,* as shown in Figures 9-10 and 9-11. Figure 9-10 shows a type of ventricular function curve called the *stroke work output curve.* Note that as the atrial pressure for each side of the heart increases, the stroke work output for that side increases until it reaches the limit of the ventricle's pumping ability.

Figure 9-11 shows another type of ventricular function curve called the *ventricular volume output curve.* The two curves of this figure represent function of the two ventricles of the human heart based on data extrapolated from lower animals. As the right and left atrial pressures increase, the respective ventricular volume outputs per minute also increase.

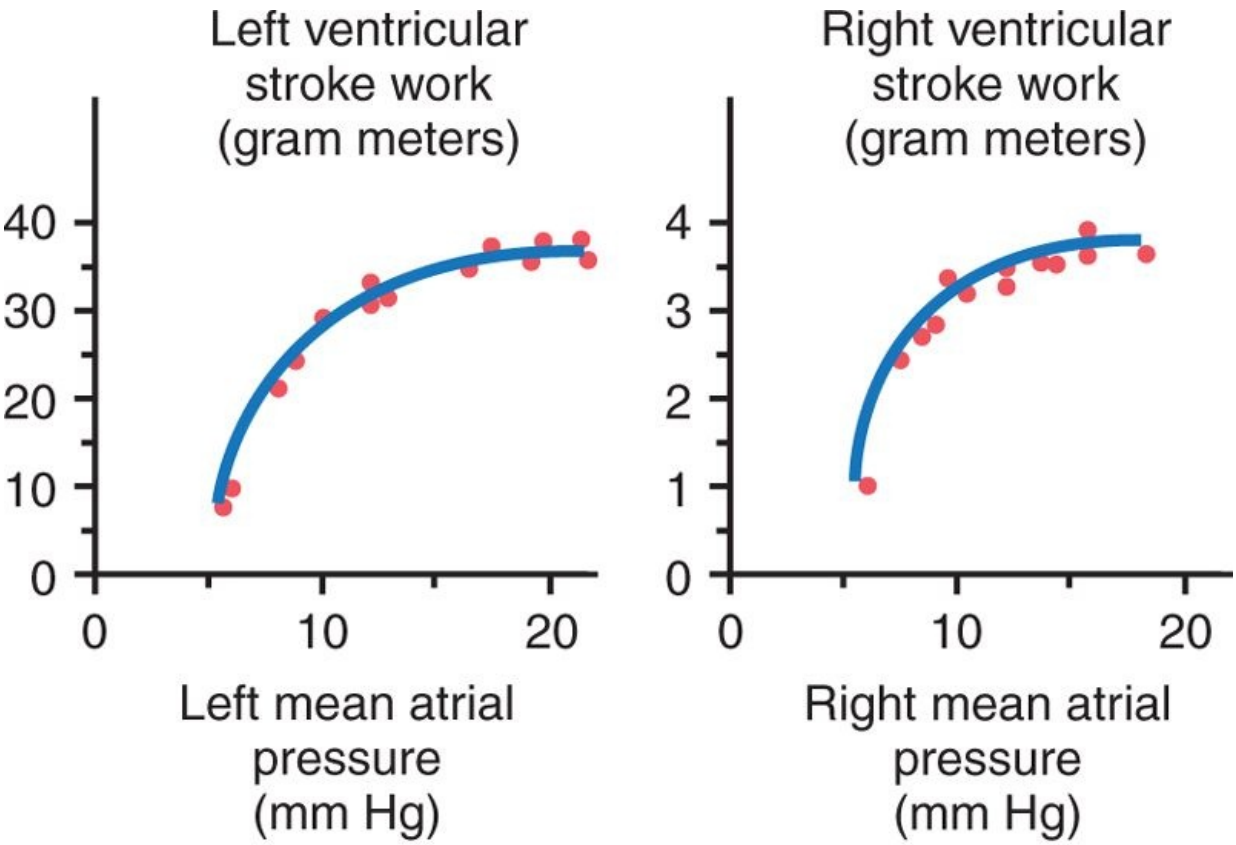

Figure 9-10 Left and right ventricular function curves recorded from dogs, depicting *ventricular stroke work output* as a function of left and right mean atrial pressures. (Curves reconstructed from data in Sarnoff SJ: Myocardial contractility as described by ventricular function curves. Physiol Rev 35:107, 1955.)

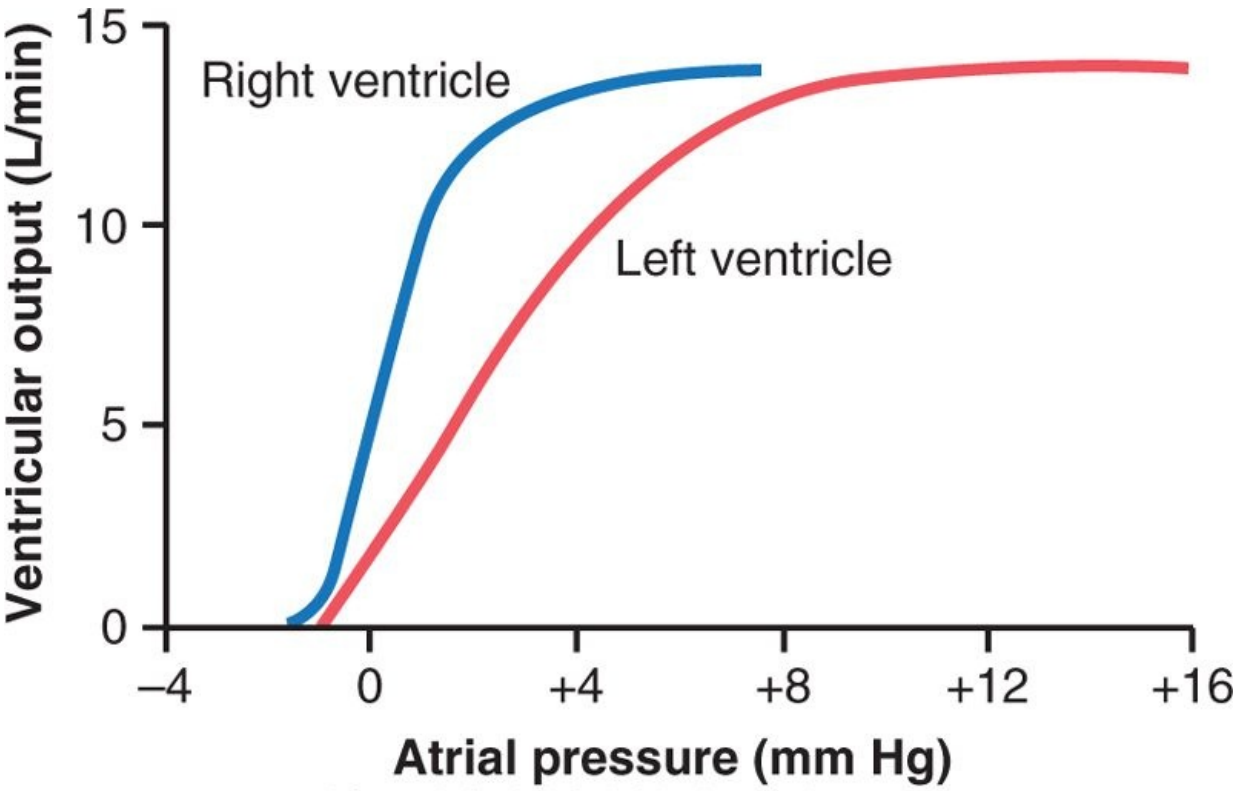

Figure 9-11 Approximate normal right and left *ventricular volume output curves* for the normal resting human heart as extrapolated from data obtained in dogs and data from human beings.

