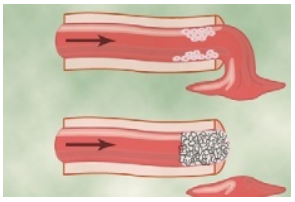
CHAPTER 36

Hemostasis and Blood Coagulation



Events in Hemostasis

The term *hemostasis* means prevention of blood loss. Whenever a vessel is severed or ruptured, hemostasis is achieved by several mechanisms: (1) vascular constriction, (2) formation of a platelet plug, (3) formation of a blood clot as a result of blood coagulation, and (4) eventual growth of fibrous tissue into the blood clot to close the hole in the vessel permanently.

Vascular Constriction

Immediately after a blood vessel has been cut or ruptured, the trauma to the vessel wall causes the smooth muscle in the wall to contract; this instantaneously reduces the flow of blood from the ruptured vessel. The contraction results from (1) local myogenic spasm, (2) local autacoid factors from the traumatized tissues and blood platelets, and (3) nervous reflexes. The nervous reflexes are initiated by pain nerve impulses or other sensory impulses that originate from the traumatized vessel or nearby tissues. However, even more vasoconstriction probably results from local *myogenic contraction* of the blood vessels initiated by direct damage to the vascular wall. And, for the smaller vessels, the platelets are responsible for much of the vasoconstriction by releasing a vasoconstrictor substance, *thromboxane* A_2.

The more severely a vessel is traumatized, the greater the degree of vascular spasm. The spasm can last for many minutes or even hours, during which time the processes of platelet plugging and blood coagulation can take place.

Formation of the Platelet Plug

If the cut in the blood vessel is very small—indeed, many very small vascular holes do develop throughout the body each day—the cut is often sealed by a *platelet plug,* rather than by a blood clot. To understand this, it is important that we first discuss the nature of platelets themselves.

Physical and Chemical Characteristics of Platelets

Platelets (also called *thrombocytes*) are minute discs 1 to 4 micrometers in diameter. They are formed in the bone marrow from *megakaryocytes*, which are extremely large cells of the hematopoietic series in the marrow; the megakaryocytes fragment into the minute platelets either in the bone marrow or soon after entering the blood, especially as they squeeze through capillaries. The normal concentration of platelets in the blood is between 150,000 and 300,000 per microliter.

Platelets have many functional characteristics of whole cells, even though they do not have nuclei and cannot reproduce. In their cytoplasm are such active factors as (1) *actin* and *myosin molecules,* which are contractile proteins similar to those found in muscle cells, and still another contractile protein, *thrombosthenin*, that can cause the platelets to contract; (2) residuals of both the *endoplasmic reticulum* and the *Golgi apparatus* that synthesize various enzymes and especially store large quantities of calcium ions; (3) mitochondria and enzyme systems that are capable of forming *adenosine triphosphate* (ATP) and *adenosine diphosphate* (ADP); (4) enzyme systems that synthesize *prostaglandins,* which are local hormones that cause many vascular and other local tissue reactions; (5) an important protein called *fibrin-stabilizing factor,* which we discuss later in relation to blood coagulation; and (6) a *growth factor* that causes vascular endothelial cells, vascular smooth muscle cells, and fibroblasts to multiply and grow, thus causing cellular growth that eventually helps repair damaged vascular walls.

The cell membrane of the platelets is also important. On its surface is a coat of *glycoproteins* that repulses adherence to normal endothelium and yet causes adherence to *injured* areas of the vessel wall, especially to injured endothelial cells and even more so to any exposed collagen from deep within the vessel wall. In addition, the platelet membrane contains large amounts of *phospholipids* that activate multiple stages in the blood-clotting process, as we discuss later.

Thus, the platelet is an active structure. It has a half-life in the blood of 8 to 12 days, so over several weeks its functional processes run out. Then it is eliminated from

the circulation mainly by the tissue macrophage system. More than one half of the platelets are removed by macrophages in the spleen, where the blood passes through a latticework of tight trabeculae.

Mechanism of the Platelet Plug

Platelet repair of vascular openings is based on several important functions of the platelet. When platelets come in contact with a damaged vascular surface, especially with collagen fibers in the vascular wall, the platelets immediately change their own characteristics drastically. They begin to swell; they assume irregular forms with numerous irradiating pseudopods protruding from their surfaces; their contractile proteins contract forcefully and cause the release of granules that contain multiple active factors; they become sticky so that they adhere to collagen in the tissues and to a protein called *von Willebrand factor* that leaks into the traumatized tissue from the plasma; they secrete large quantities of ADP; and their enzymes form *thromboxane* A_2. The ADP and thromboxane in turn act on nearby platelets to activate them as well, and the stickiness of these additional platelets causes them to adhere to the original activated platelets.

Therefore, at the site of any opening in a blood vessel wall, the damaged vascular wall activates successively increasing numbers of platelets that themselves attract more and more additional platelets, thus forming a *platelet plug.* This is at first a loose plug, but it is usually successful in blocking blood loss if the vascular opening is small. Then, during the subsequent process of blood coagulation, *fibrin threads* form. These attach tightly to the platelets, thus constructing an unyielding plug.

Importance of the Platelet Mechanism for Closing Vascular Holes. The platelet-plugging mechanism is extremely important for closing minute ruptures in very small blood vessels that occur many thousands of times daily. Indeed, multiple small holes through the endothelial cells themselves are often closed by platelets actually fusing with the endothelial cells to form additional endothelial cell membrane. A person who has few blood platelets develops each day literally thousands of small hemorrhagic areas under the skin and throughout the internal tissues, but this does not occur in the normal person.

Blood Coagulation in the Ruptured Vessel

The third mechanism for hemostasis is formation of the blood clot. The clot begins to develop in 15 to 20 seconds if the trauma to the vascular wall has been severe, and in 1 to 2 minutes if the trauma has been minor. Activator substances from the traumatized vascular wall, from platelets, and from blood proteins adhering to the traumatized vascular wall initiate the clotting process. The physical events of this process are shown in Figure 36-1, and Table 36-1 lists the most important of the clotting factors.

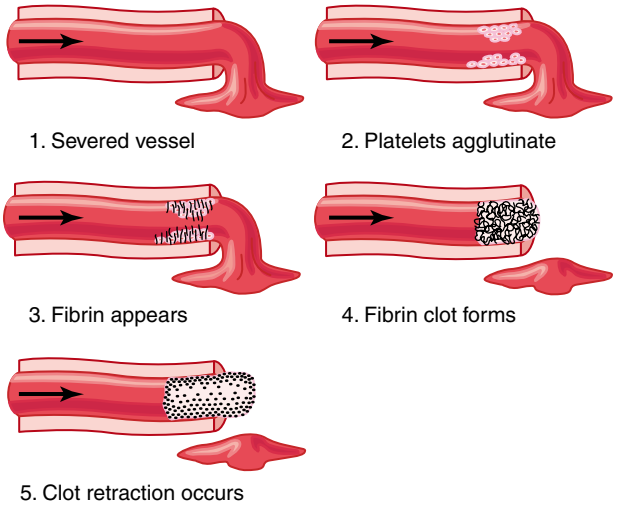


Figure 36-1 Clotting process in a traumatized blood vessel. (Modified from Seegers WH: Hemostatic Agents, 1948. Courtesy of Charles C Thomas, Publisher, Ltd., Springfield, Ill.)

Within 3 to 6 minutes after rupture of a vessel, if the vessel opening is not too large, the entire opening or broken end of the vessel is filled with clot. After 20 minutes to an hour, the clot retracts; this closes the vessel still further. Platelets also play an important role in this clot retraction, as is discussed later.

Table 36-1 Clotting Factors in Blood and Their Synonyms

Clotting Factor	Synonyms
Fibrinogen	Factor I
Prothrombin	Factor II
Tissue factor	Factor III; tissue thromboplastin
Calcium	Factor IV
Factor V	Proaccelerin; labile factor; Ac-globulin (Ac-G)
Factor VII	Serum prothrombin conversion accelerator (SPCA); proconvertin; stable factor
Factor VIII	Antihemophilic factor (AHF); antihemophilic globulin (AHG); antihemophilic factor A
Factor IX	Plasma thromboplastin component (PTC); Christmas factor; antihemophilic factor B
Factor X	Stuart factor; Stuart-Prower factor
Factor XI	Plasma thromboplastin antecedent (PTA); antihemophilic factor C
Factor XII	Hageman factor
Factor XIII	Fibrin-stabilizing factor
Prekallikrein	Fletcher factor
High-molecular-weight kininogen	Fitzgerald factor; HMWK (high-molecular-weight kininogen)
Platelets	

Fibrous Organization or Dissolution of the Blood Clot

Once a blood clot has formed, it can follow one of two courses: (1) It can become invaded by *fibroblasts,* which subsequently form connective tissue all through the clot, or (2) it can dissolve. The usual course for a clot that forms in a small hole of a vessel wall is invasion by fibroblasts, beginning within a few hours after the clot is formed (which is promoted at least partially by *growth factor* secreted by platelets). This continues to complete organization of the clot into fibrous tissue within about 1 to 2 weeks.

Conversely, when excess blood has leaked into the tissues and tissue clots have occurred where they are not needed, special substances within the clot itself usually become activated. These function as enzymes to dissolve the clot, as discussed later in the chapter.

Mechanism of Blood Coagulation

Basic Theory. More than 50 important substances that cause or affect blood coagulation have been found in the blood and in the tissues—some that promote coagulation, called *procoagulants,* and others that inhibit coagulation, called *anticoagulants.* Whether blood will coagulate depends on the balance between these two groups of substances. In the blood stream, the anticoagulants normally predominate, so the blood does not coagulate while it is circulating in the blood vessels. But when a vessel is ruptured, procoagulants from the area of tissue damage become "activated" and override the anticoagulants, and then a clot does develop.

General Mechanism. Clotting takes place in three essential steps: (1) In response to rupture of the vessel or damage to the blood itself, a complex cascade of chemical reactions occurs in the blood involving more than a dozen blood coagulation factors. The net result is formation of a complex of activated substances collectively called *prothrombin activator.* (2) The prothrombin activator catalyzes conversion of *prothrombin* into *thrombin.* (3) The thrombin acts as an enzyme to convert *fibrinogen* into *fibrin fibers* that enmesh platelets, blood cells, and plasma to form the clot.

Let us discuss first the mechanism by which the blood clot itself is formed, beginning with conversion of prothrombin to thrombin; then we will come back to the initiating stages in the clotting process by which prothrombin activator is formed.

Conversion of Prothrombin to Thrombin

First, prothrombin activator is formed as a result of rupture of a blood vessel or as a result of damage to special substances in the blood. Second, the prothrombin activator, in the presence of sufficient amounts of ionic Ca^{++}, causes conversion of prothrombin to thrombin (Figure 36-2). Third,

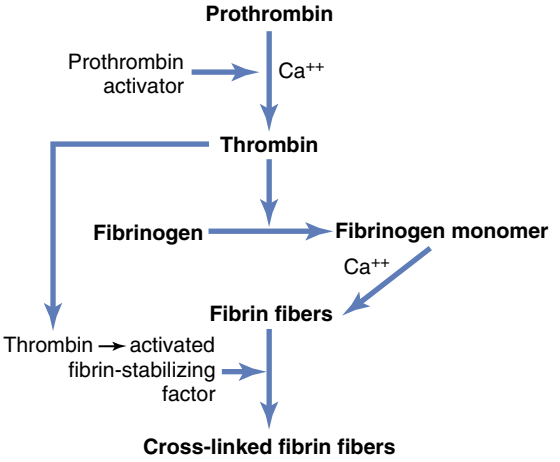


Figure 36-2 Schema for conversion of prothrombin to thrombin and polymerization of fibrinogen to form fibrin fibers.

the thrombin causes polymerization of fibrinogen molecules into fibrin fibers within another 10 to 15 seconds. Thus, the rate-limiting factor in causing blood coagulation is usually the formation of prothrombin activator and not the subsequent reactions beyond that point, because these terminal steps normally occur rapidly to form the clot.

Platelets also play an important role in the conversion of prothrombin to thrombin because much of the prothrombin first attaches to prothrombin receptors on the platelets already bound to the damaged tissue.

Prothrombin and Thrombin. Prothrombin is a plasma protein, an alpha2-globulin, having a molecular weight of 68,700. It is present in normal plasma in a concentration of about 15 mg/dl. It is an unstable protein that can split easily into smaller compounds, one of which is *thrombin,* which has a molecular weight of 33,700, almost exactly one half that of prothrombin.

Prothrombin is formed continually by the liver, and it is continually being used throughout the body for blood clotting. If the liver fails to produce prothrombin, in a day or so prothrombin concentration in the plasma falls too low to provide normal blood coagulation.

