CHAPTER 21

Muscle Blood Flow and Cardiac Output During Exercise; the Coronary Circulation and Ischemic Heart Disease

In this chapter we consider (1) blood flow to the skeletal muscles and (2) coronary artery blood flow to the heart. Regulation of each of these is achieved mainly by local control of vascular resistance in response to muscle tissue metabolic needs.

We also discuss the physiology of related subjects such as (1) cardiac output control during exercise, (2) characteristics of heart attacks, and (3) the pain of angina pectoris.

Blood Flow Regulation in Skeletal Muscle at Rest and During Exercise

Very strenuous exercise is one of the most stressful conditions that the normal circulatory system faces. This is true because there is such a large mass of skeletal muscle in the body, all of it requiring large amounts of blood flow. Also, the cardiac output often must increase in the nonathlete to four to five times normal, or in the well-trained athlete to six to seven times normal, to satisfy the metabolic needs of the exercising muscles.

Rate of Blood Flow Through the Muscles

During rest, blood flow through skeletal muscle averages 3 to 4 ml/min/100 g of muscle. During extreme exercise in the well-conditioned athlete, this can increase 25- to 50-fold, rising to 100 to 200 ml/min/100 g of muscle. Peak blood flows as high as 400 ml/min/100 g of muscle have been reported in thigh muscles of endurance-trained athletes.

Blood Flow During Muscle Contractions. Figure 21-1 shows a record of blood flow changes in a calf muscle of a human leg during strong rhythmical muscular exercise. Note that the flow increases and decreases with each muscle contraction. At the end of the contractions, the blood flow remains very high for a few seconds but then returns toward normal during the next few minutes.

The cause of the lower flow during the muscle contraction phase of exercise is compression of the blood vessels by the contracted muscle. During strong tetanic contraction, which causes sustained compression of the blood vessels, the blood flow can be almost stopped, but this also causes rapid weakening of the contraction.

Increased Blood Flow in Muscle Capillaries During Exercise. During rest, some muscle capillaries have little or no flowing blood. But during strenuous exercise, all the capillaries open. This opening of dormant capillaries diminishes the distance that oxygen and other nutrients must diffuse from the capillaries to the contracting muscle fibers and sometimes contributes a twofold to threefold increased capillary surface area through which oxygen and nutrients can diffuse from the blood to the tissues.

Control of Blood Flow in Skeletal Muscles

Local Regulation—Decreased Oxygen in Muscle Greatly Enhances Flow. The tremendous increase in muscle blood flow that occurs during skeletal muscle activity is caused mainly by chemicals acting directly on the muscle arterioles to cause dilation. One of the most important chemical effects is reduction of oxygen in the muscle tissues. When muscles are active they use oxygen rapidly, thereby decreasing the oxygen concentration in the tissue fluids. This in turn causes local arteriolar vasodilation because the arteriolar walls cannot maintain contraction in the absence of oxygen and because oxygen deficiency causes release of vasodilator substances. Adenosine may be an important vasodilator substance, but experiments have shown that even large amounts of adenosine infused directly into a muscle artery cannot increase blood flow to the same extent as during intense exercise and cannot sustain vasodilation in skeletal muscle for more than about 2 hours.

Fortunately, even after the muscle blood vessels have become insensitive to the vasodilator effects of adenosine, still other vasodilator factors continue to maintain increased capillary blood flow as long as the exercise continues. These factors include (1) potassium ions, (2) adenosine triphosphate (ATP), (3) lactic acid, and (4) carbon dioxide. We still do not know quantitatively how great a role each of these plays in increasing muscle

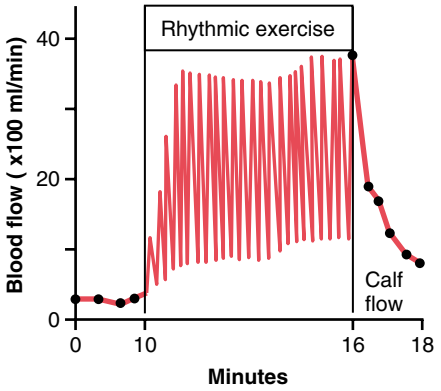

Figure 21-1 Effects of muscle exercise on blood flow in the calf of a leg during strong rhythmical contraction. The blood flow was much less during contractions than between contractions. (Adapted from Barcroft H, Dornhorst AC: The blood flow through the human calf during rhythmic exercise. J Physiol 109:402, 1949.)

blood flow during muscle activity; this subject was discussed in additional detail in Chapter 17.

Nervous Control of Muscle Blood Flow. In addition to local tissue vasodilator mechanisms, skeletal muscles are provided with sympathetic vasoconstrictor nerves and (in some species of animals) sympathetic vasodilator nerves as well.

Sympathetic Vasoconstrictor Nerves. The sympathetic vasoconstrictor nerve fibers secrete norepinephrine at their nerve endings. When maximally activated, this can decrease blood flow through resting muscles to as little as one-half to one-third normal. This vasoconstriction is of physiologic importance in circulatory shock and during other periods of stress when it is necessary to maintain a normal or even high arterial pressure.

In addition to the norepinephrine secreted at the sympathetic vasoconstrictor nerve endings, the medullae of the two adrenal glands also secrete large amounts of norepinephrine plus even more epinephrine into the circulating blood during strenuous exercise. The circulating norepinephrine acts on the muscle vessels to cause a vasoconstrictor effect similar to that caused by direct sympathetic nerve stimulation. The epinephrine, however, often has a slight vasodilator effect because epinephrine excites more of the beta-adrenergic receptors of the vessels, which are vasodilator receptors, in contrast to the alpha vasoconstrictor receptors excited especially by norepinephrine. These receptors are discussed in Chapter 60.

Total Body Circulatory Readjustments During Exercise

Three major effects occur during exercise that are essential for the circulatory system to supply the tremendous blood flow required by the muscles. They are (1) mass discharge of the sympathetic nervous system throughout the body with consequent stimulatory effects on the entire circulation, (2) increase in arterial pressure, and (3) increase in cardiac output.

Effects of Mass Sympathetic Discharge

At the onset of exercise, signals are transmitted not only from the brain to the muscles to cause muscle contraction but also into the vasomotor center to initiate sympathetic discharge throughout the body. Simultaneously, the parasympathetic signals to the heart are attenuated. Therefore, three major circulatory effects result.

First, the heart is stimulated to greatly increased heart rate and increased pumping strength as a result of the sympathetic drive to the heart plus release of the heart from normal parasympathetic inhibition.

Second, most of the arterioles of the peripheral circulation are strongly contracted, except for the arterioles in the active muscles, which are strongly vasodilated by the local vasodilator effects in the muscles, as noted earlier. Thus, the heart is stimulated to supply the increased blood flow required by the muscles, while at the same time blood flow through most nonmuscular areas of the body is temporarily reduced, thereby "lending" blood supply to the muscles. This accounts for as much as 2 L/min of extra blood flow to the muscles, which is exceedingly important when one thinks of a person running for his life—even a fractional increase in running speed may make the difference between life and death. Two of the peripheral circulatory systems, the coronary and cerebral systems, are spared this vasoconstrictor effect because both these circulatory areas have poor vasoconstrictor innervation—fortunately so because both the heart and the brain are as essential to exercise as are the skeletal muscles.

Third, the muscle walls of the veins and other capacitative areas of the circulation are contracted powerfully, which greatly increases the mean systemic filling pressure. As we learned in Chapter 20, this is one of the most important factors in promoting increase in venous return of blood to the heart and, therefore, in increasing the cardiac output.

Increase in Arterial Pressure During Exercise Due to Sympathetic Stimulation

An important effect of increased sympathetic stimulation in exercise is to increase the arterial pressure. This results from multiple stimulatory effects, including (1) vasoconstriction of the arterioles and small arteries in most tissues of the body except the active muscles, (2) increased pumping activity by the heart, and (3) a great increase in mean systemic filling pressure caused mainly by venous contraction. These effects, working together, almost always increase the arterial pressure during exercise. This increase can be as little as 20 mm Hg or as great as 80 mm Hg, depending on the conditions under which the exercise is performed. When a person performs exercise under tense conditions but uses only a few muscles, the sympathetic nervous response still occurs everywhere in the body. In the few active muscles, vasodilation occurs, but everywhere else in the body the effect is mainly vasoconstriction, often increasing the mean arterial pressure to as high as 170 mm Hg. Such a condition might occur

in a person standing on a ladder and nailing with a hammer on the ceiling above. The tenseness of the situation is obvious.