Thus, *ventricular function curves* are another way of expressing the Frank-Starling mechanism of the heart. That is, as the ventricles fill in response to higher atrial pressures, each ventricular volume and strength of cardiac muscle contraction increase, causing the heart to pump increased quantities of blood into the arteries.

Control of the Heart by the Sympathetic and Parasympathetic Nerves

The pumping effectiveness of the heart also is controlled by the *sympathetic* and *parasympathetic (vagus)* nerves, which abundantly supply the heart, as shown in Figure 9-12. For given levels of atrial pressure, the amount of blood pumped each minute *(cardiac output)* often can be increased more than 100 percent by sympathetic stimulation. By contrast, the output can be decreased to as low as zero or almost zero by vagal (parasympathetic) stimulation.

Mechanisms of Excitation of the Heart by the Sympathetic Nerves

Strong sympathetic stimulation can increase the heart rate in young adult humans from the normal rate of 70 beats/min up to 180 to 200 and, rarely, even 250 beats/min. Also, sympathetic stimulation increases the force of heart contraction to as much as double normal, thereby increasing the volume of blood pumped and increasing the ejection pressure. Thus, sympathetic stimulation often can increase the maximum cardiac output as much as twofold to threefold, in addition to the increased output caused by the Frank-Starling mechanism already discussed.

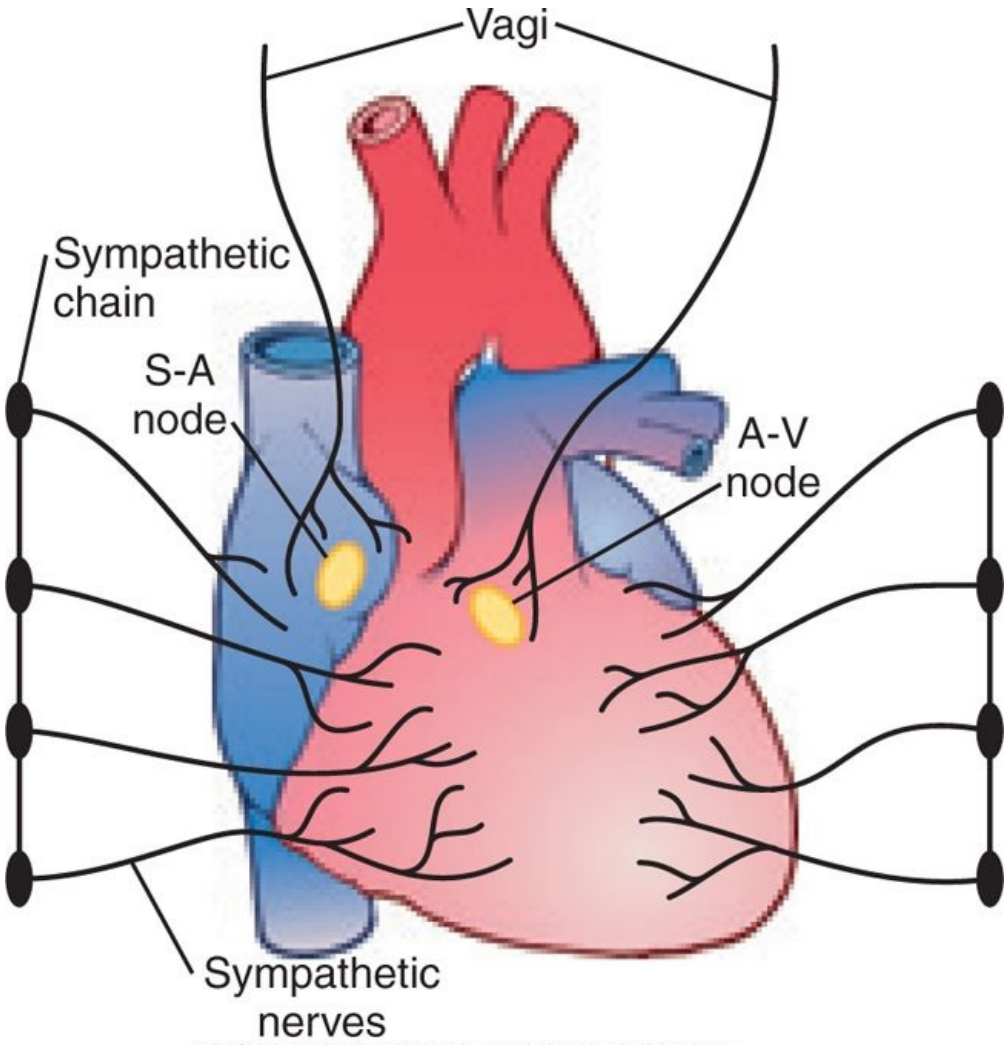

Figure 9-12 Cardiac *sympathetic* and *parasympathetic* nerves. (The vagus nerves to the heart are parasympathetic nerves.)

Conversely, *inhibition* of the sympathetic nerves to the heart can decrease cardiac pumping to a moderate extent in the following way. Under normal conditions, the sympathetic nerve fibers to the heart discharge continuously at a slow rate that maintains pumping at about 30 percent above that with no sympathetic stimulation. Therefore, when the activity of the sympathetic nervous system is depressed below normal, this decreases both heart rate and strength of ventricular muscle contraction, thereby decreasing the level of cardiac pumping as much as 30 percent below normal.

Parasympathetic (Vagal) Stimulation of the Heart

Strong stimulation of the parasympathetic nerve fibers in the vagus nerves to the heart can stop the heartbeat for a few seconds, but then the heart usually "escapes" and beats at a rate of 20 to 40 beats/min as long as the parasympathetic stimulation continues. In addition, strong vagal stimulation can decrease the strength of heart muscle contraction by 20 to 30 percent.

The vagal fibers are distributed mainly to the atria and not much to the ventricles, where the power contraction of the heart occurs. This explains the effect of vagal stimulation mainly to decrease heart rate rather than to decrease greatly the strength of heart contraction. Nevertheless, the great decrease in heart rate combined with a slight decrease in heart contraction strength can decrease ventricular pumping 50 percent or more.

Effect of Sympathetic or Parasympathetic Stimulation on the Cardiac Function Curve

Figure 9-13 shows four cardiac function curves. They are similar to the ventricular function curves of Figure 9-11. However, they represent function of the entire heart rather than of a single ventricle; they show the relation between right atrial pressure at the input of the right heart and cardiac output from the left ventricle into the aorta.

The curves of Figure 9-13 demonstrate that at any given right atrial pressure, the cardiac output increases during increased sympathetic stimulation and decreases during increased parasympathetic stimulation. These changes in output caused by autonomic nervous system stimulation result both from *changes in heart rate* and from *changes in contractile strength of the heart* because both change in response to the nerve stimulation.