Vitamin K is required by the liver for normal activation of prothrombin, as well as a few other clotting factors. Therefore, either lack of vitamin K or the presence of liver disease that prevents normal prothrombin formation can decrease the prothrombin level so low that a bleeding tendency results.

Conversion of Fibrinogen to Fibrin—Formation of the Clot

Fibrinogen. Fibrinogen is a high-molecular-weight protein (MW = 340,000) that occurs in the plasma in quantities of 100 to 700 mg/dl. Fibrinogen is formed in the liver, and liver disease can decrease the concentration of circulating fibrinogen, as it does the concentration of prothrombin, pointed out earlier.

Because of its large molecular size, little fibrinogen normally leaks from the blood vessels into the interstitial

fluids, and because fibrinogen is one of the essential factors in the coagulation process, interstitial fluids ordinarily do not coagulate. Yet, when the permeability of the capillaries becomes pathologically increased, fibrinogen does then leak into the tissue fluids in sufficient quantities to allow clotting of these fluids in much the same way that plasma and whole blood can clot.

Action of Thrombin on Fibrinogen to Form Fibrin. Thrombin is a protein *enzyme* with weak proteolytic capabilities. It acts on fibrinogen to remove four low-molecular-weight peptides from each molecule of fibrinogen, forming one molecule of *fibrin monomer* that has the automatic capability to polymerize with other fibrin monomer molecules to form fibrin fibers. Therefore, many fibrin monomer molecules polymerize within seconds into *long fibrin fibers* that constitute the *reticulum* of the blood clot.

In the early stages of polymerization, the fibrin monomer molecules are held together by weak noncovalent hydrogen bonding, and the newly forming fibers are not cross-linked with one another; therefore, the resultant clot is weak and can be broken apart with ease. But another process occurs during the next few minutes that greatly strengthens the fibrin reticulum. This involves a substance called *fibrin-stabilizing factor* that is present in small amounts in normal plasma globulins but is also released from platelets entrapped in the clot. Before fibrin-stabilizing factor can have an effect on the fibrin fibers, it must itself be activated. The same thrombin that causes fibrin formation also activates the fibrin-stabilizing factor. Then this activated substance operates as an enzyme to cause *covalent bonds* between more and more of the fibrin monomer molecules, as well as multiple cross-linkages between adjacent fibrin fibers, thus adding tremendously to the three-dimensional strength of the fibrin meshwork.

Blood Clot. The clot is composed of a meshwork of fibrin fibers running in all directions and entrapping blood cells, platelets, and plasma. The fibrin fibers also adhere to damaged surfaces of blood vessels; therefore, the blood clot becomes adherent to any vascular opening and thereby prevents further blood loss.

Clot Retraction—Serum. Within a few minutes after a clot is formed, it begins to contract and usually expresses most of the fluid from the clot within 20 to 60 minutes. The fluid expressed is called *serum* because all its fibrinogen and most of the other clotting factors have been removed; in this way, serum differs from plasma. Serum cannot clot because it lacks these factors.

Platelets are necessary for clot retraction to occur. Therefore, failure of clot retraction is an indication that the number of platelets in the circulating blood might be low. Electron micrographs of platelets in blood clots show that they become attached to the fibrin fibers in such a way that they actually bond different fibers together. Furthermore, platelets entrapped in the clot continue to release procoagulant substances, one of the most important of which is *fibrin-stabilizing factor,* which causes more and more cross-linking bonds between adjacent fibrin fibers. In addition, the platelets themselves contribute directly to clot contraction by activating platelet thrombosthenin, actin, and myosin molecules, which are all contractile proteins in the platelets and cause strong contraction of the platelet spicules attached to the fibrin. This also helps compress the fibrin meshwork into a smaller mass. The contraction is activated and accelerated by thrombin, as well as by calcium ions released from calcium stores in the mitochondria, endoplasmic reticulum, and Golgi apparatus of the platelets.

As the clot retracts, the edges of the broken blood vessel are pulled together, thus contributing still further to hemostasis.

Positive Feedback of Clot Formation

Once a blood clot has started to develop, it normally extends within minutes into the surrounding blood. That is, the clot itself initiates a positive feedback to promote more clotting. One of the most important causes of this is the fact that the proteolytic action of thrombin allows it to act on many of the other blood-clotting factors in addition to fibrinogen. For instance, thrombin has a direct proteolytic effect on prothrombin itself, tending to convert this into still more thrombin, and it acts on some of the blood-clotting factors responsible for formation of prothrombin activator. (These effects, discussed in subsequent paragraphs, include acceleration of the actions of Factors VIII, IX, X, XI, and XII and aggregation of platelets.) Once a critical amount of thrombin is formed, a positive feedback develops that causes still more blood clotting and more and more thrombin to be formed; thus, the blood clot continues to grow until blood leakage ceases.

Initiation of Coagulation: Formation of Prothrombin Activator

Now that we have discussed the clotting process, we turn to the more complex mechanisms that initiate clotting in the first place. These mechanisms are set into play by (1) trauma to the vascular wall and adjacent tissues, (2) trauma to the blood, or (3) contact of the blood with damaged endothelial cells or with collagen and other tissue elements outside the blood vessel. In each instance, this leads to the formation of *prothrombin activator,* which then causes prothrombin conversion to thrombin and all the subsequent clotting steps.

Prothrombin activator is generally considered to be formed in two ways, although, in reality, the two ways interact constantly with each other: (1) by the *extrinsic pathway* that begins with trauma to the vascular wall and surrounding tissues and (2) by the *intrinsic pathway* that begins in the blood itself.

In both the extrinsic and the intrinsic pathways, a series of different plasma proteins called *blood-clotting*

factors plays a major role. Most of these proteins are *inactive* forms of proteolytic enzymes. When converted to the active forms, their enzymatic actions cause the successive, cascading reactions of the clotting process.

Most of the clotting factors, which are listed in Table 36-1, are designated by Roman numerals. To indicate the activated form of the factor, a small letter "a" is added after the Roman numeral, such as Factor VIIIa to indicate the activated state of Factor VIII.

Extrinsic Pathway for Initiating Clotting

The extrinsic pathway for initiating the formation of prothrombin activator begins with a traumatized vascular wall or traumatized extravascular tissues that come in contact with the blood. This leads to the following steps, as shown in Figure 36-3:

1. *Release of tissue factor.* Traumatized tissue releases a complex of several factors called *tissue factor* or *tissue thromboplastin.* This factor is composed especially of *phospholipids* from the membranes of the tissue plus a *lipoprotein complex* that functions mainly as a *proteolytic enzyme.*
2. *Activation of Factor X—role of Factor VII and tissue factor.* The lipoprotein complex of tissue factor further complexes with blood coagulation Factor VII and, in the presence of calcium ions, acts enzymatically on Factor X to form *activated Factor X* (Xa).
3. *Effect of Xa to form prothrombin activator—role of Factor V.* The activated Factor X combines immediately with tissue phospholipids that are part of tissue factors or with additional phospholipids released from platelets, as well as with Factor V to form the complex called *prothrombin activator.* Within a few seconds, in the presence of calcium ions (Ca^{++}), this splits prothrombin to form thrombin, and the clotting process proceeds as already explained. At first, the Factor V in the prothrombin activator complex is inactive, but once clotting begins and thrombin begins to form, the proteolytic action of thrombin activates Factor V. This then becomes an additional strong accelerator of prothrombin activation. Thus, in the final prothrombin activator complex, activated Factor X is the actual protease that causes splitting of prothrombin to form thrombin; activated Factor V greatly accelerates this protease activity, and platelet phospholipids act as a vehicle that further accelerates the process. Note especially the *positive feedback* effect of thrombin, acting through Factor V, to accelerate the entire process once it begins.

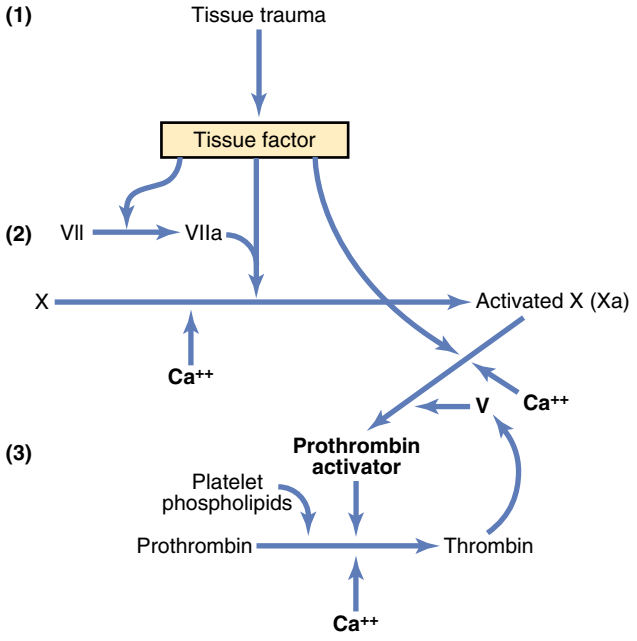


Figure 36-3 Extrinsic pathway for initiating blood clotting.

Intrinsic Pathway for Initiating Clotting

The second mechanism for initiating formation of prothrombin activator, and therefore for initiating clotting, *begins with trauma to the blood or exposure of the blood to collagen* from a traumatized blood vessel wall. Then the process continues through the series of cascading reactions shown in Figure 36-4.

1. *Blood trauma causes (1) activation of Factor XII and (2) release of platelet phospholipids.* Trauma to the blood or exposure of the blood to vascular wall collagen alters two important clotting factors in the blood: Factor XII and the platelets. When Factor XII is disturbed, such as by coming into contact with collagen or with a wettable surface such as glass, it takes on a new molecular configuration that converts it into a proteolytic enzyme called "activated Factor XII." Simultaneously, the blood trauma also damages the platelets because of adherence to either collagen or a wettable surface (or by damage in other ways), and this releases platelet phospholipids that contain the lipoprotein called *platelet factor 3,* which also plays a role in subsequent clotting reactions.
2. *Activation of Factor XI.* The activated Factor XII acts enzymatically on Factor XI to activate this factor as well, which is the second step in the intrinsic pathway. This reaction also requires *HMW (high-molecular-weight) kininogen* and is accelerated by prekallikrein.
3. *Activation of Factor IX by activated Factor XI.* The activated Factor XI then acts enzymatically on Factor IX to activate this factor as well.
4. *Activation of Factor X—role of Factor VIII.* The activated Factor IX, acting in concert with activated Factor VIII and with the platelet phospholipids and factor 3 from the traumatized platelets, activates Factor X. It is clear that when either Factor VIII or platelets are in short supply, this step is deficient. Factor VIII is the factor that is missing in a person who has classic *hemophilia,* for which reason it is called *antihemophilic factor.* Platelets are the clotting factor that is lacking in the bleeding disease called *thrombocytopenia.*

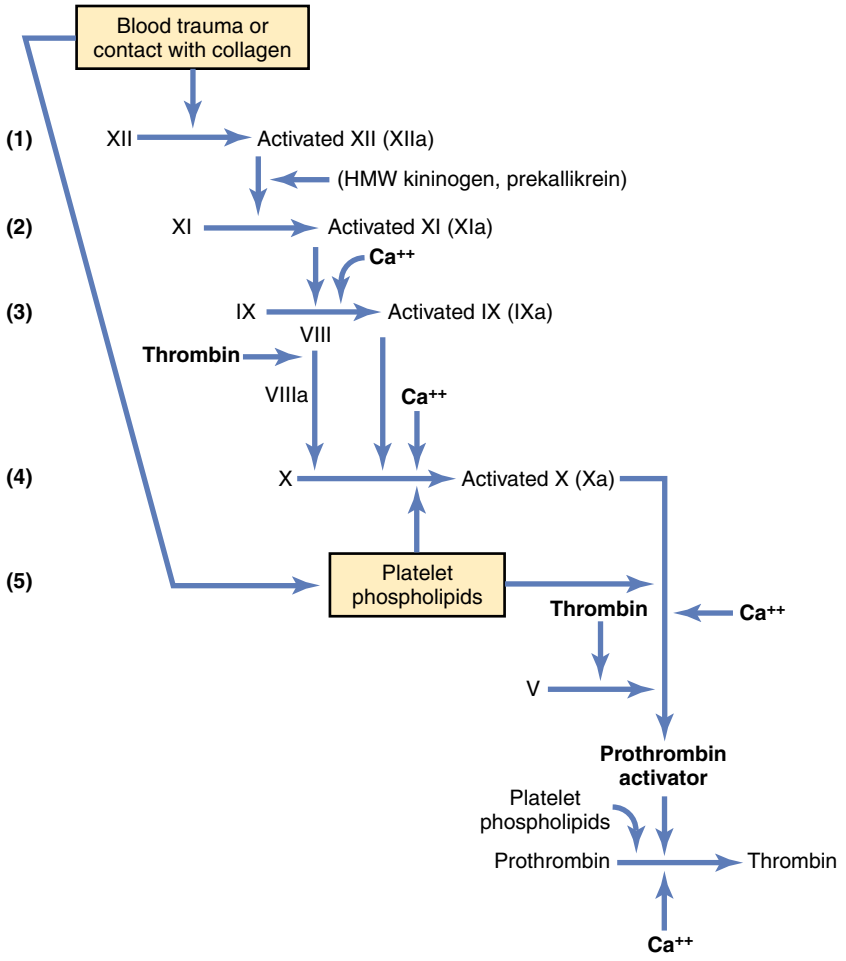


Figure 36-4 Intrinsic pathway for initiating blood clotting.