Conversely, when a person performs massive whole-body exercise, such as running or swimming, the increase in arterial pressure is often only 20 to 40 mm Hg. This lack of a large increase in pressure results from the extreme vasodilation that occurs simultaneously in large masses of active muscle.

Why Is the Arterial Pressure Increase During Exercise Important? When muscles are stimulated maximally in a laboratory experiment but without allowing the arterial pressure to rise, muscle blood flow seldom rises more than about eightfold. Yet, we know from studies of marathon runners that muscle blood flow can increase from as little as 1 L/min for the whole body during rest to more than 20 L/min during maximal activity. Therefore, it is clear that muscle blood flow can increase much more than occurs in the aforementioned simple laboratory experiment. What is the difference? Mainly, the arterial pressure rises during normal exercise. Let us assume, for instance, that the arterial pressure rises 30 percent, a common increase during heavy exercise. This 30 percent increase causes 30 percent more force to push blood through the muscle tissue vessels. But this is not the only important effect; the extra pressure also stretches the walls of the vessels, and this effect, along with the locally released vasodilators and higher blood pressure, may increase muscle total flow to more than 20 times normal.

Importance of the Increase in Cardiac Output During Exercise

Many different physiologic effects occur at the same time during exercise to increase cardiac output approximately in proportion to the degree of exercise. In fact, the ability of the circulatory system to provide increased cardiac output for delivery of oxygen and other nutrients to the muscles during exercise is equally as important as the strength of the muscles themselves in setting the limit for continued muscle work. For instance, marathon runners who can increase their cardiac outputs the most are generally the same persons who have record-breaking running times.

Graphical Analysis of the Changes in Cardiac Output During Heavy Exercise. Figure 21-2 shows a graphical analysis of the large increase in cardiac output that occurs during heavy exercise. The cardiac output and venous return curves crossing at point A give the analysis for the normal circulation, and the curves crossing at point B analyze heavy exercise. Note that the great increase in cardiac output requires significant changes in both the cardiac output curve and the venous return curve, as follows.

The increased level of the cardiac output curve is easy to understand. It results almost entirely from sympathetic stimulation of the heart that causes (1) increased heart rate, often up to rates as high as 170 to 190 beats/min, and (2) increased strength of contraction of the heart, often to as much as twice normal. Without this increased level

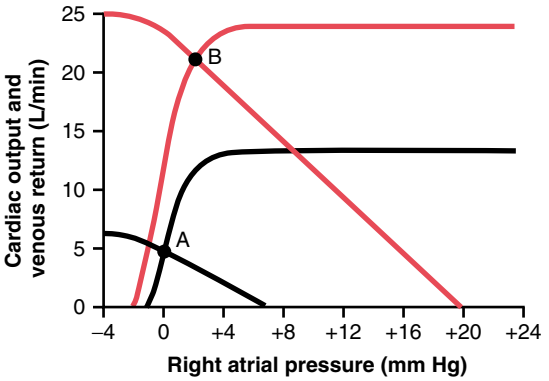

Figure 21-2 Graphical analysis of change in cardiac output and right atrial pressure with onset of strenuous exercise. *Black curves*, normal circulation. *Red curves*, heavy exercise.

of cardiac function, the increase in cardiac output would be limited to the plateau level of the normal heart, which would be a maximum increase of cardiac output of only about 2.5-fold rather than the 4-fold that can commonly be achieved by the untrained runner and the 7-fold that can be achieved in some marathon runners.

Now study the venous return curves. If no change occurred from the normal venous return curve, the cardiac output could hardly rise at all in exercise because the upper plateau level of the normal venous return curve is only 6 L/min. Yet two important changes do occur:

1. The mean systemic filling pressure rises tremendously at the onset of heavy exercise. This results partly from the sympathetic stimulation that contracts the veins and other capacitative parts of the circulation. In addition, tensing of the abdominal and other skeletal muscles of the body compresses many of the internal vessels, thus providing more compression of the entire capacitative vascular system, causing a still greater increase in mean systemic filling pressure. During maximal exercise, these two effects together can increase the mean systemic filling pressure from a normal level of 7 mm Hg to as high as 30 mm Hg.
2. The slope of the venous return curve rotates upward. This is caused by decreased resistance in virtually all the blood vessels in active muscle tissue, which also causes resistance to venous return to decrease, thus increasing the upward slope of the venous return curve.

Therefore, the combination of increased mean systemic filling pressure and decreased resistance to venous return raises the entire level of the venous return curve.

In response to the changes in both the venous return curve and the cardiac output curve, the new equilibrium point in Figure 21-2 for cardiac output and right atrial pressure is now point B, in contrast to the normal level at point A. Note especially that the right atrial pressure has hardly changed, having risen only 1.5 mm Hg. In fact, in a person with a strong heart, the right atrial pressure often falls below normal in very heavy exercise because of the greatly increased sympathetic stimulation of the heart during exercise.

Coronary Circulation

About one third of all deaths in industrialized countries of the Western world result from coronary artery disease, and almost all elderly people have at least some impairment of the coronary artery circulation. For this reason, understanding normal and pathological physiology of the coronary circulation is one of the most important subjects in medicine.

Physiologic Anatomy of the Coronary Blood Supply

Figure 21-3 shows the heart and its coronary blood supply. Note that the main coronary arteries lie on the surface of the heart and smaller arteries then penetrate from the surface into the cardiac muscle mass. It is almost entirely through these arteries that the heart receives its nutritive blood supply. Only the inner 1/10 millimeter of the endocardial surface can obtain significant nutrition directly from the blood inside the cardiac chambers, so this source of muscle nutrition is minuscule.

The *left coronary artery* supplies mainly the anterior and left lateral portions of the left ventricle, whereas the *right coronary artery* supplies most of the right ventricle, as well as the posterior part of the left ventricle in 80 to 90 percent of people.

Most of the coronary venous blood flow from the left ventricular muscle returns to the right atrium of the heart by way of the *coronary sinus*, which is about 75 percent of the total coronary blood flow. And most of the coronary venous blood from the right ventricular muscle returns through small anterior cardiac veins that flow directly into the right atrium, not by way of the coronary sinus. A very small amount of coronary venous blood also flows back into the heart through very minute *thebesian veins*, which empty directly into all chambers of the heart.

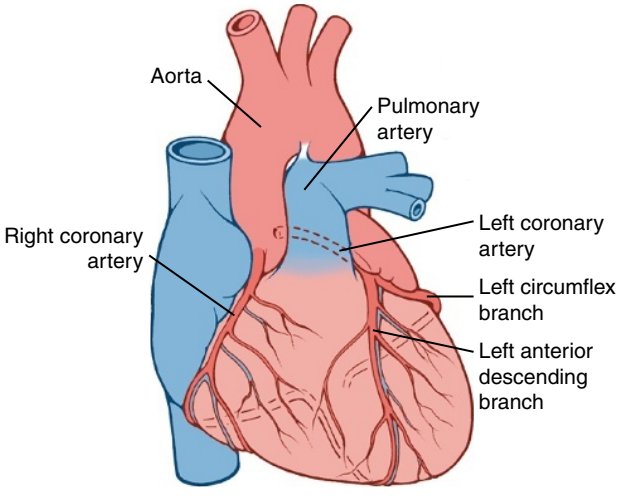

Figure 21-3 The coronary arteries.

Normal Coronary Blood Flow—About 5 Percent of Cardiac Output

The resting coronary blood flow in the resting human being averages 70 ml/min/100 g heart weight, or about 225 ml/min, which is about 4 to 5 percent of the total cardiac output.

During strenuous exercise, the heart in the young adult increases its cardiac output fourfold to sevenfold, and it pumps this blood against a higher than normal arterial pressure. Consequently, the work output of the heart under severe conditions may increase sixfold to ninefold. At the same time, the coronary blood flow increases threefold to fourfold to supply the extra nutrients needed by the heart. This increase is not as much as the increase in workload, which means that the ratio of energy expenditure by the heart to coronary blood flow increases. Thus, the "efficiency" of cardiac utilization of energy increases to make up for the relative deficiency of coronary blood supply.

Phasic Changes in Coronary Blood Flow During Systole and Diastole—Effect of Cardiac Muscle Compression. Figure 21-4 shows the changes in blood flow through the nutrient capillaries of the left ventricular coronary system in ml/min in the human heart during systole and diastole, as extrapolated from studies in experimental animals. Note from this diagram that the coronary capillary blood flow in the left ventricle muscle falls to a low value during systole, which is opposite to flow in vascular beds elsewhere in the body. The reason for this is strong compression of the left ventricular muscle around the intramuscular vessels during systolic contraction.