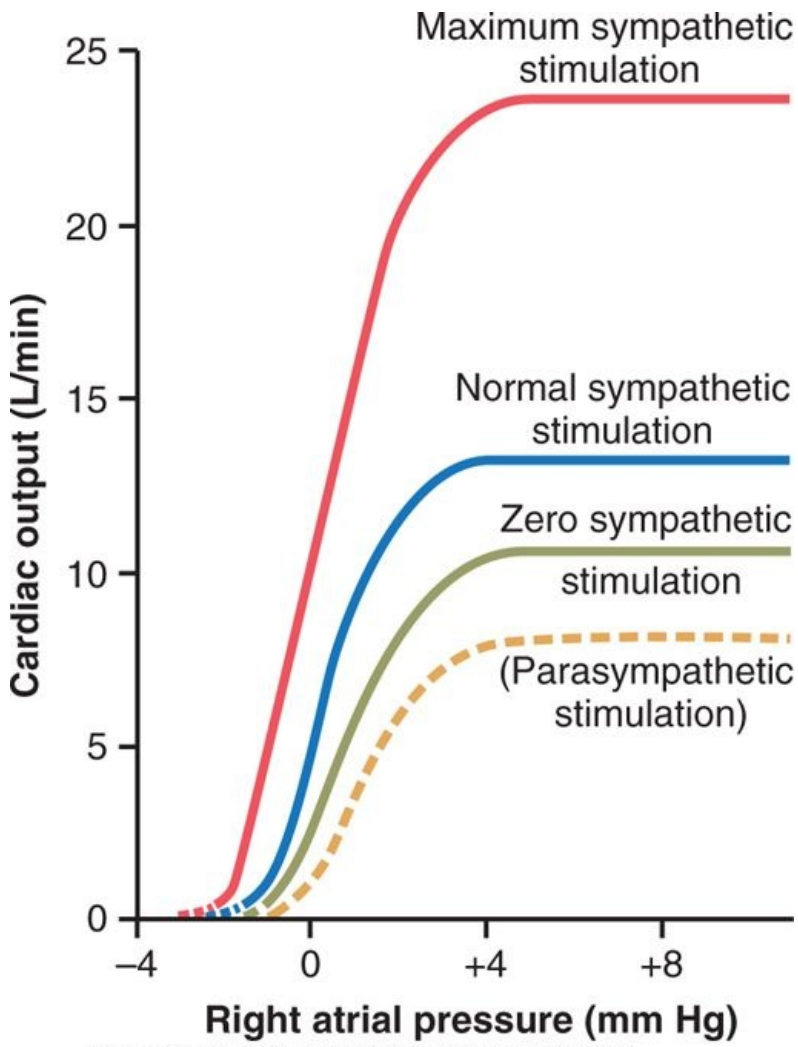

Figure 9-13 Effect on the cardiac output curve of different degrees of sympathetic or parasympathetic stimulation.

Effect of Potassium and Calcium Ions on Heart Function

In the discussion of membrane potentials in Chapter 5, it was pointed out that potassium ions have a marked effect on membrane potentials, and in Chapter 6 it was noted that calcium ions play an especially important role in activating the muscle contractile process. Therefore, it is to be expected that the concentration of each of these two ions in the extracellular fluids should also have important effects on cardiac pumping.

Effect of Potassium Ions

Excess potassium in the extracellular fluids causes the heart to become dilated and flaccid and also slows the heart rate. Large quantities also can block conduction of the cardiac impulse from the atria to the ventricles through the A-V bundle. Elevation of potassium concentration to only 8 to 12 mEq/L-two to three times the normal value-can cause such weakness of the heart and abnormal rhythm that death occurs.

These effects result partially from the fact that a high potassium concentration in the extracellular fluids decreases the resting membrane potential in the cardiac muscle fibers, as explained in Chapter 5. That is, high extracellular fluid potassium concentration partially depolarizes the cell membrane, causing the membrane potential to be less negative. As the membrane potential decreases, the intensity of the action potential also decreases, which makes contraction of the heart progressively weaker.

Effect of Calcium Ions

An excess of calcium ions causes effects almost exactly opposite to those of potassium ions, causing the heart to go toward spastic contraction. This is caused by a direct effect of calcium ions to initiate the cardiac contractile process, as explained earlier in the chapter.

Conversely, deficiency of calcium ions causes cardiac *flaccidity*, similar to the effect of high potassium. Fortunately, calcium ion levels in the blood normally are regulated within a very narrow range. Therefore, cardiac effects of abnormal calcium concentrations are seldom of clinical concern.

Effect of Temperature on Heart Function

Increased body temperature, as occurs when one has fever, causes a greatly increased heart rate, sometimes to double normal. Decreased temperature causes a greatly decreased heart rate, falling to as low as a few beats per minute when a person is near death from hypothermia in the body temperature range of 60° to 70°F. These effects presumably result from the fact that heat increases the permeability of the cardiac muscle membrane to ions that control heart rate, resulting in acceleration of the self-excitation process.

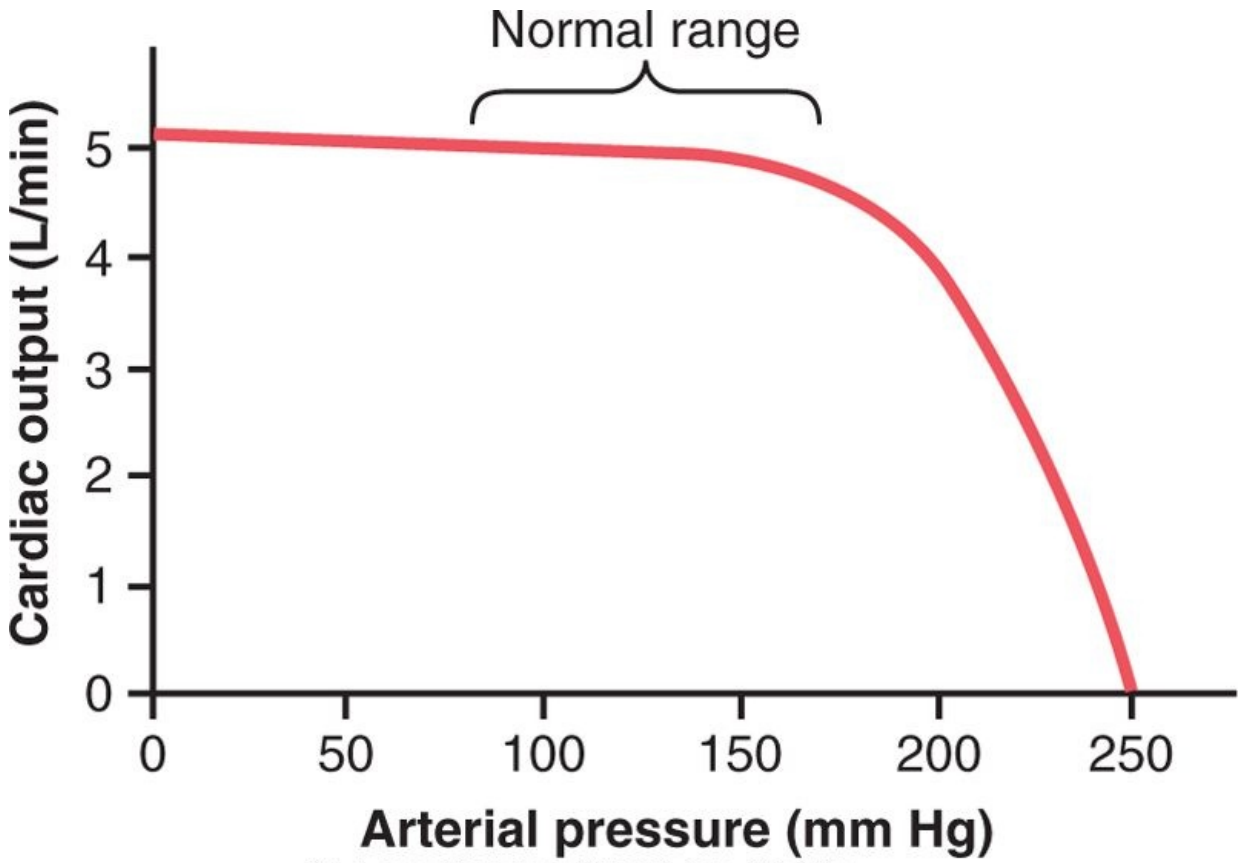

Figure 9-14 Constancy of cardiac output up to a pressure level of 160 mm Hg. Only when the arterial pressure rises above this normal limit does the increasing pressure load cause the cardiac output to fall significantly.