5. *Action of activated Factor X to form prothrombin activator—role of Factor V.* This step in the intrinsic pathway is the same as the last step in the extrinsic pathway. That is, activated Factor X combines with Factor V and platelet or tissue phospholipids to form the complex called *prothrombin activator.* The prothrombin activator in turn initiates within seconds the cleavage of prothrombin to form thrombin, thereby setting into motion the final clotting process, as described earlier.

Role of Calcium Ions in the Intrinsic and Extrinsic Pathways

Except for the first two steps in the intrinsic pathway, calcium ions are required for promotion or acceleration of all the blood-clotting reactions. Therefore, in the absence of calcium ions, blood clotting by either pathway does not occur.

In the living body, the calcium ion concentration seldom falls low enough to significantly affect the kinetics of blood clotting. But, when blood is removed from a person, it can be prevented from clotting by reducing the calcium ion concentration below the threshold level for clotting, either by deionizing the calcium by causing it to react with substances such as *citrate ion* or by precipitating the calcium with substances such as *oxalate ion.*

Interaction Between the Extrinsic and Intrinsic Pathways—Summary of Blood-Clotting Initiation

It is clear from the schemas of the intrinsic and extrinsic systems that after blood vessels rupture, clotting occurs by both pathways simultaneously. Tissue factor initiates the extrinsic pathway, whereas contact of Factor XII and platelets with collagen in the vascular wall initiates the intrinsic pathway.

An especially important difference between the extrinsic and intrinsic pathways is that *the extrinsic pathway* can be explosive; once initiated, its speed of completion to the final clot is limited only by the amount of tissue factor released from the traumatized tissues and by the quantities of Factors X, VII, and V in the blood. With severe tissue trauma, clotting can occur in as little as 15 seconds. The intrinsic pathway is much slower to proceed, usually requiring 1 to 6 minutes to cause clotting.

Prevention of Blood Clotting in the Normal Vascular System—Intravascular Anticoagulants

Endothelial Surface Factors. Probably the most important factors for preventing clotting in the normal vascular system are (1) the *smoothness* of the endothelial cell surface, which prevents contact activation of the intrinsic clotting system; (2) a layer of *glycocalyx* on the endothelium (glycocalyx is a mucopolysaccharide adsorbed

to the surfaces of the endothelial cells), which repels clotting factors and platelets, thereby preventing activation of clotting; and (3) a protein bound with the endothelial membrane, *thrombomodulin,* which binds thrombin. Not only does the binding of thrombin with thrombomodulin slow the clotting process by removing thrombin, but the thrombomodulin-thrombin complex also activates a plasma protein, *protein C,* that acts as an anticoagulant by *inactivating* activated Factors V and VIII.

When the endothelial wall is damaged, its smoothness and its glycocalyx-thrombomodulin layer are lost, which activates both Factor XII and the platelets, thus setting off the intrinsic pathway of clotting. If Factor XII and platelets come in contact with the subendothelial collagen, the activation is even more powerful.

Antithrombin Action of Fibrin and Antithrombin III. Among the most important *anticoagulants* in the blood are those that remove thrombin from the blood. The most powerful of these are (1) the *fibrin fibers* that are formed during the process of clotting and (2) an alpha-globulin called *antithrombin III* or *antithrombin-heparin cofactor.*

While a clot is forming, about 85 to 90 percent of the thrombin formed from the prothrombin becomes adsorbed to the fibrin fibers as they develop. This helps prevent the spread of thrombin into the remaining blood and, therefore, prevents excessive spread of the clot.

The thrombin that does not adsorb to the fibrin fibers soon combines with antithrombin III, which further blocks the effect of the thrombin on the fibrinogen and then also inactivates the thrombin itself during the next 12 to 20 minutes.

Heparin. Heparin is another powerful anticoagulant, but its concentration in the blood is normally low, so only under special physiologic conditions does it have significant anticoagulant effects. However, heparin is used widely as a pharmacological agent in medical practice in much higher concentrations to prevent intravascular clotting.

The heparin molecule is a highly negatively charged conjugated polysaccharide. By itself, it has little or no anticoagulant properties, but when it combines with antithrombin III, the effectiveness of antithrombin III for removing thrombin increases by a hundredfold to a thousandfold, and thus it acts as an anticoagulant. Therefore, in the presence of excess heparin, removal of free thrombin from the circulating blood by antithrombin III is almost instantaneous.

The complex of heparin and antithrombin III removes several other activated coagulation factors in addition to thrombin, further enhancing the effectiveness of anticoagulation. The others include activated Factors XII, XI, X, and IX.

Heparin is produced by many different cells of the body, but especially large quantities are formed by the basophilic *mast cells* located in the pericapillary connective tissue throughout the body. These cells continually secrete small quantities of heparin that diffuse into the circulatory system. The *basophil cells* of the blood, which are functionally almost identical to the mast cells, release small quantities of heparin into the plasma.

Mast cells are abundant in tissue surrounding the capillaries of the lungs and, to a lesser extent, capillaries of the liver. It is easy to understand why large quantities of heparin might be needed in these areas because the capillaries of the lungs and liver receive many embolic clots formed in slowly flowing venous blood; sufficient formation of heparin prevents further growth of the clots.

Lysis of Blood Clots—Plasmin

The plasma proteins contain a euglobulin called *plasminogen* (or *profibrinolysin*) that, when activated, becomes a substance called *plasmin* (or *fibrinolysin*). Plasmin is a proteolytic enzyme that resembles trypsin, the most important proteolytic digestive enzyme of pancreatic secretion. Plasmin digests fibrin fibers and some other protein coagulants such as fibrinogen, Factor V, Factor VIII, prothrombin, and Factor XII. Therefore, whenever plasmin is formed, it can cause lysis of a clot by destroying many of the clotting factors, thereby sometimes even causing hypocoagulability of the blood.

Activation of Plasminogen to Form Plasmin, Then Lysis of Clots. When a clot is formed, a large amount of plasminogen is trapped in the clot along with other plasma proteins. This will not become plasmin or cause lysis of the clot until it is activated. The injured tissues and vascular endothelium very slowly release a powerful activator called *tissue plasminogen activator* (t-PA) that a few days later, after the clot has stopped the bleeding, eventually converts plasminogen to plasmin, which in turn removes the remaining unnecessary blood clot. In fact, many small blood vessels in which blood flow has been blocked by clots are reopened by this mechanism. Thus, an especially important function of the plasmin system is to remove minute clots from millions of tiny peripheral vessels that eventually would become occluded were there no way to clear them.

Conditions That Cause Excessive Bleeding in Humans

Excessive bleeding can result from deficiency of any one of the many blood-clotting factors. Three particular types of bleeding tendencies that have been studied to the greatest extent are discussed here: bleeding caused by (1) vitamin K deficiency, (2) hemophilia, and (3) thrombocytopenia (platelet deficiency).

Decreased Prothrombin, Factor VII, Factor IX, and Factor X Caused by Vitamin K Deficiency

With few exceptions, almost all the blood-clotting factors are formed by the liver. Therefore, diseases of the liver such as *hepatitis*, *cirrhosis*, and *acute yellow atrophy* can

sometimes depress the clotting system so greatly that the patient develops a severe tendency to bleed.

Another cause of depressed formation of clotting factors by the liver is vitamin K deficiency. Vitamin K is an essential factor to a liver carboxylase that adds a carboxyl group to glutamic acid residues on five of the important clotting factors: *prothrombin*, *Factor VII*, *Factor IX*, *Factor X*, and *protein C*. In adding the carboxyl group to glutamic acid residues on the immature clotting factors, vitamin K is oxidized and becomes inactive. Another enzyme, *vitamin K epoxide reductase complex 1 (VKOR c1),* reduces vitamin K back to its active form.

In the absence of active vitamin K, subsequent insufficiency of these coagulation factors in the blood can lead to serious bleeding tendencies.

Vitamin K is continually synthesized in the intestinal tract by bacteria, so vitamin K deficiency seldom occurs in the normal person as a result of vitamin K absence from the diet (except in neonates before they establish their intestinal bacterial flora). However, in gastrointestinal disease, vitamin K deficiency often occurs as a result of poor absorption of fats from the gastrointestinal tract. The reason is that vitamin K is fat soluble and ordinarily absorbed into the blood along with the fats.

One of the most prevalent causes of vitamin K deficiency is failure of the liver to secrete bile into the gastrointestinal tract (which occurs either as a result of obstruction of the bile ducts or as a result of liver disease). Lack of bile prevents adequate fat digestion and absorption and, therefore, depresses vitamin K absorption as well. Thus, liver disease often causes decreased production of prothrombin and some other clotting factors both because of poor vitamin K absorption and because of the diseased liver cells. Because of this, vitamin K is injected into surgical patients with liver disease or with obstructed bile ducts before performing the surgical procedure. Ordinarily, if vitamin K is given to a deficient patient 4 to 8 hours before the operation and the liver parenchymal cells are at least one-half normal in function, sufficient clotting factors will be produced to prevent excessive bleeding during the operation.

Hemophilia

Hemophilia is a bleeding disease that occurs almost exclusively in males. In 85 percent of cases, it is caused by an *abnormality or deficiency of Factor VIII;* this type of hemophilia is called *hemophilia A* or *classic hemophilia.* About 1 of every 10,000 males in the United States has classic hemophilia. In the other 15 percent of hemophilia patients, the bleeding tendency is caused by deficiency of Factor IX. Both of these factors are transmitted genetically by way of the female chromosome. Therefore, almost never will a woman have hemophilia because at least one of her two X chromosomes will have the appropriate genes. If one of her X chromosomes is deficient, she will be a *hemophilia carrier,* transmitting the disease to half of her male offspring and transmitting the carrier state to half of her female offspring.

The bleeding trait in hemophilia can have various degrees of severity, depending on the character of the genetic deficiency. Bleeding usually does not occur except after trauma, but in some patients, the degree of trauma required to cause severe and prolonged bleeding may be so mild that it is hardly noticeable. For instance, bleeding can often last for days after extraction of a tooth.

Factor VIII has two active components, a large component with a molecular weight in the millions and a smaller component with a molecular weight of about 230,000. The smaller component is most important in the intrinsic pathway for clotting, and it is deficiency of this part of Factor VIII that causes classic hemophilia. Another bleeding disease with somewhat different characteristics, called *von Willebrand's disease,* results from loss of the large component.

When a person with classic hemophilia experiences severe prolonged bleeding, almost the only therapy that is truly effective is injection of purified Factor VIII. The cost of Factor VIII is high, because it is gathered from human blood and only in extremely small quantities. However, increasing production and use of recombinant Factor VIII will make this treatment available to more patients with classic hemophilia.

Thrombocytopenia

Thrombocytopenia means the presence of very low numbers of platelets in the circulating blood. People with thrombocytopenia have a tendency to bleed, as do hemophiliacs, except that the bleeding is usually from many small venules or capillaries, rather than from larger vessels, as in hemophilia. As a result, small punctate hemorrhages occur throughout all the body tissues. The skin of such a person displays many small, purplish blotches, giving the disease the name *thrombocytopenic purpura.* As stated earlier, platelets are especially important for repair of minute breaks in capillaries and other small vessels.

Ordinarily, bleeding will not occur until the number of platelets in the blood falls below 50,000/μl, rather than the normal 150,000 to 300,000. Levels as low as 10,000/μl are frequently lethal.

Even without making specific platelet counts in the blood, sometimes one can suspect the existence of thrombocytopenia if the person's blood fails to retract, because, as pointed out earlier, clot retraction is normally dependent on release of multiple coagulation factors from the large numbers of platelets entrapped in the fibrin mesh of the clot.

Most people with thrombocytopenia have the disease known as *idiopathic thrombocytopenia,* which means thrombocytopenia of unknown cause. In most of these people, it has been discovered that, for unknown reasons, specific antibodies have formed and react against the platelets themselves to destroy them. Relief from bleeding for 1 to 4 days can often be effected in a patient with thrombocytopenia by giving *fresh whole blood transfusions* that contain large numbers of platelets. Also, *splenectomy* is often helpful, sometimes effecting almost complete cure because the spleen normally removes large numbers of platelets from the blood.