During diastole, the cardiac muscle relaxes and no longer obstructs blood flow through the left ventricular muscle capillaries, so blood flows rapidly during all of diastole.

Blood flow through the coronary capillaries of the right ventricle also undergoes phasic changes during the cardiac cycle, but because the force of contraction of the right ventricular muscle is far less than that of the left ventricular muscle, the inverse phasic changes are only partial, in contrast to those in the left ventricular muscle.

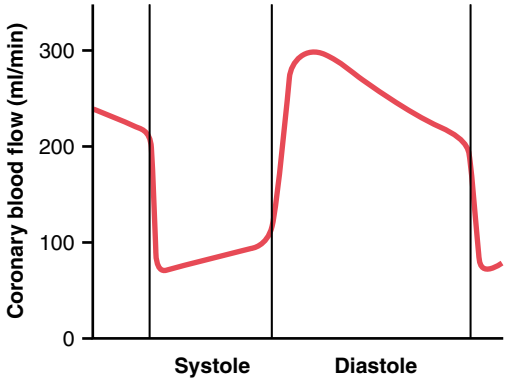

Figure 21-4 Phasic flow of blood through the coronary capillaries of the human left ventricle during cardiac systole and diastole (as extrapolated from measured flows in dogs).

Epicardial Versus Subendocardial Coronary Blood Flow—Effect of Intramyocardial Pressure. Figure 21-5 demonstrates the special arrangement of the coronary vessels at different depths in the heart muscle, showing on the outer surface *epicardial coronary arteries* that supply most of the muscle. Smaller, intramuscular arteries derived from the epicardial arteries penetrate the muscle, supplying the needed nutrients. Lying immediately beneath the endocardium is a plexus of *subendocardial arteries*. During systole, blood flow through the subendocardial plexus of the left ventricle, where the intramuscular coronary vessels are compressed greatly by ventricular muscle contraction, tends to be reduced. But the extra vessels of the subendocardial plexus normally compensate for this. Later in the chapter, we explain how this peculiar difference between blood flow in the epicardial and subendocardial arteries plays an important role in certain types of coronary ischemia.

Control of Coronary Blood Flow

Local Muscle Metabolism Is the Primary Controller of Coronary Flow

Blood flow through the coronary system is regulated mostly by local arteriolar vasodilation in response to the nutritional needs of cardiac muscle. That is, whenever the vigor of cardiac contraction is increased, the rate of coronary blood flow also increases. Conversely, decreased heart activity is accompanied by decreased coronary flow. This local regulation of coronary blood flow is almost identical to that occurring in many other tissues of the body, especially in the skeletal muscles.

Oxygen Demand as a Major Factor in Local Coronary Blood Flow Regulation. Blood flow in the coronary arteries usually is regulated almost exactly in proportion to the need of the cardiac musculature for oxygen. Normally, about 70 percent of the oxygen in the coronary arterial blood is removed as the blood flows through the heart muscle. Because not much oxygen is left, very little additional oxygen can be supplied to the heart musculature unless the coronary blood flow increases. Fortunately, the coronary blood flow does increase almost in direct proportion to any additional metabolic consumption of oxygen by the heart.

However, the exact means by which increased oxygen consumption causes coronary dilation has not been determined. It is speculated by many research workers that a decrease in the oxygen concentration in the heart causes vasodilator substances to be released from the muscle cells and that these dilate the arterioles. A substance with great vasodilator propensity is adenosine. In the presence of very low concentrations of oxygen in the muscle cells, a large proportion of the cell's ATP degrades to adenosine monophosphate; then small portions of this are further degraded and release adenosine into the tissue fluids of the heart muscle, with resultant increase in local coronary blood flow. After the adenosine causes vasodilation, much of it is reabsorbed into the cardiac cells to be reused.

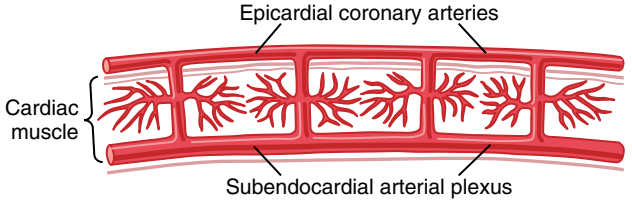

Figure 21-5 Diagram of the epicardial, intramuscular, and subendocardial coronary vasculature.

Adenosine is not the only vasodilator product that has been identified. Others include adenosine phosphate compounds, potassium ions, hydrogen ions, carbon dioxide, prostaglandins, and nitric oxide. Yet the mechanisms of coronary vasodilation during increased cardiac activity have not been fully explained by adenosine. Pharmacologic agents that block or partially block the vasodilator effect of adenosine do not prevent coronary vasodilation caused by increased heart muscle activity. Studies in skeletal muscle have also shown that continued infusion of adenosine maintains vascular dilation for only 1 to 3 hours, and yet muscle activity still dilates the local blood vessels even when the adenosine can no longer dilate them. Therefore, the other vasodilator mechanisms listed earlier should be remembered.

Nervous Control of Coronary Blood Flow

Stimulation of the autonomic nerves to the heart can affect coronary blood flow both directly and indirectly. The direct effects result from action of the nervous transmitter substances acetylcholine from the vagus nerves and norepinephrine and epinephrine from the sympathetic nerves on the coronary vessels themselves. The indirect effects result from secondary changes in coronary blood flow caused by increased or decreased activity of the heart.

The indirect effects, which are mostly opposite to the direct effects, play a far more important role in normal control of coronary blood flow. Thus, sympathetic stimulation, which releases norepinephrine and epinephrine, increases both heart rate and heart contractility and increases the rate of metabolism of the heart. In turn, the increased metabolism of the heart sets off local blood flow regulatory mechanisms for dilating the coronary vessels, and the blood flow increases approximately in proportion to the metabolic needs of the heart muscle. In contrast, vagal stimulation, with its release of acetylcholine, slows the heart and has a slight depressive effect on heart contractility. These effects in turn decrease cardiac oxygen consumption and, therefore, indirectly constrict the coronary arteries.

Direct Effects of Nervous Stimuli on the Coronary Vasculature. The distribution of parasympathetic (vagal) nerve fibers to the ventricular coronary system is not very great. However, the acetylcholine released by parasympathetic stimulation has a direct effect to dilate the coronary arteries.

There is much more extensive sympathetic innervation of the coronary vessels. In Chapter 60, we see that the sympathetic transmitter substances norepinephrine and epinephrine can have either vascular constrictor or vascular dilator effects, depending on the presence or absence of constrictor or dilator receptors in the blood vessel walls. The constrictor receptors are called *alpha receptors* and the dilator receptors are called *beta receptors.* Both alpha and beta receptors exist in the coronary vessels. In general, the epicardial coronary vessels have a preponderance of alpha receptors, whereas the intramuscular arteries may have a preponderance of beta receptors. Therefore, sympathetic stimulation can, at least theoretically, cause slight overall coronary constriction or dilation, but usually constriction. In some people, the alpha vasoconstrictor effects seem to be disproportionately severe, and these people can have vasospastic myocardial ischemia during periods of excess sympathetic drive, often with resultant anginal pain.

Metabolic factors, especially myocardial oxygen consumption, are the major controllers of myocardial blood flow. Whenever the direct effects of nervous stimulation alter the coronary blood flow in the wrong direction, the metabolic control of coronary flow usually overrides the direct coronary nervous effects within seconds.

Special Features of Cardiac Muscle Metabolism

The basic principles of cellular metabolism, discussed in Chapters 67 through 72, apply to cardiac muscle the same as for other tissues, but there are some quantitative differences. Most important, under resting conditions, cardiac muscle normally consumes fatty acids to supply most of its energy instead of carbohydrates (about 70 percent of the energy is derived from fatty acids). However, as is also true of other tissues, under anaerobic or ischemic conditions, cardiac metabolism must call on anaerobic glycolysis mechanisms for energy. Unfortunately, glycolysis consumes tremendous quantities of the blood glucose and at the same time forms large amounts of lactic acid in the cardiac tissue, which is probably one of the causes of cardiac pain in cardiac ischemic conditions, as discussed later in this chapter.

As is true in other tissues, more than 95 percent of the metabolic energy liberated from foods is used to form ATP in the mitochondria. This ATP in turn acts as the conveyer of energy for cardiac muscular contraction and other cellular functions. In severe coronary ischemia, the ATP degrades first to adenosine diphosphate, then to adenosine monophosphate and adenosine. Because the cardiac muscle cell membrane is slightly permeable to adenosine, much of this can diffuse from the muscle cells into the circulating blood.