Contractile strength of the heart often is enhanced temporarily by a moderate increase in temperature, as occurs during body exercise, but prolonged elevation of temperature exhausts the metabolic systems of the heart and eventually causes weakness. Therefore, optimal function of the heart depends greatly on proper control of body temperature by the temperature control mechanisms explained in Chapter 73.

Increasing the Arterial Pressure Load (up to a Limit) Does Not Decrease the Cardiac Output

Note in Figure 9-14 that increasing the arterial pressure in the aorta does not decrease the cardiac output until the mean arterial pressure rises above about 160 mm Hg. In other words, during normal function of the heart at normal systolic arterial pressures (80 to 140 mm Hg), the cardiac output is determined almost entirely by the ease of blood flow through the body's tissues, which in turn controls *venous return* of blood to the heart. This is the principal subject of Chapter 20.

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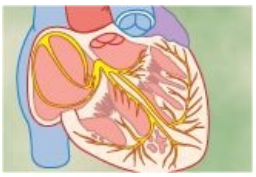
10 Rhythmical Excitation of the Heart



The heart is endowed with a special system for (1) generating rhythmical electrical impulses to cause rhythmical contraction of the heart muscle and (2) conducting these impulses rapidly through the heart. When this system functions normally, the atria contract about one sixth of a second ahead of ventricular contraction, which allows filling of the ventricles before they pump the blood through the lungs and peripheral circulation. Another special importance of the system is that it allows all portions of the ventricles to contract almost simultaneously, which is essential for most effective pressure generation in the ventricular chambers.

This rhythmical and conductive system of the heart is susceptible to damage by heart disease, especially by ischemia of the heart tissues resulting from poor coronary blood flow. The effect is often a bizarre heart rhythm or abnormal sequence of contraction of the heart chambers, and the pumping effectiveness of the heart often is affected severely, even to the extent of causing death.

Specialized Excitatory and Conductive System of the Heart

Figure 10-1 shows the specialized excitatory and conductive system of the heart that controls cardiac contractions. The figure shows the sinus node (also called sinoatrial or S-Anode), in which the normal rhythmical impulses are generated; the internodal pathways that conduct impulses from the sinus node to the atrioventricular (A-V) node; the A-V node, in which impulses from the atria are delayed before passing into the ventricles; the A-V bundle, which conducts impulses from the atria into the ventricles; and the left and right bundle branches of Purkinje fibers, which conduct the cardiac impulses to all parts of the ventricles.

Sinus (Sinoatrial) Node

The sinus node (also called *sinoatrial node*) is a small, flattened, ellipsoid strip of specialized cardiac muscle about 3 millimeters wide, 15 millimeters long, and 1 millimeter thick. It is located in the superior posterolateral wall of the right atrium immediately below and slightly lateral to the opening of the superior vena cava. The fibers of this node have almost no contractile muscle filaments and are each only 3 to 5 micrometers in diameter, in contrast to a diameter of 10 to 15 micrometers for the surrounding atrial muscle fibers. However, the sinus nodal fibers connect directly with the atrial muscle fibers so that any action potential that begins in the sinus node spreads immediately into the atrial muscle wall.

Automatic Electrical Rhythmicity of the Sinus Fibers

Some cardiac fibers have the capability of *self-excitation*, a process that can cause automatic rhythmical discharge and contraction. This is especially true of the fibers of the heart's specialized conducting system, including the fibers of the sinus node. For this reason, the sinus node ordinarily controls the rate of beat of the entire heart, as discussed in detail later in this chapter. First, let us describe this automatic rhythmicity.

Mechanism of Sinus Nodal Rhythmicity

Figure 10-2 shows action potentials recorded from inside a sinus nodal fiber for three heartbeats and, by comparison, a single ventricular muscle fiber action potential. Note that the "resting membrane potential" of the sinus nodal fiber between discharges has a negativity of about -55 to -60 millivolts, in comparison with -85 to -90 millivolts for the ventricular muscle fiber. The cause of this lesser negativity is that the cell membranes of the sinus fibers are naturally leaky to sodium and calcium ions, and positive charges of the entering sodium and calcium ions neutralize some of the intracellular negativity.

Before attempting to explain the rhythmicity of the sinus nodal fibers, first recall from the discussions of Chapters 5 and 9 that cardiac muscle has three types of membrane ion channels that play important roles in causing the voltage changes of the action potential. They are (1) *fast sodium channels*, (2) *slow sodium-calcium channels*, and (3) *potassium channels*.

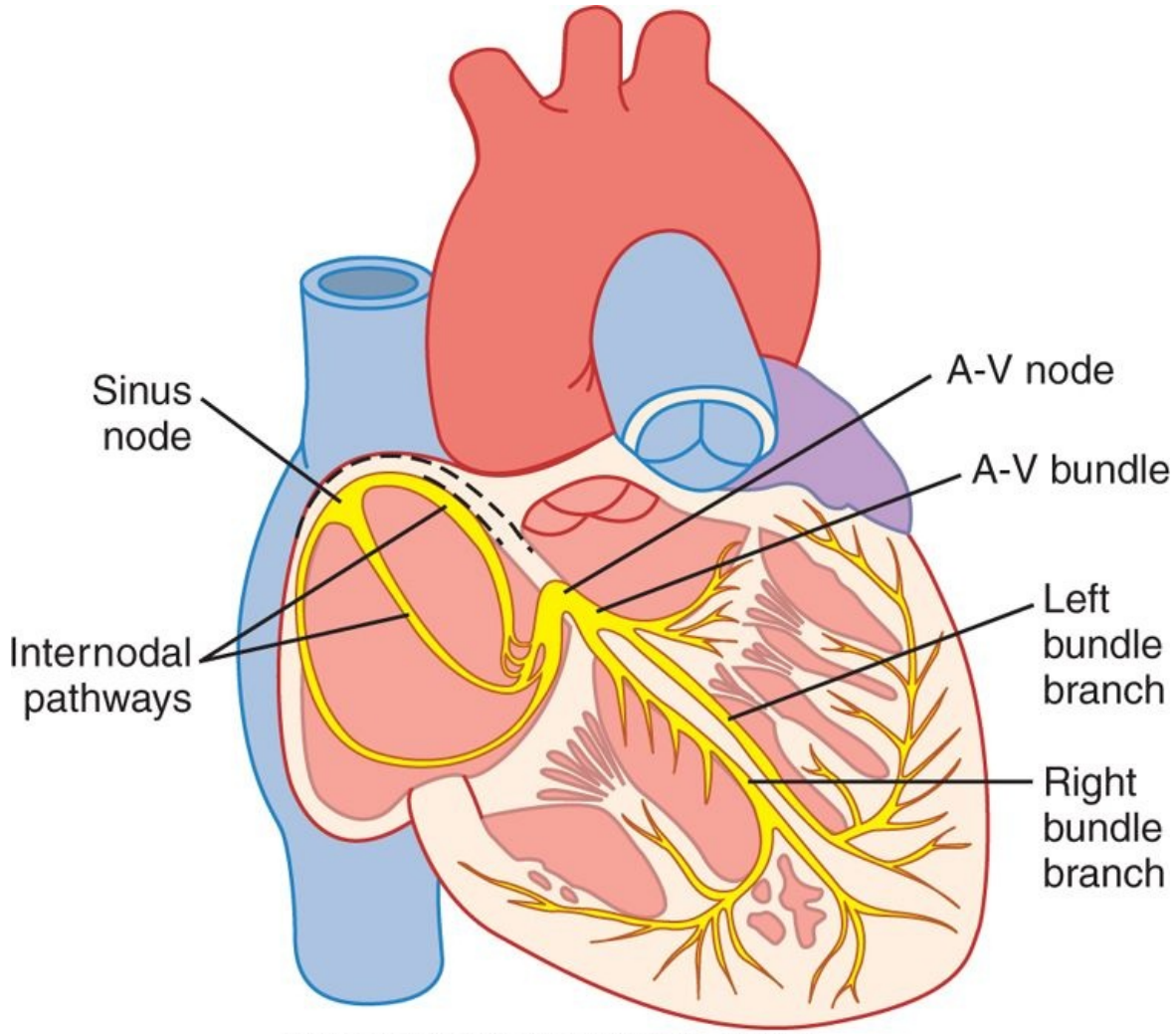


Figure 10-1 Sinus node and the Purkinje system of the heart, showing also the A-V node, atrial internodal pathways, and ventricular bundle branches.