Thromboembolic Conditions in the Human Being

Thrombi and Emboli. An abnormal clot that develops in a blood vessel is called a *thrombus.* Once a clot has developed, continued flow of blood past the clot is likely to break it away from its attachment and cause the clot to flow with the blood; such freely flowing clots are known as *emboli.* Also, emboli that originate in large arteries or in the left side of the heart can flow peripherally and plug arteries or arterioles in the brain, kidneys, or elsewhere. Emboli that originate in the venous system or in the right side of the heart generally flow into the lungs to cause pulmonary arterial embolism.

Cause of Thromboembolic Conditions. The causes of thromboembolic conditions in the human being are usually twofold: (1) Any *roughened endothelial surface of a vessel*—as may be caused by arteriosclerosis, infection, or trauma—is likely to initiate the clotting process. (2) Blood often clots *when it flows very slowly* through blood vessels, where small quantities of thrombin and other procoagulants are always being formed.

Use of t-PA in Treating Intravascular Clots. Genetically engineered t-PA (tissue plasminogen activator) is available. When delivered directly to a thrombosed area through a catheter, it is effective in activating plasminogen to plasmin, which in turn can dissolve some intravascular clots. For instance, if used within the first hour or so after thrombotic occlusion of a coronary artery, the heart is often spared serious damage.

Femoral Venous Thrombosis and Massive Pulmonary Embolism

Because clotting almost always occurs when blood flow is blocked for many hours in any vessel of the body, the immobility of patients confined to bed plus the practice of propping the knees with pillows often causes intravascular clotting because of blood stasis in one or more of the leg veins for hours at a time. Then the clot grows, mainly in the direction of the slowly moving venous blood, sometimes growing the entire length of the leg veins and occasionally even up into the common iliac vein and inferior vena cava. Then, about 1 time out of every 10, a large part of the clot disengages from its attachments to the vessel wall and flows freely with the venous blood through the right side of the heart and into the pulmonary arteries to cause massive blockage of the pulmonary arteries, called *massive pulmonary embolism.* If the clot is large enough to occlude both of the pulmonary arteries at the same time, immediate death ensues. If only one pulmonary artery is blocked, death may not occur, or the embolism may lead to death a few hours to several days later because of further growth of the clot within the pulmonary vessels. But, again, t-PA therapy can be a lifesaver.

Disseminated Intravascular Coagulation

Occasionally the clotting mechanism becomes activated in widespread areas of the circulation, giving rise to the condition called *disseminated intravascular coagulation.* This often results from the presence of large amounts of traumatized or dying tissue in the body that releases great quantities of tissue factor into the blood. Frequently, the clots are small but numerous, and they plug a large share of the small peripheral blood vessels. This occurs especially in patients with widespread septicemia, in which either circulating bacteria or bacterial toxins—especially *endotoxins*—activate the clotting mechanisms. Plugging of small peripheral vessels greatly diminishes delivery of oxygen and other nutrients to the tissues—a situation that leads to or exacerbates circulatory shock. It is partly for this reason that *septicemic shock* is lethal in 85 percent or more of patients.

A peculiar effect of disseminated intravascular coagulation is that the patient on occasion begins to bleed. The reason for this is that so many of the clotting factors are removed by the widespread clotting that too few procoagulants remain to allow normal hemostasis of the remaining blood.

Anticoagulants for Clinical Use

In some thromboembolic conditions, it is desirable to delay the coagulation process. Various anticoagulants have been developed for this purpose. The ones most useful clinically are *heparin* and the *coumarins.*

Heparin as an Intravenous Anticoagulant

Commercial heparin is extracted from several different animal tissues and prepared in almost pure form. Injection of relatively small quantities, about 0.5 to 1 mg/kg of body weight, causes the blood-clotting time to increase from a normal of about 6 minutes to 30 or more minutes. Furthermore, this change in clotting time occurs instantaneously, thereby immediately preventing or slowing further development of a thromboembolic condition.

The action of heparin lasts about 1.5 to 4 hours. The injected heparin is destroyed by an enzyme in the blood known as *heparinase*.

Coumarins as Anticoagulants

When a coumarin, such as *warfarin,* is given to a patient, the amounts of active prothrombin and Factors VII, IX, and X, all formed by the liver, begin to fall. Warfarin causes this effect by inhibiting the enzyme, *vitamin K epoxide reductase complex 1 (VKOR c1).* As discussed previously, this enzyme converts the inactive, oxidized form of vitamin K to its active, reduced form. By inhibiting VKOR c1, warfarin decreases the available active form of vitamin K in the tissues. When this occurs, the coagulation factors are no longer carboxylated and are biologically inactive. Over several days the body stores of the active

coagulation factors degrade and are replaced by inactive factors. Although the coagulation factors continue to be produced, they have greatly decreased coagulant activity.

After administration of an effective dose of warfarin, the coagulant activity of the blood decreases to about 50 percent of normal by the end of 12 hours and to about 20 percent of normal by the end of 24 hours. In other words, the coagulation process is not blocked immediately but must await the degradation of the active prothrombin and the other affected coagulation factors already present in the plasma. Normal coagulation usually returns 1 to 3 days after discontinuing coumarin therapy.

Prevention of Blood Coagulation Outside the Body

Although blood removed from the body and held in a glass test tube normally clots in about 6 minutes, blood collected in *siliconized containers* often does not clot for 1 hour or more. The reason for this delay is that preparing the surfaces of the containers with silicone prevents contact activation of platelets and Factor XII, the two principal factors that initiate the intrinsic clotting mechanism. Conversely, untreated glass containers allow contact activation of the platelets and Factor XII, with rapid development of clots.

Heparin can be used for preventing coagulation of blood outside the body, as well as in the body. Heparin is especially used in surgical procedures in which the blood must be passed through a heart-lung machine or artificial kidney machine and then back into the person.

Various substances that *decrease the concentration of calcium ions* in the blood can also be used for preventing blood coagulation *outside* the body. For instance, a soluble *oxalate* compound mixed in a very small quantity with a sample of blood causes precipitation of calcium oxalate from the plasma and thereby decreases the ionic calcium level so much that blood coagulation is blocked.

Any substance that deionizes the blood calcium will prevent coagulation. The negatively charged *citrate ion* is especially valuable for this purpose, mixed with blood usually in the form of *sodium*, *ammonium*, or *potassium citrate.* The citrate ion combines with calcium in the blood to cause an un-ionized calcium compound, and the lack of *ionic* calcium prevents coagulation. Citrate anticoagulants have an important advantage over the oxalate anticoagulants because oxalate is toxic to the body, whereas moderate quantities of citrate can be injected intravenously. After injection, the citrate ion is removed from the blood within a few minutes by the liver and is polymerized into glucose or metabolized directly for energy. Consequently, 500 milliliters of blood that has been rendered incoagulable by citrate can ordinarily be transfused into a recipient within a few minutes without dire consequences. But if the liver is damaged or if large quantities of citrated blood or plasma are given too rapidly (within fractions of a minute), the citrate ion may not be removed quickly enough, and the citrate can, under these conditions, greatly depress the level of calcium ion in the blood, which can result in tetany and convulsive death.

Blood Coagulation Tests

Bleeding Time

When a sharp-pointed knife is used to pierce the tip of the finger or lobe of the ear, bleeding ordinarily lasts for 1 to 6 minutes. The time depends largely on the depth of the wound and the degree of hyperemia in the finger or ear lobe at the time of the test. Lack of any one of several of the clotting factors can prolong the bleeding time, but it is especially prolonged by lack of platelets.

Clotting Time

Many methods have been devised for determining blood clotting times. The one most widely used is to collect blood in a chemically clean glass test tube and then to tip the tube back and forth about every 30 seconds until the blood has clotted. By this method, the normal clotting time is 6 to 10 minutes. Procedures using multiple test tubes have also been devised for determining clotting time more accurately.

Unfortunately, the clotting time varies widely, depending on the method used for measuring it, so it is no longer used in many clinics. Instead, measurements of the clotting factors themselves are made, using sophisticated chemical procedures.

Prothrombin Time and International Normalized Ratio

Prothrombin time gives an indication of the concentration of prothrombin in the blood. Figure 36-5 shows the relation of prothrombin concentration to prothrombin

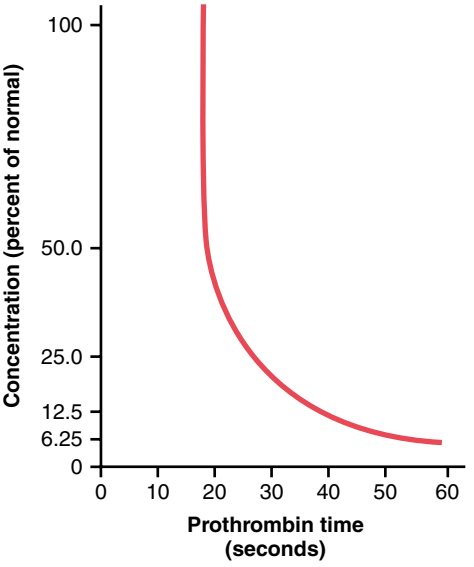


Figure 36-5 Relation of prothrombin concentration in the blood to "prothrombin time."

time. The method for determining prothrombin time is the following.

Blood removed from the patient is immediately oxalated so that none of the prothrombin can change into thrombin. Then, a large excess of calcium ion and tissue factor is quickly mixed with the oxalated blood. The excess calcium nullifies the effect of the oxalate, and the tissue factor activates the prothrombin-to-thrombin reaction by means of the extrinsic clotting pathway. The time required for coagulation to take place is known as the *prothrombin time.* The *shortness of the time* is determined mainly by prothrombin concentration. The normal prothrombin time is about 12 seconds. In each laboratory, a curve relating prothrombin concentration to prothrombin time, such as that shown in Figure 36-5, is drawn for the method used so that the prothrombin in the blood can be quantified.

The results obtained for prothrombin time may vary considerably even in the same individual if there are differences in activity of the tissue factor and the analytical system used to perform the test. Tissue factor is isolated from human tissues, such as placental tissue, and different batches may have different activity. The *international normalized ratio (INR)* was devised as a way to standardize measurements of prothrombin time. For each batch of tissue factor, the manufacturer assigns an international sensitivity index (ISI), which indicates the activity of the tissue factor with a standardized sample. The ISI usually varies between 1.0 and 2.0. The INR is the ratio of the person's prothrombin time to a normal control sample raised to the power of the ISI:

$$\text{INR} = \left(\frac{\text{PT}_{\text{test}}}{\text{PT}_{\text{normal}}} \right)^{\text{ISI}}$$

The normal range for INR in a healthy person is 0.9 to 1.3. A high INR level (e.g., 4 or 5) indicates a high risk of bleeding, whereas a low INR (e.g., 0.5) suggests that there is a chance of having a clot. Patients on warfarin therapy usually have an INR of 2.0 to 3.0.

Tests similar to that for prothrombin time and INR have been devised to determine the quantities of other blood clotting factors. In each of these tests, excesses of calcium ions and all the other factors *besides the one being tested* are added to oxalated blood all at once. Then the time required for coagulation is determined in the same manner as for prothrombin time. If the factor being tested is deficient, the coagulation time is prolonged. The time itself can then be used to quantitate the concentration of the factor.

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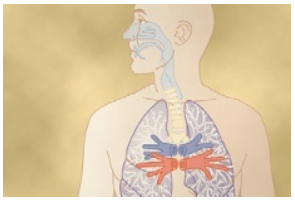
CHAPTER 37

Pulmonary Ventilation



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

Mechanics of Pulmonary Ventilation

Muscles That Cause Lung Expansion and Contraction

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

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

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

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

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

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

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

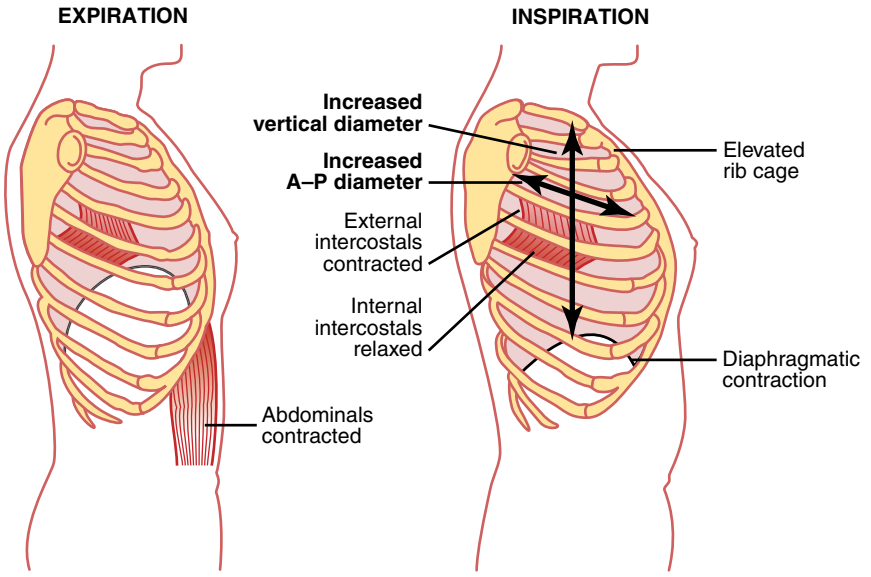


Figure 37-1 Contraction and expansion of the thoracic cage during expiration and inspiration, demonstrating diaphragmatic contraction, function of the intercostal muscles, and elevation and depression of the rib cage.