The released adenosine is believed to be one of the substances that causes dilation of the coronary arterioles during coronary hypoxia, as discussed earlier. However, loss of adenosine also has a serious cellular consequence. Within as little as 30 minutes of severe coronary ischemia, as occurs after a myocardial infarct, about one half of the adenine base can be lost from the affected cardiac muscle cells. Furthermore, this loss can be replaced by new synthesis of adenine at a rate of only 2 percent per hour. Therefore, once a serious bout of coronary ischemia has persisted for 30 or more minutes, relief of the ischemia may be too late to prevent injury and death of the cardiac cells. This almost certainly is one of the major causes of cardiac cellular death during myocardial ischemia.

Ischemic Heart Disease

The most common cause of death in Western culture is ischemic heart disease, which results from insufficient coronary blood flow. About 35 percent of people in the United States die of this cause. Some deaths occur suddenly as a result of acute coronary occlusion or fibrillation of the heart, whereas other deaths occur slowly over a period of weeks to years as a result of progressive weakening of the heart pumping process. In this chapter, we discuss acute coronary ischemia caused by acute coronary occlusion and myocardial infarction. In Chapter 22, we discuss congestive heart failure, the most frequent cause of which is slowly increasing coronary ischemia and weakening of the cardiac muscle.

Atherosclerosis as a Cause of Ischemic Heart Disease. The most frequent cause of diminished coronary blood flow is atherosclerosis. The atherosclerotic process is discussed in connection with lipid metabolism in Chapter 68. Briefly, this process is the following.

In people who have genetic predisposition to atherosclerosis, who are overweight or obese and have a sedentary lifestyle, or who have high blood pressure and damage to the endothelial cells of the coronary blood vessels, large quantities of cholesterol gradually become deposited beneath the endothelium at many points in arteries throughout the body. Gradually, these areas of deposit are invaded by fibrous tissue and frequently become calcified. The net result is the development of atherosclerotic plaques that actually protrude into the vessel lumens and either block or partially block blood flow. A common site for development of atherosclerotic plaques is the first few centimeters of the major coronary arteries.

Acute Coronary Occlusion

Acute occlusion of a coronary artery most frequently occurs in a person who already has underlying atherosclerotic coronary heart disease but almost never in a person with a normal coronary circulation. Acute occlusion can result from any one of several effects, two of which are the following:

1. The atherosclerotic plaque can cause a local blood clot called a *thrombus,* which in turn occludes the artery. The thrombus usually occurs where the arteriosclerotic plaque has broken through the endothelium, thus coming in direct contact with the flowing blood. Because the plaque presents an unsmooth surface, blood platelets adhere to it, fibrin is deposited, and red

blood cells become entrapped to form a blood clot that grows until it occludes the vessel. Or, occasionally, the clot breaks away from its attachment on the atherosclerotic plaque and flows to a more peripheral branch of the coronary arterial tree, where it blocks the artery at that point. A thrombus that flows along the artery in this way and occludes the vessel more distally is called a *coronary embolus.*

2. Many clinicians believe that local muscular spasm of a coronary artery also can occur. The spasm might result from direct irritation of the smooth muscle of the arterial wall by the edges of an arteriosclerotic plaque, or it might result from local nervous reflexes that cause excess coronary vascular wall contraction. The spasm may then lead to *secondary thrombosis* of the vessel.

Lifesaving Value of Collateral Circulation in the Heart. The degree of damage to the heart muscle caused either by slowly developing atherosclerotic constriction of the coronary arteries or by sudden coronary occlusion is determined to a great extent by the degree of collateral circulation that has already developed or that can open within minutes after the occlusion.

In a normal heart, almost no large communications exist among the larger coronary arteries. But many anastomoses do exist among the smaller arteries sized 20 to 250 micrometers in diameter, as shown in Figure 21-6.

When a sudden occlusion occurs in one of the larger coronary arteries, the small anastomoses begin to dilate within seconds. But the blood flow through these minute collaterals is usually less than one-half that needed to keep alive most of the cardiac muscle that they now supply; the diameters of the collateral vessels do not enlarge much more for the next 8 to 24 hours. But then collateral flow does begin to increase, doubling by the second or third day and often reaching normal or almost normal coronary flow within about 1 month. Because of these developing collateral channels, many patients recover almost completely from various degrees of coronary occlusion when the area of muscle involved is not too great.

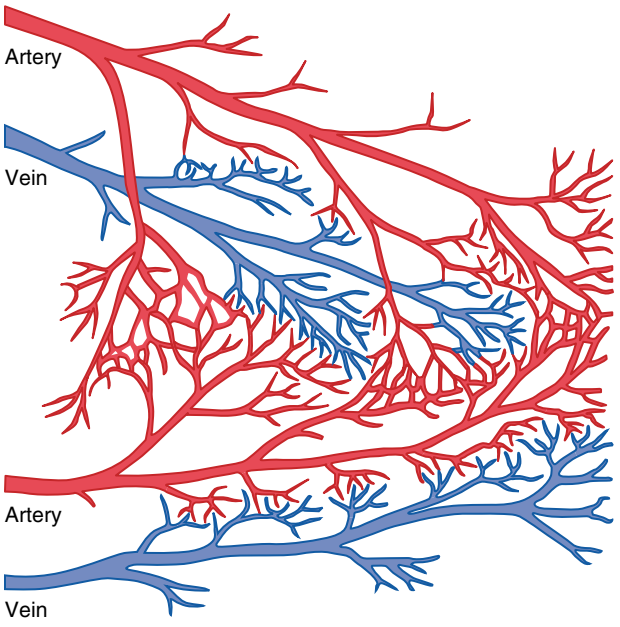

Figure 21-6 Minute anastomoses in the normal coronary arterial system.

When atherosclerosis constricts the coronary arteries slowly over a period of many years rather than suddenly, collateral vessels can develop at the same time while the atherosclerosis becomes more and more severe. Therefore, the person may never experience an acute episode of cardiac dysfunction. But, eventually, the sclerotic process develops beyond the limits of even the collateral blood supply to provide the needed blood flow, and sometimes the collateral blood vessels themselves develop atherosclerosis. When this occurs, the heart muscle becomes severely limited in its work output, often so much so that the heart cannot pump even normally required amounts of blood flow. This is one of the most common causes of the cardiac failure that occurs in vast numbers of older people.

Myocardial Infarction

Immediately after an acute coronary occlusion, blood flow ceases in the coronary vessels beyond the occlusion except for small amounts of collateral flow from surrounding vessels. The area of muscle that has either zero flow or so little flow that it cannot sustain cardiac muscle function is said to be *infarcted.* The overall process is called a *myocardial infarction.*

Soon after the onset of the infarction, small amounts of collateral blood begin to seep into the infarcted area, and this, combined with progressive dilation of local blood vessels, causes the area to become overfilled with stagnant blood. Simultaneously the muscle fibers use the last vestiges of the oxygen in the blood, causing the hemoglobin to become totally deoxygenated. Therefore, the infarcted area takes on a bluish-brown hue, and the blood vessels of the area appear to be engorged despite lack of blood flow. In later stages, the vessel walls become highly permeable and leak fluid; the local muscle tissue becomes edematous, and the cardiac muscle cells begin to swell because of diminished cellular metabolism. Within a few hours of almost no blood supply, the cardiac muscle cells die.

Cardiac muscle requires about 1.3 ml of oxygen per 100 grams of muscle tissue per minute just to remain alive. This is in comparison with about 8 ml of oxygen per 100 grams delivered to the normal resting left ventricle each minute. Therefore, if there is even 15 to 30 percent of normal resting coronary blood flow, the muscle will not die. In the central portion of a large infarct, however, where there is almost no collateral blood flow, the muscle does die.

Subendocardial Infarction. The subendocardial muscle frequently becomes infarcted even when there is no evidence of infarction in the outer surface portions of the heart. The reason for this is that the subendocardial muscle has extra difficulty obtaining adequate blood flow because the blood vessels in the subendocardium

are intensely compressed by systolic contraction of the heart, as explained earlier. Therefore, any condition that compromises blood flow to any area of the heart usually causes damage first in the subendocardial regions, and the damage then spreads outward toward the epicardium.

Causes of Death After Acute Coronary Occlusion

The most common causes of death after acute myocardial infarction are (1) decreased cardiac output; (2) damming of blood in the pulmonary blood vessels and then death resulting from pulmonary edema; (3) fibrillation of the heart; and, occasionally, (4) rupture of the heart.