Opening of the fast sodium channels for a few 10,000 ths of a second is responsible for the rapid upstroke spike of the action potential observed in ventricular muscle, because of rapid influx of positive sodium ions to the interior of the fiber. Then the "plateau" of the ventricular action potential is caused primarily by slower opening of the slow sodium-calcium channels, which lasts for about 0.3 second. Finally, opening of potassium channels allows diffusion of large amounts of positive potassium ions in the outward direction through the fiber membrane and returns the membrane potential to its resting level.

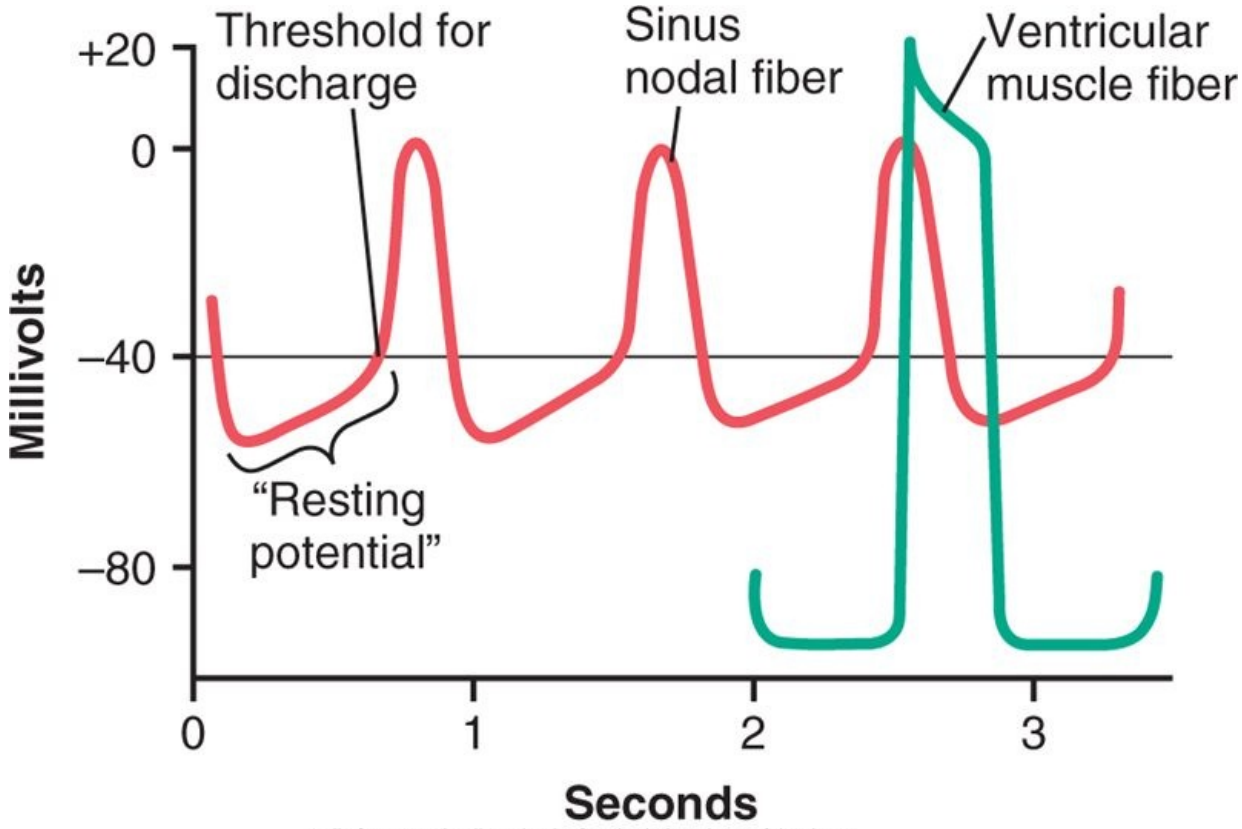


Figure 10-2 Rhythmical discharge of a sinus nodal fiber. Also, the sinus nodal action potential is compared with that of a ventricular muscle fiber.

But there is a difference in the function of these channels in the sinus nodal fiber because the "resting" potential is much less negative-only -55 millivolts in the nodal fiber instead of the -90 millivolts in the ventricular muscle fiber. At this level of -55 millivolts, the fast sodium channels mainly have already become "inactivated," which means that they have become blocked. The cause of this is that any time the membrane potential remains less negative than about -55 millivolts for more than a few milliseconds, the inactivation gates on the inside of the cell membrane that close the fast sodium channels become closed and remain so. Therefore, only the slow sodium-calcium channels can open (i.e., can become "activated") and thereby cause the action potential. As a result, the atrial nodal action potential is slower to develop than the action potential of the ventricular muscle. Also, after the action potential does occur, return of the potential to its negative state occurs slowly as well, rather than the abrupt return that occurs for the ventricular fiber.

Self-Excitation of Sinus Nodal Fibers

Because of the high sodium ion concentration in the extracellular fluid outside the nodal fiber, as well as a moderate number of already open sodium channels, positive sodium ions from outside the fibers normally tend to leak to the inside. Therefore, between heartbeats, influx of positively charged sodium ions causes a slow rise in the resting membrane potential in the positive direction. Thus, as shown in Figure 10-2, the "resting" potential gradually rises and becomes less negative between each two heartbeats. When the potential reaches a threshold voltage of about -40 millivolts, the sodium-calcium channels become "activated," thus causing the action potential. Therefore, basically, the inherent leakiness of the sinus nodal fibers to sodium and calcium ions causes their self-excitation.

Why does this leakiness to sodium and calcium ions not cause the sinus nodal fibers to remain depolarized all the time? The answer is that two events occur during the course of the action potential to prevent this. First, the sodium-calcium channels become inactivated (i.e., they close) within about 100 to 150 milliseconds after opening, and second, at about the same time, greatly increased numbers of potassium channels open. Therefore, influx of positive calcium and sodium ions through the sodium-calcium channels ceases, while at the same time large quantities of positive potassium ions diffuse out of the fiber. Both of these effects reduce the intracellular potential back to its negative resting level and therefore terminate the action potential. Furthermore, the potassium channels remain open for another few tenths of a second, temporarily continuing movement of positive charges out of the cell, with resultant excess negativity inside the fiber; this is called *hyperpolarization.* The hyperpolarization state initially carries the "resting" membrane potential down to about -55 to -60 millivolts at the termination of the action potential.

Why is this new state of hyperpolarization not maintained forever? The reason is that during the next few tenths of a second after the action potential is over, progressively more and more potassium channels close. The inward-leaking sodium and calcium ions once again overbalance the outward flux of potassium ions, and this causes the "resting" potential to drift upward once more, finally reaching the threshold level for discharge at a potential of about -40 millivolts. Then the entire process begins again: self-excitation to cause the action potential, recovery from the action potential, hyperpolarization after the action potential is over, drift of the "resting" potential to threshold, and finally re-excitation to elicit another cycle. This process continues indefinitely throughout a person's life.