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

Pleural Pressure and Its Changes During Respiration

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

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

Alveolar Pressure

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

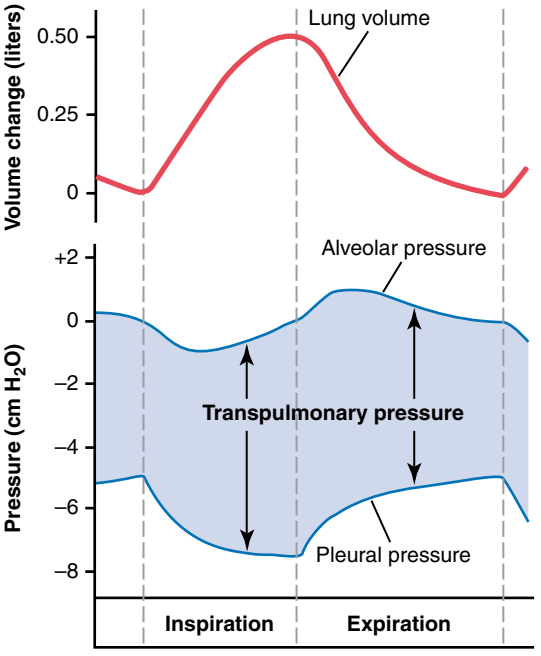


Figure 37-2 Changes in lung volume, alveolar pressure, pleural pressure, and transpulmonary pressure during normal breathing.

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

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

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

Compliance of the Lungs

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

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

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

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

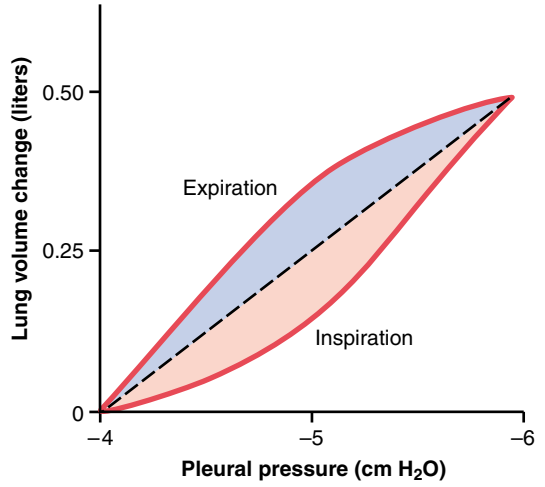


Figure 37-3 Compliance diagram in a healthy person. This diagram shows compliance of the lungs alone.

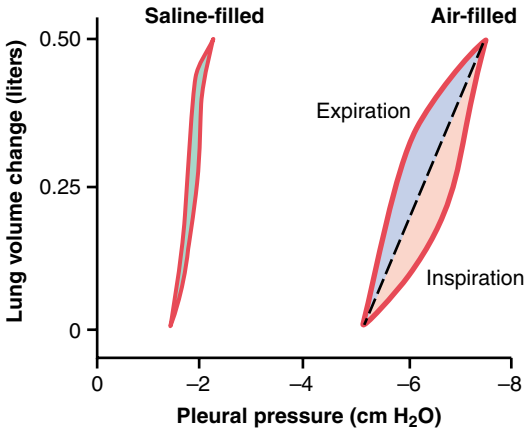


Figure 37-4 Comparison of the compliance diagrams of saline-filled and air-filled lungs when the alveolar pressure is maintained at atmospheric pressure (0 cm H_2O) and pleural pressure is changed.

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

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

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

Surfactant, Surface Tension, and Collapse of the Alveoli

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

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

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

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

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

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

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

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

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

Effect of the Thoracic Cage on Lung Expansibility

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

Compliance of the Thorax and the Lungs Together

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

"Work" of Breathing

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

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

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

Pulmonary Volumes and Capacities

Recording Changes in Pulmonary Volume—Spirometry

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

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

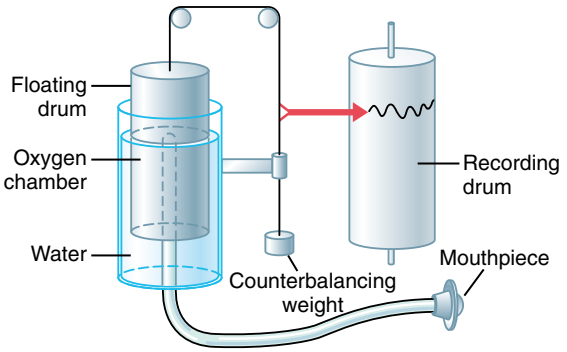


Figure 37-5 Spirometer.

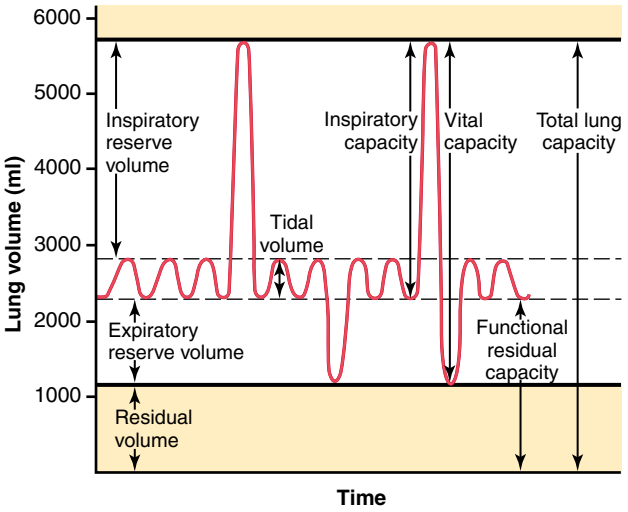


Figure 37-6 Diagram showing respiratory excursions during normal breathing and during maximal inspiration and maximal expiration.

Pulmonary Volumes

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

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

Pulmonary Capacities

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

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

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

Abbreviations and Symbols Used in Pulmonary Function Studies

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

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

$VC = IRV + V_T + ERV$

$VC = IC + ERV$

$TLC = VC + RV$

$TLC = IC + FRC$

$FRC = ERV + RV$

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

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

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

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

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

Table 37-1 Abbreviations and Symbols for Pulmonary Function

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

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

$$RV = FRC - ERV$$

and

$$TLC = FRC + IC$$

Minute Respiratory Volume Equals Respiratory Rate Times Tidal Volume

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

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

Alveolar Ventilation

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

"Dead Space" and Its Effect on Alveolar Ventilation

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

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

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

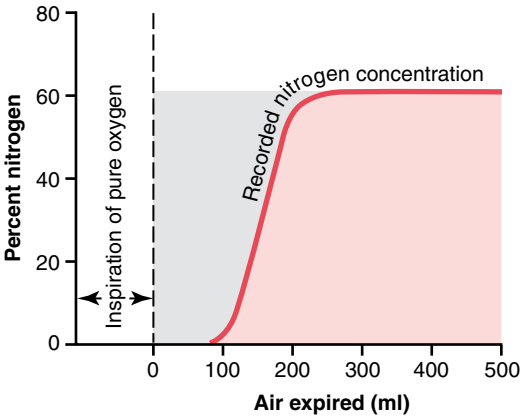


Figure 37-7 Record of the changes in nitrogen concentration in the expired air after a single previous inspiration of pure oxygen. This record can be used to calculate dead space, as discussed in the text.

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

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

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

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

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

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

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

Rate of Alveolar Ventilation

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

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

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

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

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

Functions of the Respiratory Passageways

Trachea, Bronchi, and Bronchioles

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

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

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

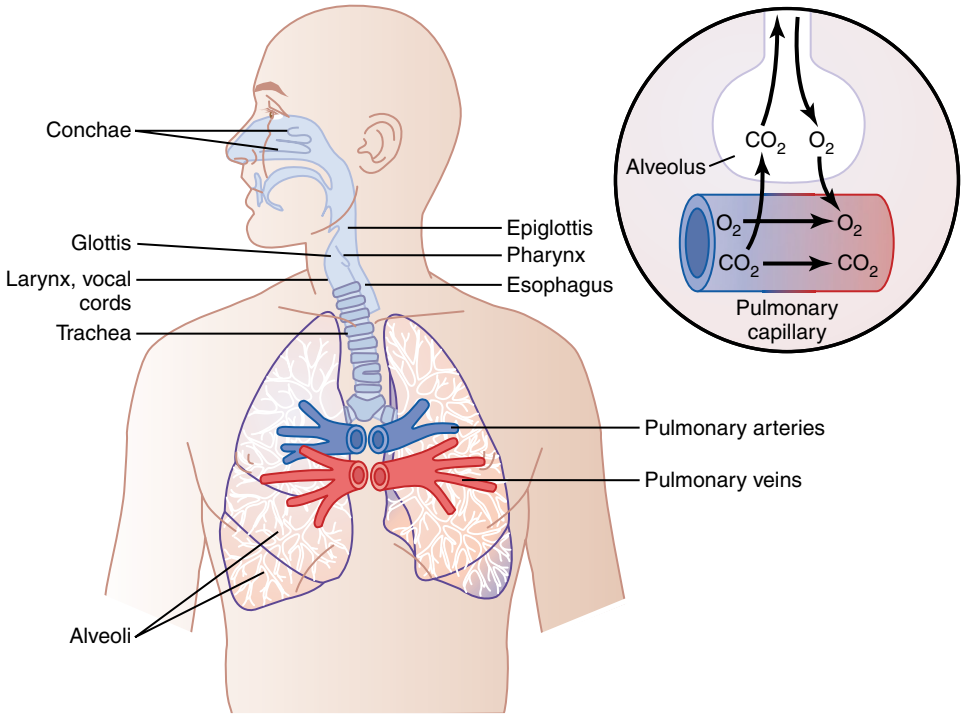


Figure 37-8 Respiratory passages.

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

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

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

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

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

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

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

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

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

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

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

Cough Reflex

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

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

Sneeze Reflex

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

Normal Respiratory Functions of the Nose

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

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

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

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

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

Vocalization

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

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

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

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

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

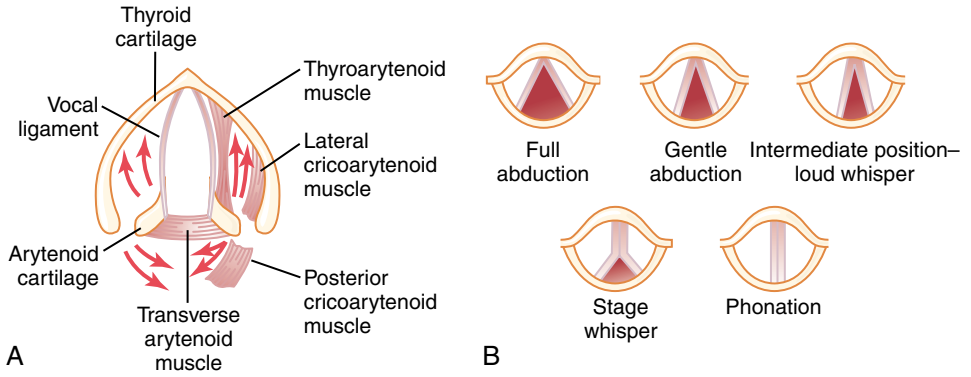


Figure 37-9 *A*, Anatomy of the larynx. *B*, Laryngeal function in phonation, showing the positions of the vocal cords during different types of phonation. (Modified from Greene MC: The Voice and Its Disorders, 4th ed. Philadelphia: JB Lippincott, 1980.)

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

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

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

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

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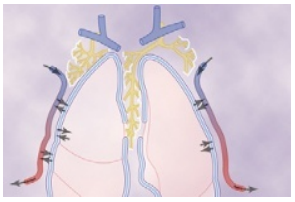
CHAPTER 38

Pulmonary Circulation, Pulmonary Edema, Pleural Fluid



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

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

Physiologic Anatomy of the Pulmonary Circulatory System

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

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

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

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

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

Pressures in the Pulmonary System

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

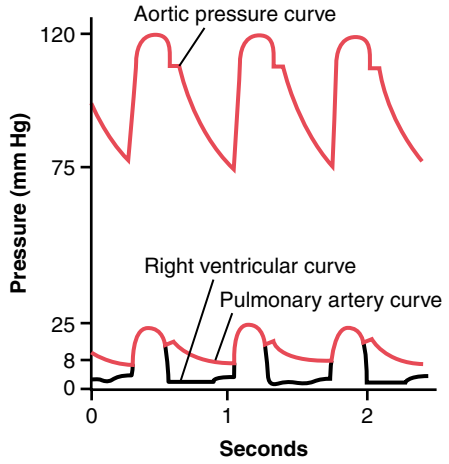


Figure 38-1 Pressure pulse contours in the right ventricle, pulmonary artery, and aorta.