Decreased Cardiac Output—Systolic Stretch and Cardiac Shock. When some of the cardiac muscle fibers are not functioning and others are too weak to contract with great force, the overall pumping ability of the affected ventricle is proportionately depressed. Indeed, the overall pumping strength of the infarcted heart is often decreased more than one might expect because of a phenomenon called *systolic stretch,* shown in Figure 21-7. That is, when the normal portions of the ventricular muscle contract, the ischemic portion of the muscle, whether it is dead or simply nonfunctional, instead of contracting is forced outward by the pressure that develops inside the ventricle. Therefore, much of the pumping force of the ventricle is dissipated by bulging of the area of nonfunctional cardiac muscle.

When the heart becomes incapable of contracting with sufficient force to pump enough blood into the peripheral arterial tree, cardiac failure and death of peripheral tissues ensue as a result of peripheral ischemia. This condition is called *coronary shock, cardiogenic shock, cardiac shock,* or *low cardiac output failure.* It is discussed more fully in the next chapter. Cardiac shock almost always occurs when more than 40 percent of the left ventricle is infarcted. And death occurs in over 70 percent of patients once they develop cardiac shock.

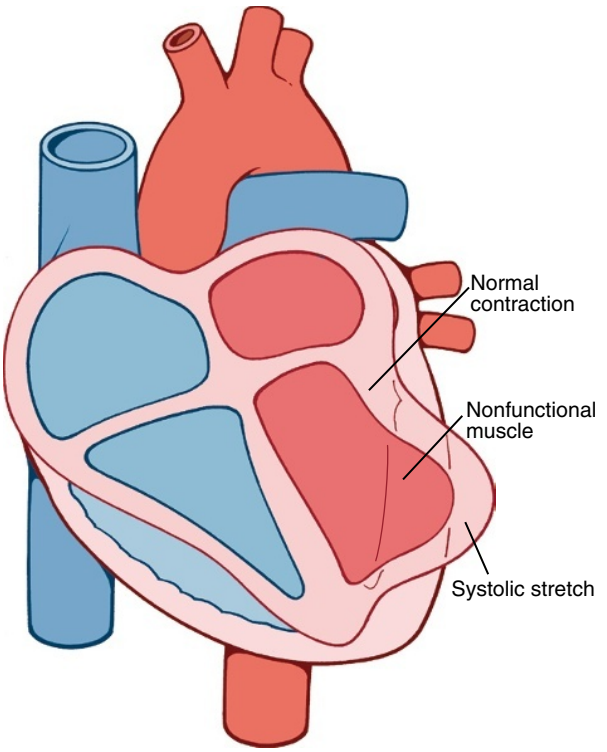

Figure 21-7 Systolic stretch in an area of ischemic cardiac muscle.

Damming of Blood in the Body's Venous System. When the heart is not pumping blood forward, it must be damming blood in the atria and in the blood vessels of the lungs or in the systemic circulation. This leads to increased capillary pressures, particularly in the lungs.

This damming of blood in the veins often causes little difficulty during the first few hours after myocardial infarction. Instead, symptoms develop a few days later for the following reason: The acutely diminished cardiac output leads to diminished blood flow to the kidneys. Then, for reasons that are discussed in Chapter 22, the kidneys fail to excrete enough urine. This adds progressively to the total blood volume and, therefore, leads to congestive symptoms. Consequently, many patients who seemingly are getting along well during the first few days after onset of heart failure will suddenly develop acute pulmonary edema and often will die within a few hours after appearance of the initial pulmonary symptoms.

Fibrillation of the Ventricles After Myocardial Infarction. Many people who die of coronary occlusion die because of sudden ventricular fibrillation. The tendency to develop fibrillation is especially great after a large infarction, but fibrillation can sometimes occur after small occlusions as well. Indeed, some patients with chronic coronary insufficiency die suddenly from fibrillation without any acute infarction.

There are two especially dangerous periods after coronary infarction during which fibrillation is most likely to occur. The first is during the first 10 minutes after the infarction occurs. Then there is a short period of relative safety, followed by a second period of cardiac irritability beginning 1 hour or so later and lasting for another few hours. Fibrillation can also occur many days after the infarct but less likely so.

At least four factors enter into the tendency for the heart to fibrillate:

1. Acute loss of blood supply to the cardiac muscle causes rapid depletion of potassium from the ischemic musculature. This also increases the potassium concentration in the extracellular fluids surrounding the cardiac muscle fibers. Experiments in which potassium has been injected into the coronary system have demonstrated that an elevated extracellular potassium concentration increases the irritability of the cardiac musculature and, therefore, its likelihood of fibrillating.
2. Ischemia of the muscle causes an "injury current," which is described in Chapter 12 in relation to electrocardiograms in patients with acute myocardial infarction.

That is, the ischemic musculature often cannot completely repolarize its membranes after a heartbeat, so the external surface of this muscle remains negative with respect to normal cardiac muscle membrane potential elsewhere in the heart. Therefore, electric current flows from this ischemic area of the heart to the normal area and can elicit abnormal impulses that can cause fibrillation.

3. Powerful sympathetic reflexes often develop after massive infarction, principally because the heart does not pump an adequate volume of blood into the arterial tree, which leads to reduced blood pressure. The sympathetic stimulation also increases irritability of the cardiac muscle and thereby predisposes to fibrillation.
4. Cardiac muscle weakness caused by the myocardial infarction often causes the ventricle to dilate excessively. This increases the pathway length for impulse conduction in the heart and frequently causes abnormal conduction pathways all the way around the infarcted area of the cardiac muscle. Both of these effects predispose to development of circus movements because, as discussed in Chapter 13, excess prolongation of conduction pathways in the ventricles allows impulses to re-enter muscle that is already recovering from refractoriness, thereby initiating a "circus movement" cycle of new excitation and causing the process to continue on and on.

Rupture of the Infarcted Area. During the first day or so after an acute infarct, there is little danger of rupture of the ischemic portion of the heart, but a few days later, the dead muscle fibers begin to degenerate, and the heart wall becomes stretched very thin. When this happens, the dead muscle bulges outward severely with each heart contraction, and this systolic stretch becomes greater and greater until finally the heart ruptures. In fact, one of the means used in assessing progress of severe myocardial infarction is to record by cardiac imaging (i.e., x-rays) whether the degree of systolic stretch is worsening.

When a ventricle does rupture, loss of blood into the pericardial space causes rapid development of *cardiac tamponade*—that is, compression of the heart from the outside by blood collecting in the pericardial cavity. Because of this compression of the heart, blood cannot flow into the right atrium, and the patient dies of suddenly decreased cardiac output.

Stages of Recovery from Acute Myocardial Infarction

The upper left part of Figure 21-8 shows the effects of acute coronary occlusion in a patient with a small area of muscle ischemia; to the right is shown a heart with a large area of ischemia. When the area of ischemia is small, little or no death of the muscle cells may occur, but part of the muscle often does become temporarily nonfunctional because of inadequate nutrition to support muscle contraction.

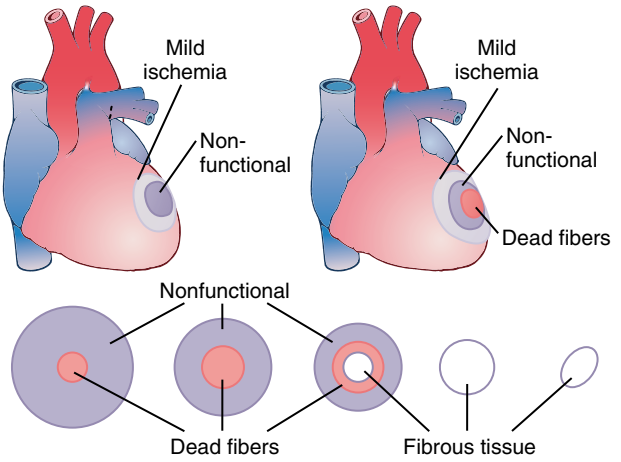

Figure 21-8 *Top,* Small and large areas of coronary ischemia. *Bottom,* Stages of recovery from myocardial infarction.

When the area of ischemia is large, some of the muscle fibers in the center of the area die rapidly, within 1 to 3 hours where there is total cessation of coronary blood supply. Immediately around the dead area is a nonfunctional area, with failure of contraction and usually failure of impulse conduction. Then, extending circumferentially around the nonfunctional area is an area that is still contracting but weakly so because of mild ischemia.