Internodal Pathways and Transmission of the Cardiac Impulse Through the Atria

The ends of the sinus nodal fibers connect directly with surrounding atrial muscle fibers. Therefore, action potentials originating in the sinus node travel outward into these atrial muscle fibers. In this way, the action potential spreads through the entire atrial muscle mass and, eventually, to the A-V node. The velocity of conduction in most atrial muscle is about 0.3 m/sec, but conduction is more rapid, about 1 m/sec, in several small bands of atrial fibers. One of these, called the *anterior interatrial band,* passes through the anterior walls of the atria to the left atrium. In addition, three other small bands curve through the anterior, lateral, and posterior atrial walls and terminate in the A-V node; shown in Figures 10-1 and 10-3, these are called, respectively, the *anterior, middle, and posterior internodal pathways*. The cause of more rapid velocity of conduction in these bands is the presence of specialized conduction fibers. These fibers are similar to even more rapidly conducting "Purkinje fibers" of the ventricles, which are discussed as follows.

Atrioventricular Node and Delay of Impulse Conduction from the Atria to the Ventricles

The atrial conductive system is organized so that the cardiac impulse does not travel from the atria into the ventricles too rapidly, this delay allows time for the atria to empty their blood into the ventricles before ventricular contraction begins. It is primarily the A-V node and its adjacent conductive fibers that delay this transmission into the ventricles.

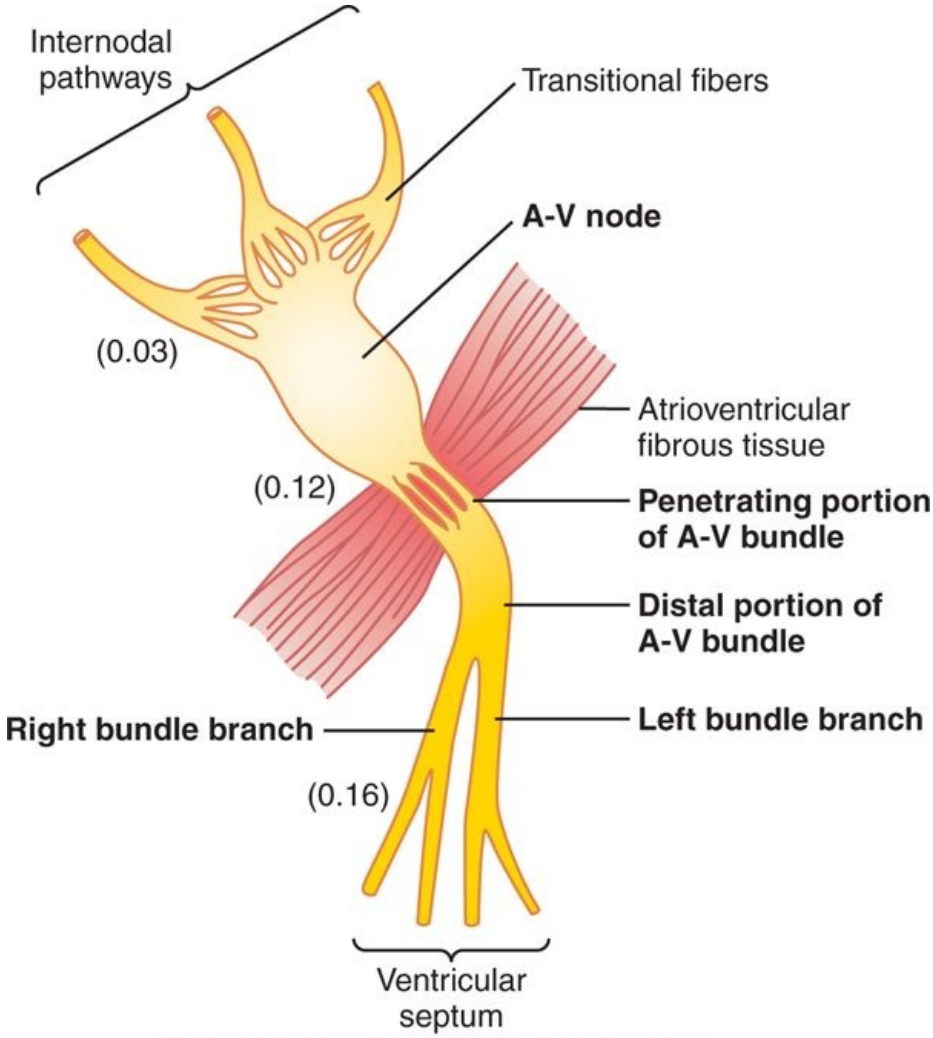


Figure 10-3 Organization of the A-V node. The numbers represent the interval of time from the origin of the impulse in the sinus node. The values have been extrapolated to human beings.

The A-V node is located in the posterior wall of the right atrium immediately behind the tricuspid valve, as shown in Figure 10-1. And Figure 10-3 shows diagrammatically the different parts of this node, plus its connections with the entering atrial internodal pathway fibers and the exiting A-V bundle. The figure also shows the approximate intervals of time in fractions of a second between initial onset of the cardiac impulse in the sinus node and its subsequent appearance in the A-V nodal system. Note that the impulse, after traveling through the internodal pathways, reaches the A-V node about 0.03 second after its origin in the sinus node. Then there is a delay of another 0.09 second in the A-V node itself before the impulse enters the penetrating portion of the A-V bundle, where it passes into the ventricles. A final delay of another 0.04 second occurs mainly in this penetrating A-V bundle, which is composed of multiple small fascicles passing through the fibrous tissue separating the atria from the ventricles.

Thus, the total delay in the A-V nodal and A-V bundle system is about 0.13 second. This, in addition to the initial conduction delay of 0.03 second from the sinus node to the A-V node, makes a total delay of 0.16 second before the excitatory signal finally reaches the contracting muscle of the ventricles.

Cause of the Slow Conduction

The slow conduction in the transitional, nodal, and penetrating A-V bundle fibers is caused mainly by diminished numbers of gap junctions between successive cells in the conducting pathways, so there is great resistance to conduction of excitatory ions from one conducting fiber to the next. Therefore, it is easy to see why each succeeding cell is slow to be excited.

Rapid Transmission in the Ventricular Purkinje System

Special Purkinje fibers lead from the A-V node through the A-V bundle into the ventricles. Except for the initial portion of these fibers where they penetrate the A-V fibrous barrier, they have functional characteristics that are quite the opposite of those of the A-V nodal fibers. They are very large fibers, even larger than the normal ventricular muscle fibers, and they transmit action potentials at a velocity of 1.5 to 4.0 m/sec, a velocity about 6 times that in the usual ventricular muscle and 150 times that in some of the A-V nodal fibers. This allows almost instantaneous transmission of the cardiac impulse throughout the entire remainder of the ventricular muscle.

The rapid transmission of action potentials by Purkinje fibers is believed to be caused by a very high level of permeability of the gap junctions at the intercalated discs between the successive cells that make up the Purkinje fibers. Therefore, ions are transmitted easily from one cell to the next, thus enhancing the velocity of transmission. The Purkinje fibers also have very few myofibrils, which means that they contract little or not at all during the course of impulse transmission.

One-Way Conduction Through the A-V Bundle

A special characteristic of the A-V bundle is the inability, except in abnormal states, of action potentials to travel backward from the ventricles to the atria. This prevents re-entry of cardiac impulses by this route from the ventricles to the atria, allowing only forward conduction from the atria to the ventricles.