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

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

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

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

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

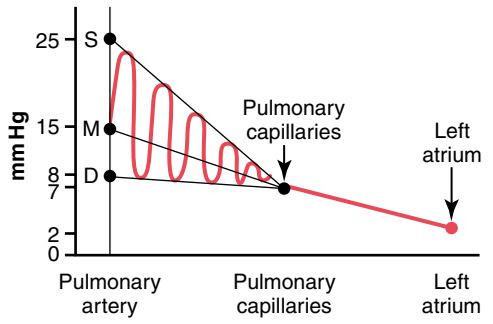


Figure 38-2 Pressures in the different vessels of the lungs. D, diastolic; M, mean; S, systolic; red curve, arterial pulsations.

Blood Volume of the Lungs

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

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

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

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

Blood Flow Through the Lungs and Its Distribution

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

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

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

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

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

Zones 1, 2, and 3 of Pulmonary Blood Flow

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

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

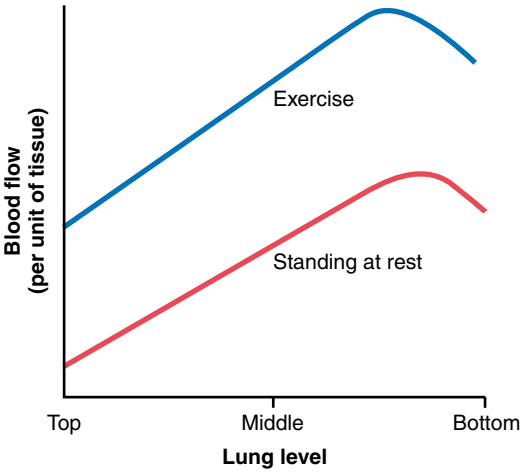


Figure 38-3 Blood flow at different levels in the lung of an upright person *at rest* and *during exercise*. Note that when the person is at rest, the blood flow is very low at the top of the lungs; most of the flow is through the bottom of the lung.

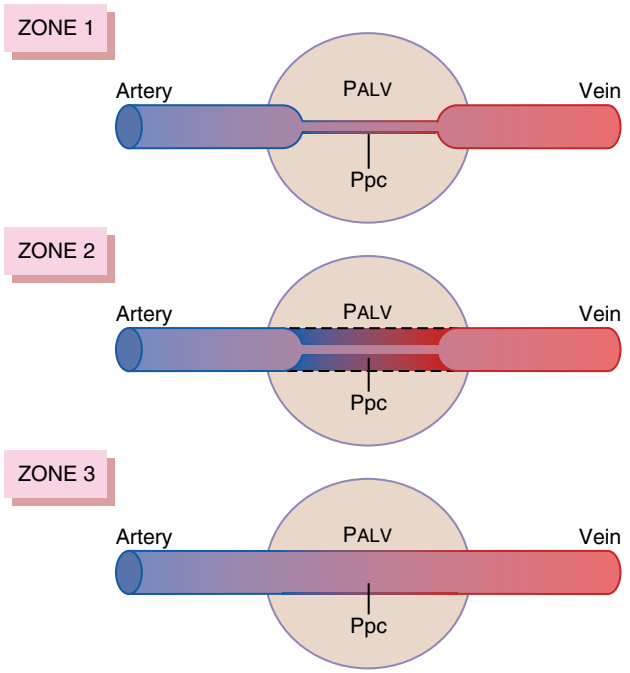


Figure 38-4 Mechanics of blood flow in the three blood flow zones of the lung: *zone 1, no flow*—alveolar air pressure (PALV) is greater than arterial pressure; *zone 2, intermittent flow*—systolic arterial pressure rises higher than alveolar air pressure, but diastolic arterial pressure falls below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

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

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

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

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

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

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

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

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

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

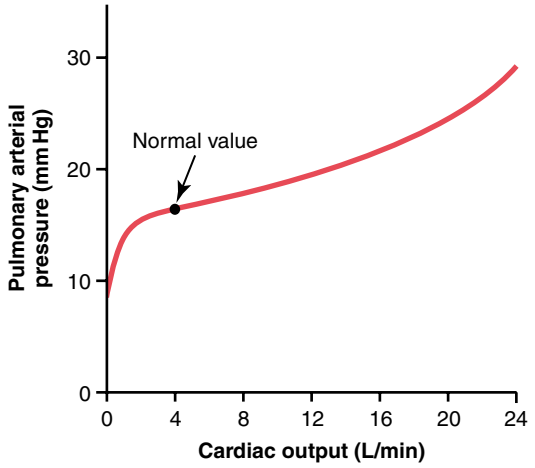


Figure 38-5 Effect on mean pulmonary arterial pressure caused by increasing the cardiac output during exercise.

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

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

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

Pulmonary Capillary Dynamics

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

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

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

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

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

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

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

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

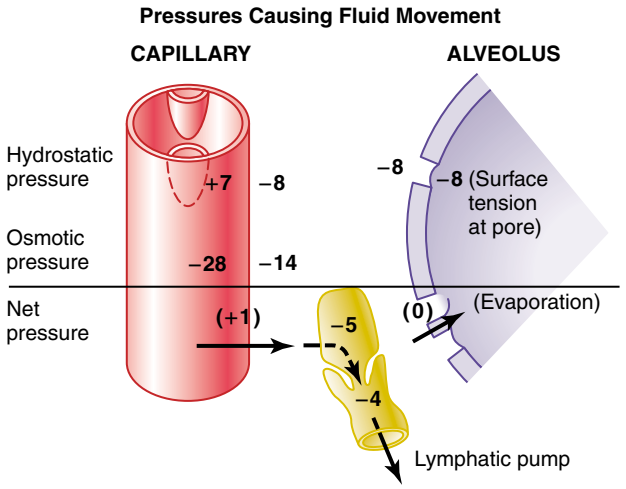


Figure 38-6 Hydrostatic and osmotic forces in mm Hg at the capillary (*left*) and alveolar membrane (*right*) of the lungs. Also shown is the tip end of a lymphatic vessel (*center*) that pumps fluid from the pulmonary interstitial spaces. (Modified from Guyton AC, Taylor AE, Granger HJ: Circulatory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

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

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

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

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

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

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

Pulmonary Edema

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

The most common causes of pulmonary edema are as follows:

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

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

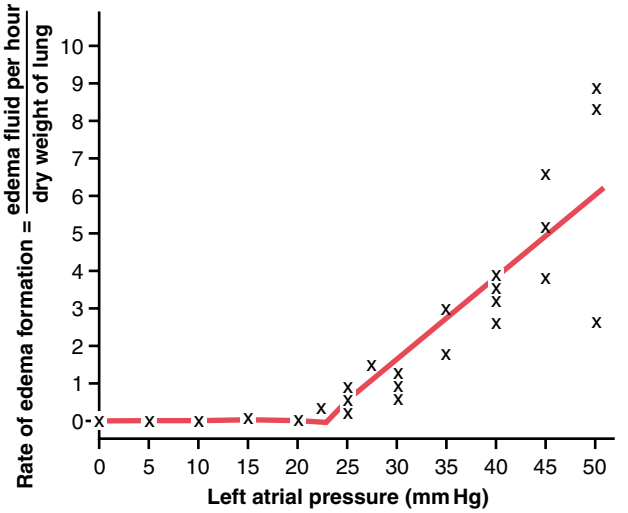


Figure 38-7 Rate of fluid loss into the lung tissues when the left atrial pressure (and pulmonary capillary pressure) is increased. (From Guyton AC, Lindsey AW: Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. Circ Res 7:649, 1959.)

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

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

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

Fluid in the Pleural Cavity

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

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

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

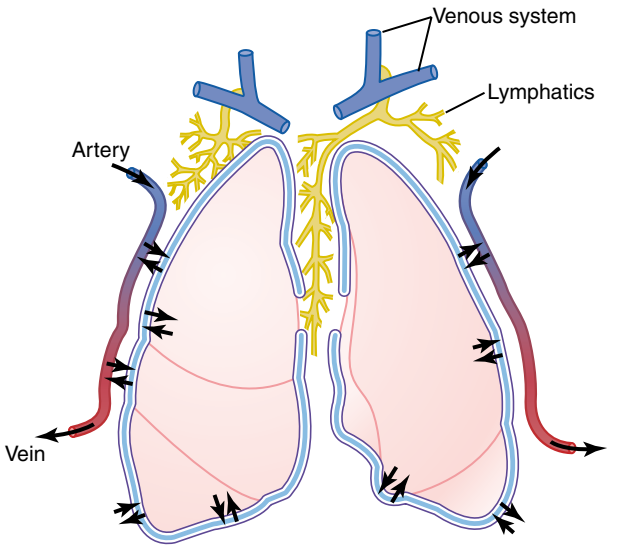


Figure 38-8 Dynamics of fluid exchange in the intrapleural space.

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

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

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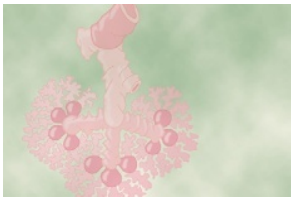
CHAPTER 39

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



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

Physics of Gas Diffusion and Gas Partial Pressures

Molecular Basis of Gas Diffusion

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

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

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

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

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

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

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

Pressures of Gases Dissolved in Water and Tissues

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

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

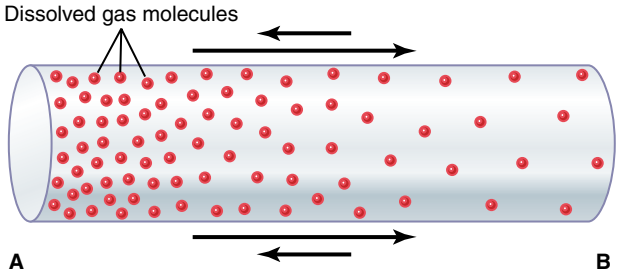


Figure 39-1 Diffusion of oxygen from one end of a chamber (*A*) to the other (*B*). The difference between the lengths of the arrows represents *net diffusion*.

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

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

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

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

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

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

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

Vapor Pressure of Water

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

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

Diffusion of Gases Through Fluids—Pressure Difference Causes Net Diffusion

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

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

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

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

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

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

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

Diffusion of Gases Through Tissues

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

Compositions of Alveolar Air and Atmospheric Air Are Different

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

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

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

Rate at Which Alveolar Air Is Renewed by Atmospheric Air

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

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

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

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

*On an average cool, clear day.

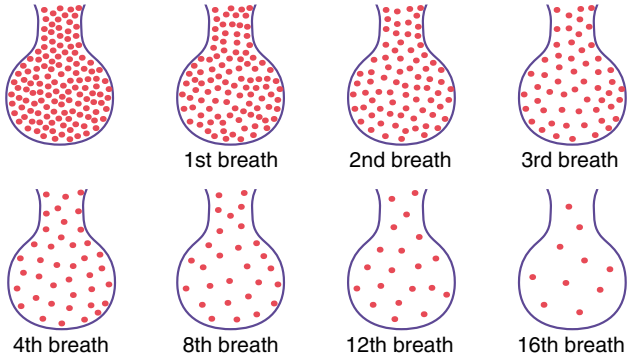


Figure 39-2 Expiration of a gas from an alveolus with successive breaths.

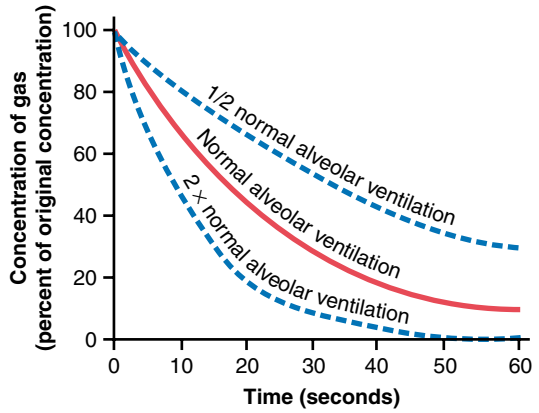


Figure 39-3 Rate of removal of excess gas from alveoli.