Replacement of Dead Muscle by Scar Tissue. In the lower part of Figure 21-8, the various stages of recovery after a large myocardial infarction are shown. Shortly after the occlusion, the muscle fibers in the center of the ischemic area die. Then, during the ensuing days, this area of dead fibers becomes bigger because many of the marginal fibers finally succumb to the prolonged ischemia. At the same time, because of enlargement of collateral arterial channels supplying the outer rim of the infarcted area, much of the nonfunctional muscle recovers. After a few days to 3 weeks, most of the nonfunctional muscle becomes functional again or dies—one or the other. In the meantime, fibrous tissue begins developing among the dead fibers because ischemia can stimulate growth of fibroblasts and promote development of greater than normal quantities of fibrous tissue. Therefore, the dead muscle tissue is gradually replaced by fibrous tissue. Then, because it is a general property of fibrous tissue to undergo progressive contraction and dissolution, the fibrous scar may grow smaller over a period of several months to a year.

Finally, the normal areas of the heart gradually hypertrophy to compensate at least partially for the lost dead cardiac musculature. By these means, the heart recovers either partially or almost completely within a few months.

Value of Rest in Treating Myocardial Infarction. The degree of cardiac cellular death is determined by the degree of ischemia and the workload on the heart muscle.

When the workload is greatly increased, such as during exercise, in severe emotional strain, or as a result of fatigue, the heart needs increased oxygen and other nutrients for sustaining its life. Furthermore, anastomotic blood vessels that supply blood to ischemic areas of the heart must also still supply the areas of the heart that they normally supply. When the heart becomes excessively active, the vessels of the normal musculature become greatly dilated. This allows most of the blood flowing into the coronary vessels to flow through the normal muscle tissue, thus leaving little blood to flow through the small anastomotic channels into the ischemic area so that the ischemic condition worsens. This condition is called the *"coronary steal" syndrome*. Consequently, one of the most important factors in the treatment of a patient with myocardial infarction is observance of absolute body rest during the recovery process.

Function of the Heart After Recovery from Myocardial Infarction

Occasionally, a heart that has recovered from a large myocardial infarction returns almost to full functional capability, but more frequently its pumping capability is permanently decreased below that of a healthy heart. This does not mean that the person is necessarily a cardiac invalid or that the resting cardiac output is depressed below normal, because the normal heart is capable of pumping 300 to 400 percent more blood per minute than the body requires during rest—that is, a normal person has a "cardiac reserve" of 300 to 400 percent. Even when the cardiac reserve is reduced to as little as 100 percent, the person can still perform most normal daily activities but not strenuous exercise that would overload the heart.

Pain in Coronary Heart Disease

Normally, a person cannot "feel" his or her heart, but ischemic cardiac muscle often does cause pain sensation, sometimes severe. Exactly what causes this pain is not known, but it is believed that ischemia causes the muscle to release acidic substances, such as lactic acid, or other pain-promoting products, such as histamine, kinins, or cellular proteolytic enzymes, that are not removed rapidly enough by the slowly moving coronary blood flow. The high concentrations of these abnormal products then stimulate pain nerve endings in the cardiac muscle, sending pain impulses through sensory afferent nerve fibers into the central nervous system.

Angina Pectoris

In most people who develop progressive constriction of their coronary arteries, cardiac pain, called *angina pectoris,* begins to appear whenever the load on the heart becomes too great in relation to the available coronary blood flow. This pain is usually felt beneath the upper sternum over the heart, and in addition it is often referred to distant surface areas of the body, most commonly to the left arm and left shoulder but also frequently to the neck and even to the side of the face. The reason for this distribution of pain is that the heart originates during embryonic life in the neck, as do the arms. Therefore, both the heart and these surface areas of the body receive pain nerve fibers from the same spinal cord segments.

Most people who have chronic angina pectoris feel pain when they exercise or when they experience emotions that increase metabolism of the heart or temporarily constrict the coronary vessels because of sympathetic vasoconstrictor nerve signals. Anginal pain is also exacerbated by cold temperatures or by having a full stomach, both of which increase the workload of the heart. The pain usually lasts for only a few minutes. However, some patients have such severe and lasting ischemia that the pain is present all the time. The pain is frequently described as hot, pressing, and constricting; it is of such quality that it usually makes the patient stop all unnecessary body activity and come to a complete state of rest.

Treatment with Drugs. Several vasodilator drugs, when administered during an acute anginal attack, can often give immediate relief from the pain. Commonly used short-acting vasodilators are *nitroglycerin* and other *nitrate drugs*. Other vasodilators, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and ranolazine, may be beneficial in treating chronic stable angina pectoris.

Another class of drugs used for prolonged treatment of angina pectoris is the *beta blockers*, such as propranolol. These drugs block sympathetic beta-adrenergic receptors, which prevents sympathetic enhancement of heart rate and cardiac metabolism during exercise or emotional episodes. Therefore, therapy with a beta blocker decreases the need of the heart for extra metabolic oxygen during stressful conditions. For obvious reasons, this can also reduce the number of anginal attacks, as well as their severity.

Surgical Treatment of Coronary Artery Disease

Aortic-Coronary Bypass Surgery. In many patients with coronary ischemia, the constricted areas of the coronary arteries are located at only a few discrete points blocked by atherosclerotic disease and the coronary vessels elsewhere are normal or almost normal. A surgical procedure was developed in the 1960s, called *aortic-coronary bypass,* for removing a section of a subcutaneous vein from an arm or leg and then grafting this vein from the root of the aorta to the side of a peripheral coronary artery beyond the atherosclerotic blockage point. One to five such grafts are usually performed, each of which supplies a peripheral coronary artery beyond a block.

Anginal pain is relieved in most patients. Also, in patients whose hearts have not become too severely damaged before the operation, the coronary bypass procedure may provide the patient with normal survival expectation. If the heart has already been severely damaged, however, the bypass procedure is likely to be of little value.

Coronary Angioplasty. Since the 1980s, a procedure has been used to open partially blocked coronary vessels before they become totally occluded. This procedure, called *coronary artery angioplasty,* is the following: A small balloon-tipped catheter, about 1 millimeter in diameter, is passed under radiographic guidance into the coronary system and pushed through the partially occluded artery until the balloon portion of the catheter straddles the partially occluded point. Then the balloon is inflated with high pressure, which markedly stretches the diseased artery. After this procedure is performed, the blood flow through the vessel often increases threefold to fourfold, and more than 75 percent of the patients who undergo the procedure are relieved of the coronary ischemic symptoms for at least several years, although many of the patients still eventually require coronary bypass surgery.

Small stainless steel mesh tubes called "stents" are sometimes placed inside a coronary artery dilated by angioplasty to hold the artery open, thus preventing its restenosis. Within a few weeks after the stent is placed in the coronary artery, the endothelium usually grows over the metal surface of the stent, allowing blood to flow smoothly through the stent. However, reclosure (restenosis) of the blocked coronary artery occurs in about 25 to 40 percent of patients treated with angioplasty, often within 6 months of the initial procedure. This is usually due to excessive formation of scar tissue that develops underneath the healthy new endothelium that has grown over the stent. Stents that slowly release drugs (drug-eluting stents) may help to prevent the excessive growth of scar tissue.

Newer procedures for opening atherosclerotic coronary arteries are constantly in experimental development. One of these employs a laser beam from the tip of a coronary artery catheter aimed at the atherosclerotic lesion. The laser literally dissolves the lesion without substantially damaging the rest of the arterial wall.

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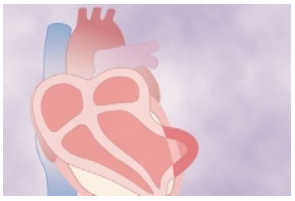
CHAPTER 22

Cardiac Failure



One of the most important ailments that must be treated by the physician is cardiac failure ("heart failure"). This can result from any heart condition that reduces the ability of the heart to pump blood. The cause is usually decreased contractility of the myocardium resulting from diminished coronary blood flow. However, failure can also be caused by damaged heart valves, external pressure around the heart, vitamin B deficiency, primary cardiac muscle disease, or any other abnormality that makes the heart a hypoeffective pump.

In this chapter, we discuss mainly cardiac failure caused by ischemic heart disease resulting from partial blockage of the coronary blood vessels, the most common cause of heart failure. In Chapter 23, we discuss valvular and congenital heart disease.

Definition of Cardiac Failure. The term "cardiac failure" means simply failure of the heart to pump enough blood to satisfy the needs of the body.

Circulatory Dynamics in Cardiac Failure

Acute Effects of Moderate Cardiac Failure

If a heart suddenly becomes severely damaged, such as by myocardial infarction, the pumping ability of the heart is immediately depressed. As a result, two main effects occur: (1) reduced cardiac output and (2) damming of blood in the veins, resulting in increased venous pressure.