Furthermore, it should be recalled that everywhere, except at the A-V bundle, the atrial muscle is separated from the ventricular muscle by a continuous fibrous barrier, a portion of which is shown in Figure 10-3. This barrier normally acts as an insulator to prevent passage of the cardiac impulse between atrial and ventricular muscle through any other route besides forward conduction through the A-V bundle itself. (In rare instances, an abnormal muscle bridge does penetrate the fibrous barrier elsewhere besides at the A-V bundle. Under such conditions, the cardiac impulse can re-enter the atria from the ventricles and cause a serious cardiac arrhythmia.)

Distribution of the Purkinje Fibers in the Ventricles-The Left and Right Bundle Branches

After penetrating the fibrous tissue between the atrial and ventricular muscle, the distal portion of the A-V bundle passes downward in the ventricular septum for 5 to 15 millimeters toward the apex of the heart, as shown in Figures 10-1 and 10-3. Then the bundle divides into left and right bundle branches that lie beneath the endocardium on the two respective sides of the ventricular septum. Each branch spreads downward toward the apex of the ventricle, progressively dividing into smaller branches. These branches in turn course sidewise around each ventricular chamber and back toward the base of the heart. The ends of the Purkinje fibers penetrate about one third of the way into the muscle mass and finally become continuous with the cardiac muscle fibers.

From the time the cardiac impulse enters the bundle branches in the ventricular septum until it reaches the terminations of the Purkinje fibers, the total elapsed time averages only 0.03 second. Therefore, once the cardiac impulse enters the ventricular Purkinje conductive system, it spreads almost immediately to the entire ventricular muscle mass.

Transmission of the Cardiac Impulse in the Ventricular Muscle

Once the impulse reaches the ends of the Purkinje fibers, it is transmitted through the ventricular muscle mass by the ventricular muscle fibers themselves. The velocity of transmission is now only 0.3 to 0.5 m/sec, one sixth that in the Purkinje fibers.

The cardiac muscle wraps around the heart in a double spiral, with fibrous septa between the spiraling layers; therefore, the cardiac impulse does not necessarily travel directly outward toward the surface of the heart but instead angulates toward the surface along the directions of the spirals. Because of this, transmission from the endocardial surface to the epicardial surface of the ventricle requires as much as another 0.03 second, approximately equal to the time required for transmission through the entire ventricular portion of the Purkinje system. Thus, the total time for transmission of the cardiac impulse from the initial bundle branches to the last of the ventricular muscle fibers in the normal heart is about 0.06 second.

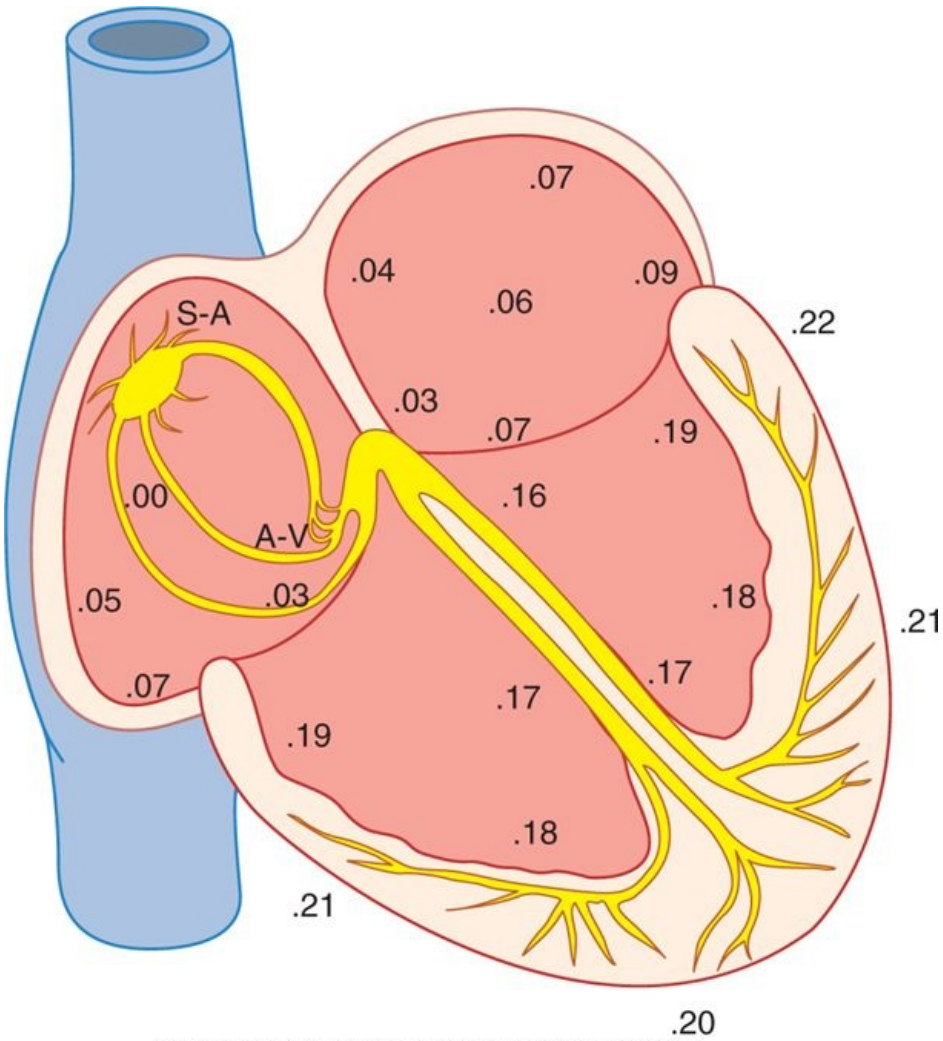


Figure 10-4 Transmission of the cardiac impulse through the heart, showing the time of appearance (in fractions of a second after initial appearance at the sinoatrial node) in different parts of the heart.

Summary of the Spread of the Cardiac Impulse Through the Heart

Figure 10-4 shows in summary form the transmission of the cardiac impulse through the human heart. The numbers on the figure represent the intervals of time, in fractions of a second, that lapse between the origin of the cardiac impulse in the sinus node and its appearance at each respective point in the heart. Note that the impulse spreads at moderate velocity through the atria but is delayed more than 0.1 second in the A-V nodal region before appearing in the ventricular septal A-V bundle. Once it has entered this bundle, it spreads very rapidly through the Purkinje fibers to the entire endocardial surfaces of the ventricles. Then the impulse once again spreads slightly less rapidly through the ventricular muscle to the epicardial surfaces.

It is important that the student learn in detail the course of the cardiac impulse through the heart and the precise times of its appearance in each separate part of the heart, because a thorough quantitative knowledge of this process is essential to the understanding of electrocardiography, which is discussed in Chapters 11 through 13.

Control of Excitation and Conduction in the Heart

Sinus Node as the Pacemaker of the Heart

In the discussion thus far of the genesis and transmission of the cardiac impulse through the heart, we have noted that the impulse normally arises in the sinus node. In some abnormal conditions, this is not the case. Other parts of the heart can also exhibit intrinsic rhythmical excitation in the same way that the sinus nodal fibers do; this is particularly true of the A-V nodal and Purkinje fibers.

The A-V nodal fibers, when not stimulated from some outside source, discharge at an intrinsic rhythmical rate of 40 to 60 times per minute, and the Purkinje fibers discharge at a rate somewhere between 15 and 40 times per minute. These rates are in contrast to the normal rate of the sinus node of 70 to 80 times per minute.

Why then does the sinus node rather than the A-V node or the Purkinje fibers control the heart's rhythmicity? The answer derives from the fact that the discharge rate of the sinus node is considerably faster than the natural self-excitatory discharge rate of either the A-V node or the Purkinje fibers. Each time the sinus node discharges, its impulse is conducted into both the A-V node and the Purkinje fibers, also discharging their excitable membranes. But the sinus node discharges again before either the A-V node or the Purkinje fibers can reach their own thresholds for self-excitation. Therefore, the new impulse from the sinus node discharges both the A-V node and the Purkinje fibers before self-excitation can occur in either of these.