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

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

Oxygen Concentration and Partial Pressure in the Alveoli

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

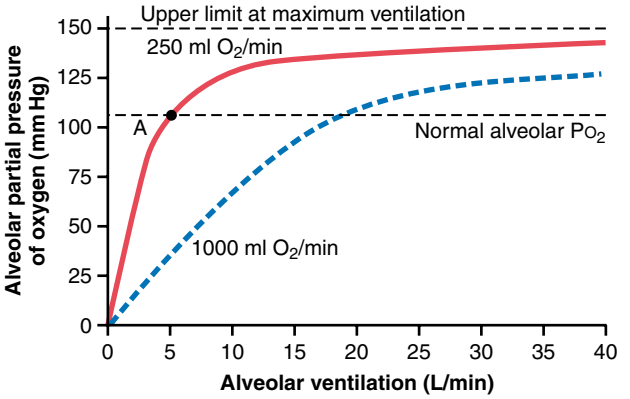


Figure 39-4 Effect of alveolar ventilation on the alveolar P_{O_2} at two rates of oxygen absorption from the alveoli—250 ml/min and 1000 ml/min. *Point A* is the normal operating point.

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

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

CO_2 Concentration and Partial Pressure in the Alveoli

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

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

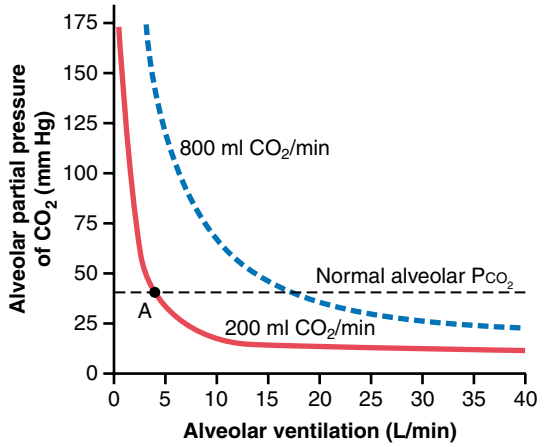


Figure 39-5 Effect of alveolar ventilation on the alveolar P_{CO_2} at two rates of carbon dioxide excretion from the blood—800 ml/min and 200 ml/min. *Point A* is the normal operating point.

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

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

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

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

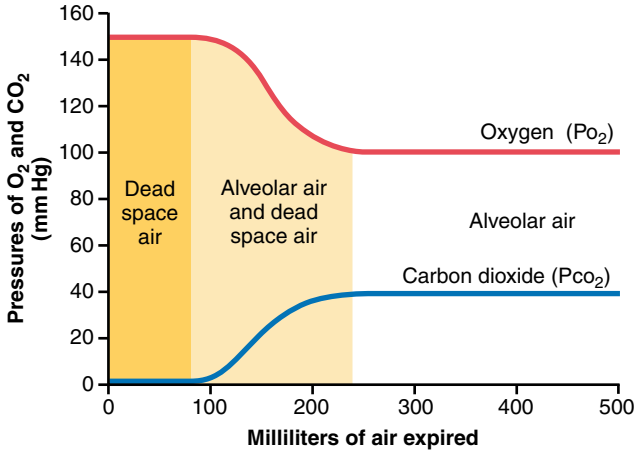


Figure 39-6 Oxygen and carbon dioxide partial pressures in the various portions of normal expired air.

Diffusion of Gases Through the Respiratory Membrane

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

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

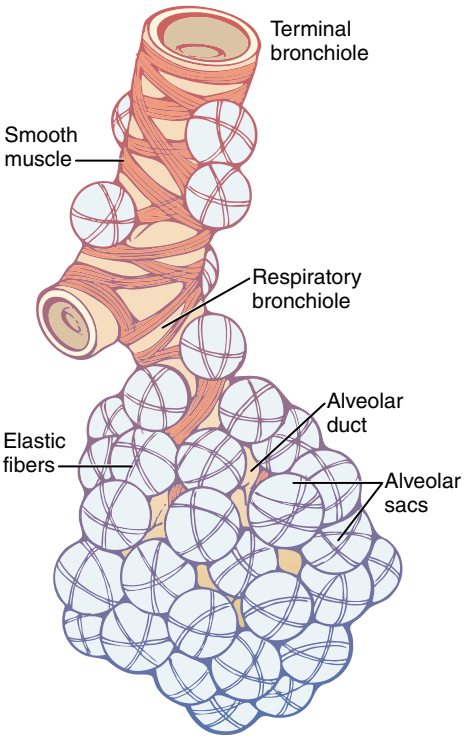


Figure 39-7 Respiratory unit.

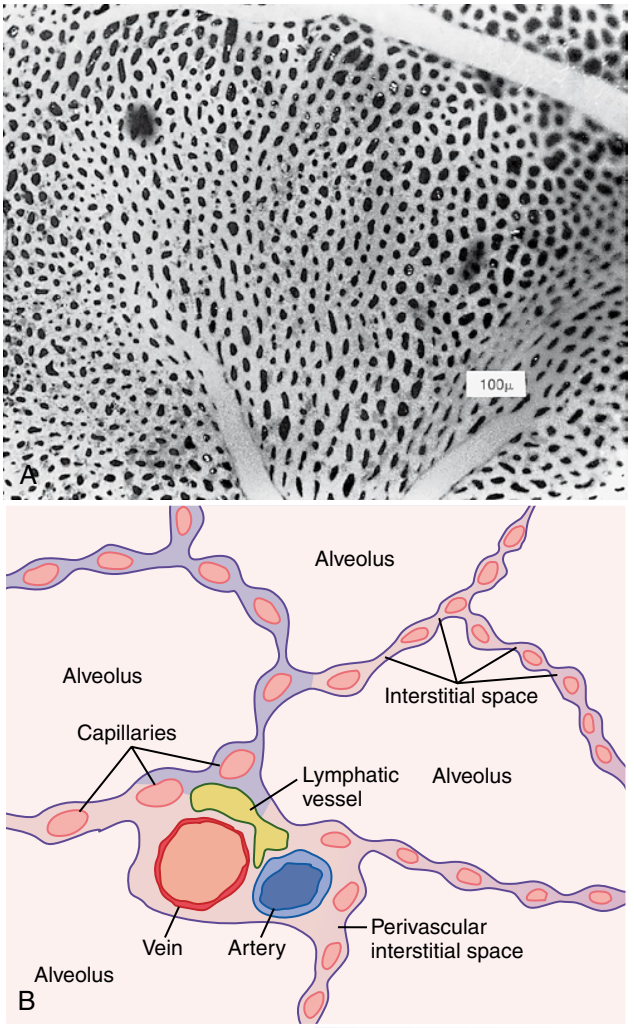


Figure 39-8 *A*, Surface view of capillaries in an alveolar wall. *B*, Cross-sectional view of alveolar walls and their vascular supply. (*A*, From Maloney JE, Castle BL: Pressure-diameter relations of capillaries and small blood vessels in frog lung. Respir Physiol 7:150, 1969. Reproduced by permission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

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

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

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

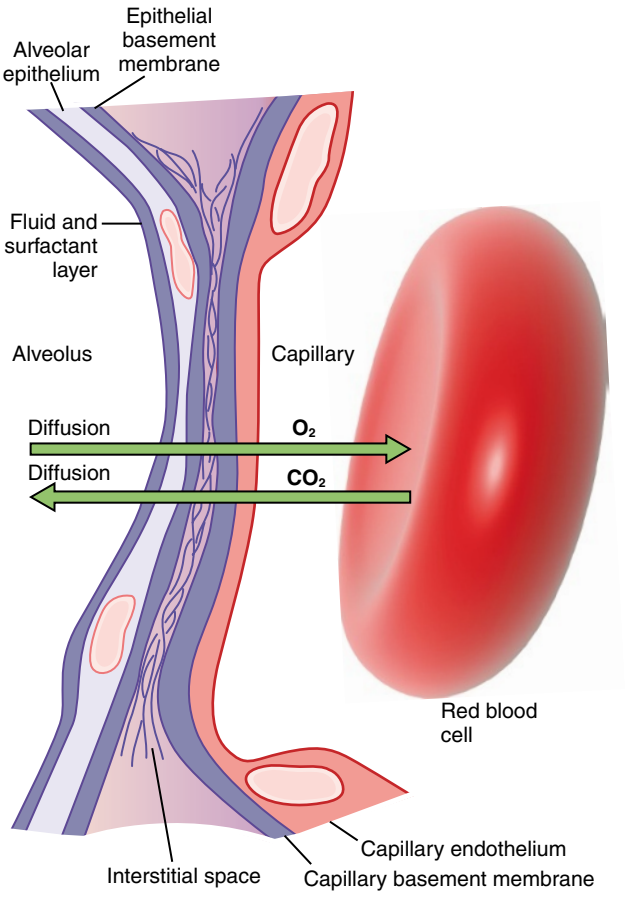


Figure 39-9 Ultrastructure of the alveolar respiratory membrane, shown in cross section.

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

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

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

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

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

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

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

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

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

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

Diffusing Capacity of the Respiratory Membrane

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

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

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

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

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

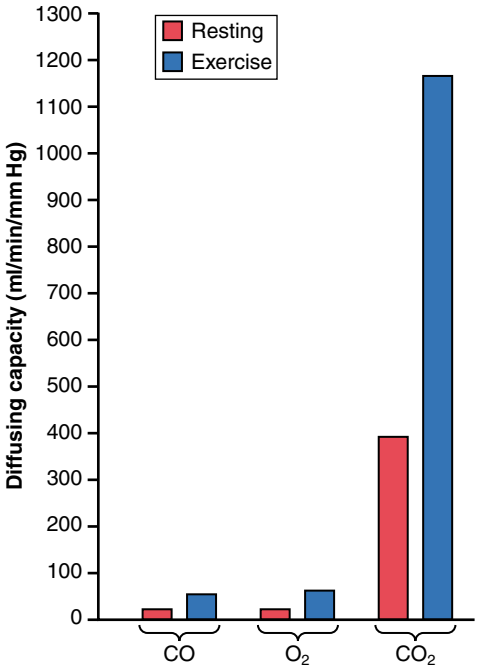


Figure 39-10 *Diffusing capacities* for carbon monoxide, oxygen, and carbon dioxide in the normal lungs under resting conditions and during exercise.

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

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

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

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

Effect of the Ventilation-Perfusion Ratio on Alveolar Gas Concentration

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Abnormalities of Ventilation-Perfusion Ratio

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

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

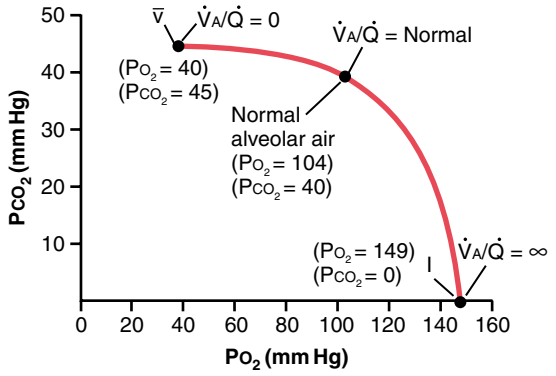


Figure 39-11 Normal P_{O_2}-P_{CO_2}, $\dot{V}_A/\dot{Q}$ diagram.

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

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

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

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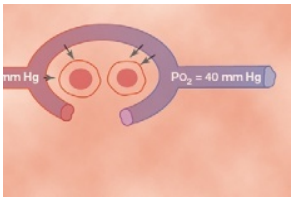
CHAPTER 40

Transport of Oxygen and Carbon Dioxide in Blood and Tissue Fluids



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

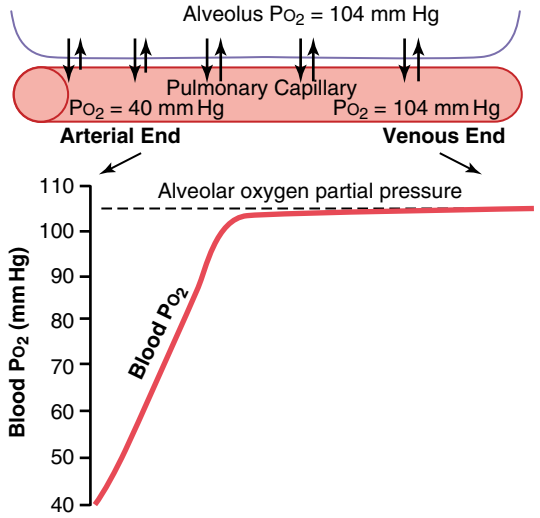


Figure 40-1 Uptake of oxygen by the pulmonary capillary blood. (The curve in this figure was constructed from data in Milhorn HT Jr, Pulley PE Jr: A theoretical study of pulmonary capillary gas exchange and venous admixture. Biophys J 8:337, 1968.)