The progressive changes in heart pumping effectiveness at different times after an acute myocardial infarction are shown graphically in Figure 22-1. The top curve of this figure shows a normal cardiac output curve. Point A on this curve is the normal operating point, showing a normal cardiac output under resting conditions of 5 L/min and a right atrial pressure of 0 mm Hg.

Immediately after the heart becomes damaged, the cardiac output curve becomes greatly lowered, falling to the lowest curve at the bottom of the graph. Within a few seconds, a new circulatory state is established at point B, illustrating that the cardiac output has fallen to 2 L/min, about two-fifths normal, whereas the right atrial pressure has risen to +4 mm Hg because venous blood returning to the heart from the body is dammed up in the right atrium. This low cardiac output is still sufficient to sustain life for perhaps a few hours, but it is likely to be associated with fainting. Fortunately, this acute stage usually lasts for only a few seconds because sympathetic nervous reflexes occur almost immediately and compensate, to a great extent, for the damaged heart, as follows.

Compensation for Acute Cardiac Failure by Sympathetic Nervous Reflexes. When the cardiac output falls precariously low, many of the circulatory reflexes discussed in Chapter 18 are rapidly activated. The best known of these is the *baroreceptor reflex,* which is activated by diminished arterial pressure. The *chemoreceptor reflex,* the *central nervous system ischemic response,* and even *reflexes that originate in the damaged heart* also likely contribute to activating the sympathetic nervous system. The sympathetics therefore become strongly stimulated within a few seconds, and the parasympathetic nervous signals to the heart become reciprocally inhibited at the same time.

Strong sympathetic stimulation has major effects on the heart itself and on the peripheral vasculature. If all the ventricular musculature is diffusely damaged but is still functional, sympathetic stimulation strengthens this damaged musculature. If part of the muscle is nonfunctional and part of it is still normal, the normal muscle is strongly stimulated by sympathetic stimulation, in this way partially compensating for the nonfunctional muscle. Thus, *the heart becomes a stronger pump* as a result of sympathetic stimulation. This effect is illustrated in Figure 22-1, showing after sympathetic compensation about twofold elevation of the very low cardiac output curve.

Sympathetic stimulation also increases venous return because it increases the tone of most of the blood vessels of the circulation, especially the veins, *raising the mean systemic filling* pressure to 12 to 14 mm Hg, almost 100 percent above normal. As discussed in Chapter 20, this increased filling pressure greatly increases the tendency for blood to flow from the veins back into the heart.

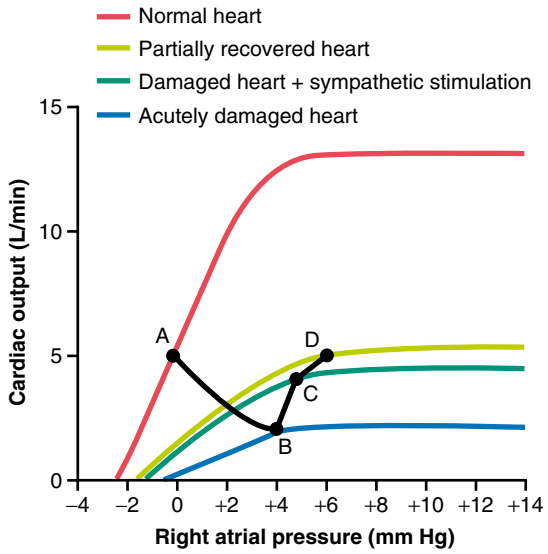


Figure 22-1 Progressive changes in the cardiac output curve after acute myocardial infarction. Both the cardiac output and right atrial pressure change progressively from point A to point D (illustrated by the black line) over a period of seconds, minutes, days, and weeks.

Therefore, the damaged heart becomes primed with more inflowing blood than usual, and the right atrial pressure rises still further, which helps the heart to pump still larger quantities of blood. Thus, in Figure 22-1, the new circulatory state is depicted by point C, showing a cardiac output of 4.2 L/min and a right atrial pressure of 5 mm Hg.

The sympathetic reflexes become maximally developed in about 30 seconds. Therefore, a person who has a sudden, moderate heart attack might experience nothing more than cardiac pain and a few seconds of fainting. Shortly thereafter, with the aid of the sympathetic reflex compensations, the cardiac output may return to a level adequate to sustain the person if he or she remains quiet, although the pain might persist.

Chronic Stage of Failure—Fluid Retention and Compensated Cardiac Output

After the first few minutes of an acute heart attack, a prolonged semichronic state begins, characterized mainly by two events: (1) retention of fluid by the kidneys and (2) varying degrees of recovery of the heart itself over a period of weeks to months, as illustrated by the light green curve in Figure 22-1; this was also discussed in Chapter 21.

Renal Retention of Fluid and Increase in Blood Volume Occur for Hours to Days

A low cardiac output has a profound effect on renal function, sometimes causing anuria when the cardiac output falls to 50 to 60 percent of normal. In general, the urine output remains below normal as long as the cardiac output and arterial pressure remain significantly less than normal; urine output usually does not return all the way to normal after an acute heart attack until the cardiac output and arterial pressure rise almost to normal levels.

Moderate Fluid Retention in Cardiac Failure Can Be Beneficial. Many cardiologists have considered fluid retention always to have a detrimental effect in cardiac failure. But it is now known that a moderate increase in body fluid and blood volume is an important factor in helping to compensate for the diminished pumping ability of the heart by increasing the venous return. The increased blood volume increases venous return in two ways: First, it increases the mean systemic filling pressure, which *increases the pressure gradient for causing venous flow of blood toward the heart.* Second, it distends the veins, which *reduces the venous resistance* and allows even more ease of flow of blood to the heart.

If the heart is not too greatly damaged, this increased venous return can often fully compensate for the heart's diminished pumping ability—enough that even when the heart's pumping ability is reduced to as low as 40 to 50 percent of normal, the increased venous return can often cause entirely nearly normal cardiac output as long as the person remains in a quiet resting state.

When the heart's pumping capability is reduced further, blood flow to the kidneys finally becomes too low for the kidneys to excrete enough salt and water to equal salt and water intake. Therefore, fluid retention begins and continues indefinitely, unless major therapeutic procedures are used to prevent this. Furthermore, because the heart is already pumping at its maximum pumping capacity, *this excess fluid no longer has a beneficial effect* on the circulation. Instead, the fluid retention increases the workload on the already damaged heart and severe edema develops throughout the body, which can be very detrimental in itself and can lead to death.

Detrimental Effects of Excess Fluid Retention in Severe Cardiac Failure. In contrast to the beneficial effects of moderate fluid retention in cardiac failure, in severe failure extreme excesses of fluid can have serious physiological consequences. They include (1) increasing the workload on the damaged heart, (2) overstretching of the heart, thus weakening the heart still more; (3) filtration of fluid into the lungs, causing pulmonary edema and consequent deoxygenation of the blood; and (4) development of extensive edema in most parts of the body. These detrimental effects of excessive fluid are discussed in later sections of this chapter.

Recovery of the Myocardium After Myocardial Infarction

After a heart becomes suddenly damaged as a result of myocardial infarction, the natural reparative processes of the body begin to help restore normal cardiac function. For instance, a new collateral blood supply begins to penetrate the peripheral portions of the infarcted area of the heart, often causing much of the heart muscle in the fringe areas to become functional again. Also, the undamaged portion of the heart musculature hypertrophies, in this way offsetting much of the cardiac damage.

The degree of recovery depends on the type of cardiac damage, and it varies from no recovery to almost

complete recovery. After acute myocardial infarction, the heart ordinarily recovers rapidly during the first few days and weeks and achieves most of its final state of recovery within 5 to 7 weeks, although mild degrees of additional recovery can continue for months.

Cardiac Output Curve After Partial Recovery. Figure 22-1 shows function of the partially recovered heart a week or so after acute myocardial infarction. By this time, considerable fluid has been retained in the body and the tendency for venous return has increased markedly as well; therefore, the right atrial pressure has risen even more. As a result, the state of the circulation is now changed from point C to point D, which shows a normal cardiac output of 5 L/min but right atrial pressure increased to 6 mm Hg.

Because the cardiac output has returned to normal, renal output of fluid also returns to normal and no further fluid retention occurs, except that *the retention of fluid that has already occurred continues to maintain moderate excesses of fluid*. Therefore, except for the high right atrial pressure represented by point D in this figure, the person now has essentially normal cardiovascular dynamics *as long as he or she remains at rest*.

If the heart recovers to a significant extent and if adequate fluid volume has been retained, the sympathetic stimulation gradually abates toward normal for the following reasons: The partial recovery of the heart can elevate the cardiac output curve the same as sympathetic stimulation can. Therefore, as the heart recovers even slightly, the fast pulse rate, cold skin, and pallor resulting from sympathetic stimulation in the acute stage of cardiac failure gradually disappear.