Thus, the sinus node controls the beat of the heart because its rate of rhythmical discharge is faster than that of any other part of the heart. Therefore, the sinus node is virtually always the pacemaker of the normal heart.

Abnormal Pacemakers-"Ectopic" Pacemaker

Occasionally some other part of the heart develops a rhythmical discharge rate that is more rapid than that of the sinus node. For instance, this sometimes occurs in the A-V node or in the Purkinje fibers when one of these becomes abnormal. In either case, the pacemaker of the heart shifts from the sinus node to the A-V node or to the excited Purkinje fibers. Under rarer conditions, a place in the atrial or ventricular muscle develops excessive excitability and becomes the pacemaker.

A pacemaker elsewhere than the sinus node is called an "*ectopic*" *pacemaker*. An ectopic pacemaker causes an abnormal sequence of contraction of the different parts of the heart and can cause significant debility of heart pumping.

Another cause of shift of the pacemaker is blockage of transmission of the cardiac impulse from the sinus node to the other parts of the heart. The new pacemaker then occurs most frequently at the A-V node or in the penetrating portion of the A-V bundle on the way to the ventricles.

When A-V block occurs-that is, when the cardiac impulse fails to pass from the atria into the ventricles through the A-V nodal and bundle system-the atria continue to beat at the normal rate of rhythm of the sinus node, while a new pacemaker usually develops in the Purkinje system of the ventricles and drives the ventricular muscle at a new rate somewhere between 15 and 40 beats per minute. After sudden A-V bundle block, the Purkinje system does not begin to emit its intrinsic rhythmical impulses until 5 to 20 seconds later because, before the blockage, the Purkinje fibers had been "overdriven" by the rapid sinus impulses and, consequently, are in a suppressed state. During these 5 to 20 seconds, the ventricles fail to pump blood, and the person faints after the first 4 to 5 seconds because of lack of blood flow to the brain. This delayed pickup of the heartbeat is called *Stokes-Adams syndrome*. If the delay period is too long, it can lead to death.

Role of the Purkinje System in Causing Synchronous Contraction of the Ventricular Muscle

It is clear from our description of the Purkinje system that normally the cardiac impulse arrives at almost all portions of the ventricles within a narrow span of time, exciting the first ventricular muscle fiber only 0.03 to 0.06 second ahead of excitation of the last ventricular muscle fiber. This causes all portions of the ventricular muscle in both ventricles to begin contracting at almost the same time and then to continue contracting for about another 0.3 second.

Effective pumping by the two ventricular chambers requires this synchronous type of contraction. If the cardiac impulse should travel through the ventricles slowly, much of the ventricular mass would contract before contraction of the remainder, in which case the overall pumping effect would be greatly depressed. Indeed, in some types of cardiac debilities, several of which are discussed in Chapters 12 and 13, slow transmission does occur, and the pumping effectiveness of the ventricles is decreased as much as 20 to 30 percent.

Control of Heart Rhythmicity and Impulse Conduction by the Cardiac Nerves: Sympathetic and Parasympathetic Nerves

The heart is supplied with both sympathetic and parasympathetic nerves, as shown in Figure 9-10 of Chapter 9. The parasympathetic nerves (the vagi) are distributed mainly to the S-A and A-V nodes, to a lesser extent to the muscle of the two atria, and very little directly to the ventricular muscle. The sympathetic nerves, conversely, are distributed to all parts of the heart, with strong representation to the ventricular muscle, as well as to all the other areas.

Parasympathetic (Vagal) Stimulation Can Slow or Even Block Cardiac Rhythm and Conduction-"Ventricular Escape."

Stimulation of the parasympathetic nerves to the heart (the vagi) causes the hormone *acetylcholine* to be released at the vagal endings. This hormone has two major effects on the heart. First, it decreases the rate of rhythm of the sinus node, and second, it decreases the excitability of the A-V junctional fibers between the atrial musculature and the A-V node, thereby slowing transmission of the cardiac impulse into the ventricles.

Weak to moderate vagal stimulation slows the rate of heart pumping, often to as little as one-half normal. And strong stimulation of the vagi can stop completely the rhythmical excitation by the sinus node or block completely transmission of the cardiac impulse from the atria into the ventricles through the A-V mode. In either case, rhythmical excitatory signals are no longer transmitted into the ventricles. The ventricles stop beating for 5 to 20 seconds, but then some small area in the Purkinje fibers, usually in the ventricular septal portion of the A-V bundle, develops a rhythm of its own and causes ventricular contraction at a rate of 15 to 40 beats per minute. This phenomenon is called *ventricular escape.*

Mechanism of the Vagal Effects

The acetylcholine released at the vagal nerve endings greatly increases the permeability of the fiber membranes to potassium ions, which allows rapid leakage of potassium out of the conductive fibers. This causes increased negativity inside the fibers, an effect called *hyperpolarization,* which makes this excitable tissue much less excitable, as explained in Chapter 5.

In the sinus node, the state of hyperpolarization decreases the "resting" membrane potential of the sinus nodal fibers to a level considerably more negative than usual, to -65 to -75 millivolts rather than the normal level of -55 to -60 millivolts. Therefore, the initial rise of the sinus nodal membrane potential caused by inward sodium and calcium leakage requires much longer to reach the threshold potential for excitation. This greatly slows the rate of rhythmicity of these nodal fibers. If the vagal stimulation is strong enough, it is possible to stop entirely the rhythmical self-excitation of this node.

In the A-V node, a state of hyperpolarization caused by vagal stimulation makes it difficult for the small atrial fibers entering the node to generate enough electricity to excite the nodal fibers. Therefore, the safety factor for transmission of the cardiac impulse through the transitional fibers into the A-V nodal fibers decreases. A moderate decrease simply delays conduction of the impulse, but a large decrease blocks conduction entirely.

Effect of Sympathetic Stimulation on Cardiac Rhythm and Conduction

Sympathetic stimulation causes essentially the opposite effects on the heart to those caused by vagal stimulation, as follows: First, it increases the rate of sinus nodal discharge. Second, it increases the rate of conduction, as well as the level of excitability in all portions of the heart. Third, it increases greatly the force of contraction of all the cardiac musculature, both atrial and ventricular, as discussed in Chapter 9.

In short, sympathetic stimulation increases the overall activity of the heart. Maximal stimulation can almost triple the frequency of heartbeat and can increase the strength of heart contraction as much as twofold.

Mechanism of the Sympathetic Effect

Stimulation of the sympathetic nerves releases the hormone *norepinephrine* at the sympathetic nerve endings. Norepinephrine in turn stimulates *beta-1 adrenergic receptors*, which mediate the effects on heart rate. The precise mechanism by which beta-1 adrenergic stimulation acts on cardiac muscle fibers is somewhat unclear, but the belief is that it increases the permeability of the fiber membrane to sodium and calcium ions. In the sinus node, an increase of sodium-calcium permeability causes a more positive resting potential and also causes increased rate of upward drift of the diastolic membrane potential toward the threshold level for self-excitation, thus accelerating self-excitation and, therefore, increasing the heart rate.

In the A-V node and A-V bundles, increased sodium-calcium permeability makes it easier for the action potential to excite each succeeding portion of the conducting fiber bundles, thereby decreasing the conduction time from the atria to the ventricles.

The increase in permeability to calcium ions is at least partially responsible for the increase in contractile strength of the cardiac muscle under the influence of sympathetic stimulation, because calcium ions play a powerful role in exciting the contractile process of the myofibrils.

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