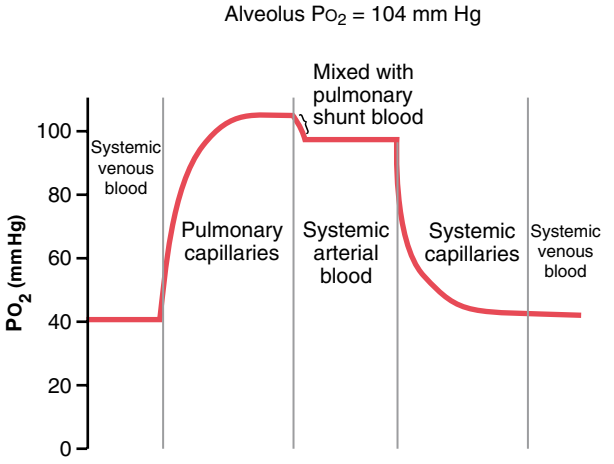


Figure 40-2 Changes in P_{O_2} in the pulmonary capillary blood, systemic arterial blood, and systemic capillary blood, demonstrating the effect of "venous admixture."

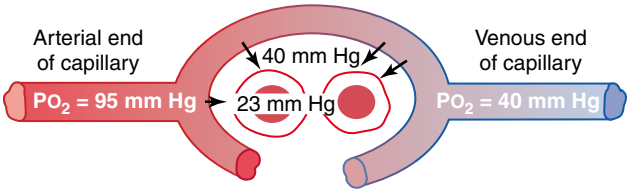


Figure 40-3 Diffusion of oxygen from a peripheral tissue capillary to the cells. (P_{O_2} in interstitial fluid = 40 mm Hg, and in tissue cells = 23 mm Hg.)

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

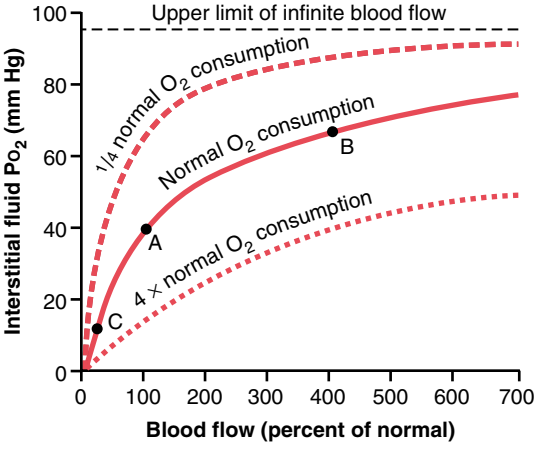


Figure 40-4 Effect of blood flow and rate of oxygen consumption on tissue P_{O_2}.

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

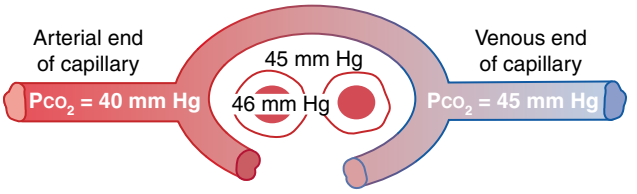


Figure 40-5 Uptake of carbon dioxide by the blood in the tissue capillaries. (P_{CO_2} in tissue cells = 46 mm Hg, and in interstitial fluid = 45 mm Hg.)

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

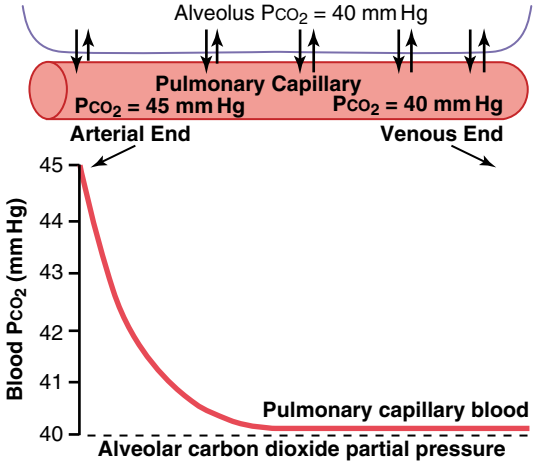


Figure 40-6 Diffusion of carbon dioxide from the pulmonary blood into the alveolus. (This curve was constructed from data in Milhorn HT Jr, Pulley PE Jr: A theoretical study of pulmonary capillary gas exchange and venous admixture. Biophys J 8:337, 1968.)

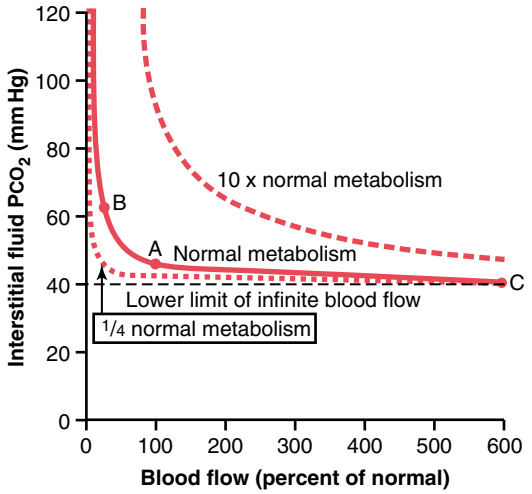


Figure 40-7 Effect of blood flow and metabolic rate on peripheral tissue P_{CO_2}.

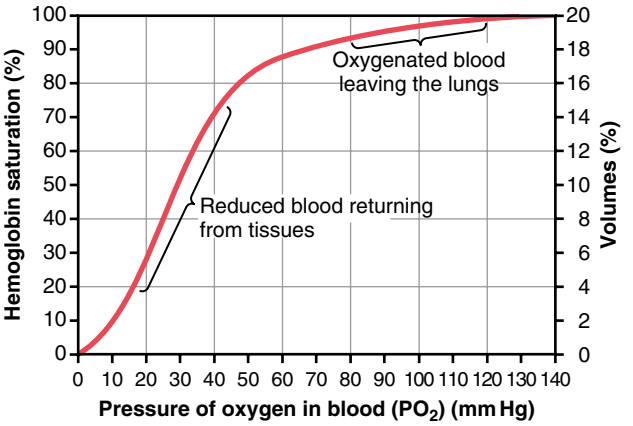


Figure 40-8 Oxygen-hemoglobin dissociation curve.

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

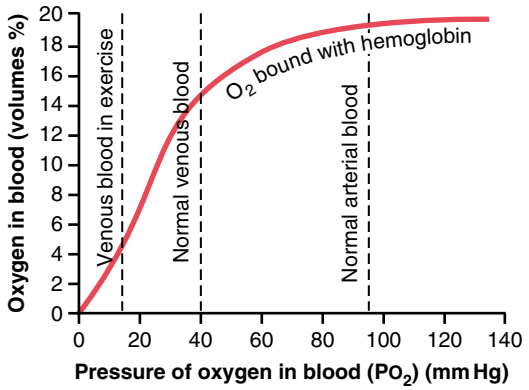


Figure 40-9 Effect of blood PO_2 on the quantity of oxygen bound with hemoglobin in each 100 milliliters of blood.

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

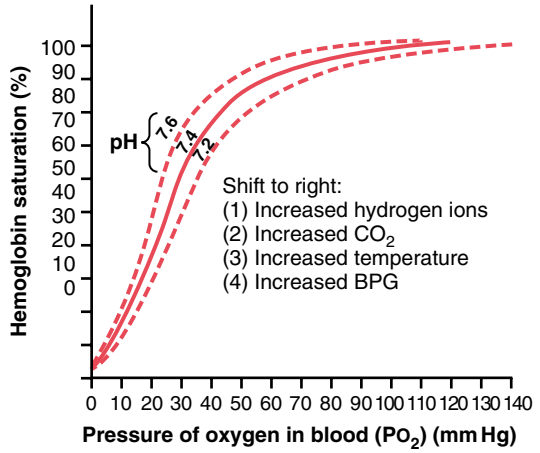


Figure 40-10 Shift of the oxygen-hemoglobin dissociation curve to the right caused by an increase in hydrogen ion concentration (decrease in pH). BPG, 2,3-biphosphoglycerate.

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

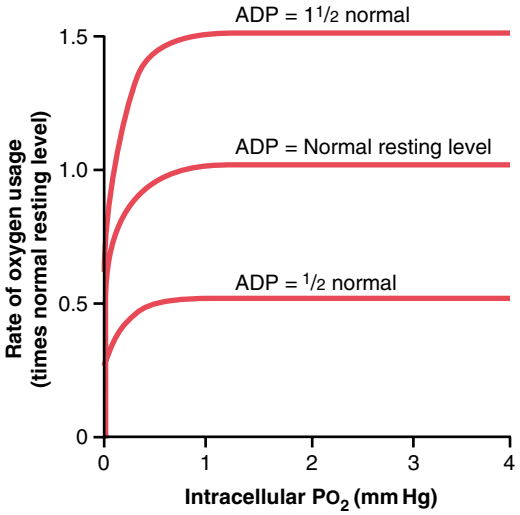


Figure 40-11 Effect of intracellular adenosine diphosphate (ADP) and P_{O_2} on rate of oxygen usage by the cells. Note that as long as the intracellular P_{O_2} remains above 1 mm Hg, the controlling factor for the rate of oxygen usage is the intracellular concentration of ADP.

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

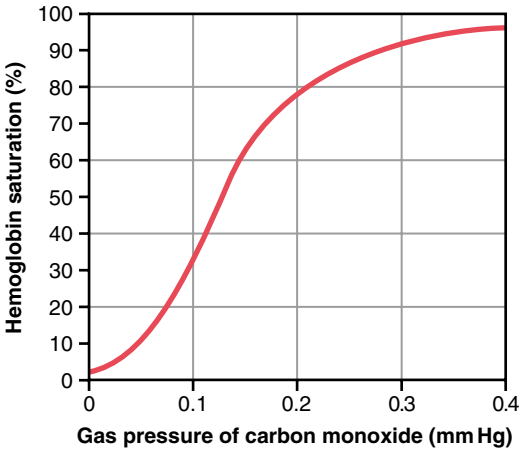


Figure 40-12 Carbon monoxide–hemoglobin dissociation curve. Note the extremely low carbon monoxide pressures at which carbon monoxide combines with hemoglobin.

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

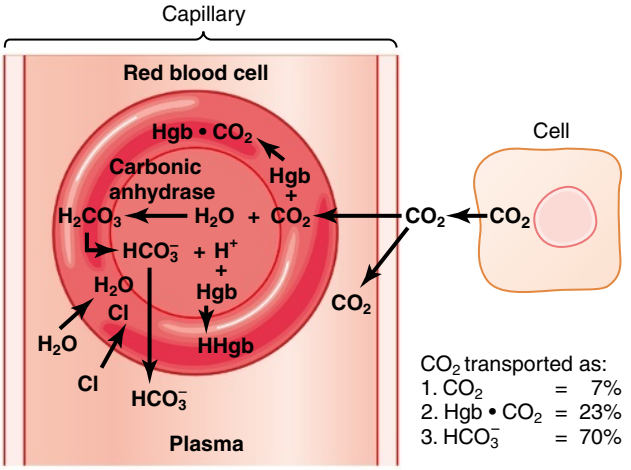


Figure 40-13 Transport of carbon dioxide in the blood.

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

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

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

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

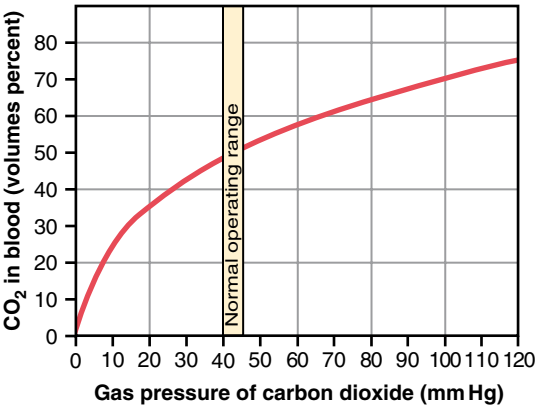


Figure 40-14 Carbon dioxide dissociation curve.

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

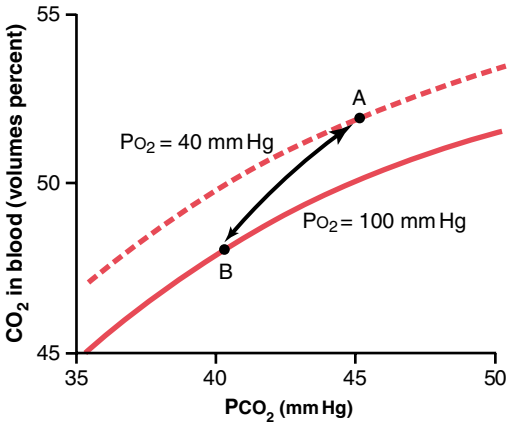


Figure 40-15 Portions of the carbon dioxide dissociation curve when the Po_2 is 100 mm Hg or 40 mm Hg. The arrow represents the Haldane effect on the transport of carbon dioxide, as discussed in the text.