Summary of the Changes That Occur After Acute Cardiac Failure—"Compensated Heart Failure"

To summarize the events discussed in the past few sections describing the dynamics of circulatory changes after an acute, moderate heart attack, we can divide the stages into (1) the instantaneous effect of the cardiac damage; (2) compensation by the sympathetic nervous system, which occurs mainly within the first 30 seconds to 1 minute; and (3) chronic compensations resulting from partial heart recovery and renal retention of fluid. All these changes are shown graphically by the black line in Figure 22-1. The progression of this line shows the normal state of the circulation (point A), the state a few seconds after the heart attack but before sympathetic reflexes have occurred (point B), the rise in cardiac output toward normal caused by sympathetic stimulation (point C), and final return of the cardiac output to almost normal after several days to several weeks of partial cardiac recovery and fluid retention (point D). This final state is called *compensated heart failure*.

Compensated Heart Failure. Note especially in Figure 22-1 that the maximum pumping ability of the partly recovered heart, as depicted by the plateau level of the light green curve, is still depressed to less than one-half normal. This demonstrates that an increase in right atrial pressure can maintain the cardiac output at a normal level despite continued weakness of the heart. Thus, many people, especially older people, have normal resting cardiac outputs but mildly to moderately elevated right atrial pressures because of various degrees of "compensated heart failure." These persons may not know that they have cardiac damage because the damage often has occurred a little at a time, and the compensation has occurred concurrently with the progressive stages of damage.

When a person is in compensated heart failure, any attempt to perform heavy exercise usually causes immediate return of the symptoms of acute failure because the heart is not able to increase its pumping capacity to the levels required for the exercise. Therefore, it is said that the *cardiac reserve* is reduced in compensated heart failure. This concept of cardiac reserve is discussed more fully later in the chapter.

Dynamics of Severe Cardiac Failure—Decompensated Heart Failure

If the heart becomes severely damaged, no amount of compensation, either by sympathetic nervous reflexes or by fluid retention, can make the excessively weakened heart pump a normal cardiac output. As a consequence, the cardiac output cannot rise high enough to make the kidneys excrete normal quantities of fluid. Therefore, fluid continues to be retained, the person develops more and more edema, and this state of events eventually leads to death. This is called *decompensated heart failure*. Thus, the main cause of decompensated heart failure is failure of the heart to pump sufficient blood to make the kidneys excrete daily the necessary amounts of fluid.

Graphical Analysis of Decompensated Heart Failure. Figure 22-2 shows greatly depressed cardiac output at different times (points A to F) after the heart has become severely weakened. Point A on this curve represents the approximate state of the circulation before any compensation has occurred, and point B, the state a few minutes later after sympathetic stimulation has

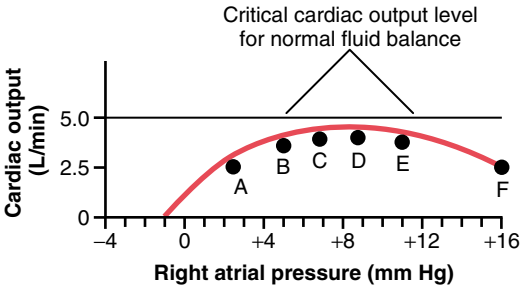


Figure 22-2 Greatly depressed cardiac output that indicates decompensated heart disease. Progressive fluid retention raises the right atrial pressure over a period of days, and the cardiac output progresses from point A to point F, until death occurs.

compensated as much as it can but before fluid retention has begun. At this time, the cardiac output has risen to 4 L/min and the right atrial pressure has risen to 5 mm Hg. The person appears to be in reasonably good condition, but this state will not remain stable because the cardiac output has not risen high enough to cause adequate kidney excretion of fluid; therefore, fluid retention continues and can eventually be the cause of death. These events can be explained quantitatively in the following way.

Note the straight line in Figure 22-2, at a cardiac output level of 5 L/min. This is approximately the critical cardiac output level that is required in the normal adult person to make the kidneys re-establish normal fluid balance—that is, for the output of salt and water to be as great as the intake of these. At any cardiac output below this level, all the fluid-retaining mechanisms discussed in the earlier section remain in play and the body fluid volume increases progressively. And because of this progressive increase in fluid volume, the mean systemic filling pressure of the circulation continues to rise; this forces progressively increasing quantities of blood from the person's peripheral veins into the right atrium, thus increasing the right atrial pressure. After 1 day or so, the state of the circulation changes in Figure 22-2 from point B to point C—the right atrial pressure rising to 7 mm Hg and the cardiac output to 4.2 L/min. Note again that the cardiac output is still not high enough to cause normal renal output of fluid; therefore, fluid continues to be retained. After another day or so, the right atrial pressure rises to 9 mm Hg, and the circulatory state becomes that depicted by point D. Still, the cardiac output is not enough to establish normal fluid balance.

After another few days of fluid retention, the right atrial pressure has risen still further, but by now, cardiac function is beginning to decline toward a lower level. This decline is caused by overstretch of the heart, edema of the heart muscle, and other factors that diminish the heart's pumping performance. It is now clear that further retention of fluid will be more detrimental than beneficial to the circulation. Yet the cardiac output still is not high enough to bring about normal renal function, so fluid retention not only continues but accelerates because of the falling cardiac output (and falling arterial pressure that also occurs). Consequently, within a few days, the state of the circulation has reached point F on the curve, with the cardiac output now less than 2.5 L/min and the right atrial pressure 16 mm Hg. This state has approached or reached incompatibility with life, and the patient dies unless this chain of events can be reversed. This state of heart failure in which the failure continues to worsen is called *decompensated heart failure*.

Thus, one can see from this analysis that failure of the cardiac output (and arterial pressure) to rise to the critical level required for normal renal function results in (1) progressive retention of more and more fluid, which causes (2) progressive elevation of the mean systemic filling pressure, and (3) progressive elevation of the right atrial pressure until finally the heart is so overstretched or so edematous that it cannot pump even moderate quantities of blood and, therefore, fails completely. Clinically, one detects this serious condition of decompensation principally by the progressing edema, especially edema of the lungs, which leads to bubbling *rales* (a crackling sound) in the lungs and to *dyspnea* (air hunger). Lack of appropriate therapy when this state of events occurs rapidly leads to death.

Treatment of Decompensation. The decompensation process can often be stopped by (1) *strengthening the heart* in any one of several ways, especially by administration of a cardiotonic drug, such as *digitalis,* so that the heart becomes strong enough to pump adequate quantities of blood required to make the kidneys function normally again, or (2) *administering diuretic drugs to increase kidney excretion* while at the same time reducing water and salt intake, which brings about a balance between fluid intake and output despite low cardiac output.

Both methods stop the decompensation process by re-establishing normal fluid balance so that at least as much fluid leaves the body as enters it.

Mechanism of Action of the Cardiotonic Drugs Such as Digitalis. Cardiotonic drugs, such as digitalis, when administered to a person with a healthy heart, have little effect on increasing the contractile strength of the cardiac muscle. However, when administered to a person with a chronically failing heart, the same drugs can sometimes increase the strength of the failing myocardium as much as 50 to 100 percent. Therefore, they are one of the mainstays of therapy in chronic heart failure.

Digitalis and other cardiotonic glycosides are believed to strengthen heart contractions by increasing the quantity of calcium ions in muscle fibers. This effect is likely due to inhibition of sodium-potassium ATPase in cardiac cell membranes. Inhibition of the sodium-potassium pump increases intracellular sodium concentration and slows the sodium-calcium exchange pump, which extrudes calcium from the cell in exchange for sodium. Because the sodium-calcium exchange pump relies on a high sodium gradient across the cell membrane, accumulation of sodium inside the cell reduces its activity.

In the failing heart muscle, the sarcoplasmic reticulum fails to accumulate normal quantities of calcium and, therefore, cannot release enough calcium ions into the free-fluid compartment of the muscle fibers to cause full contraction of the muscle. The effect of digitalis to depress the sodium-calcium exchange pump and raise calcium ion concentration in cardiac muscle provides the extra calcium needed to increase the muscle contractile force. Therefore, it is usually beneficial to depress the calcium pumping mechanism a moderate amount using digitalis, allowing the muscle fiber intracellular calcium level to rise slightly.

Unilateral Left Heart Failure

In the discussions thus far in this chapter, we have considered failure of the heart as a whole. Yet, in a large number of patients, especially those with early acute failure, left-sided failure predominates over right-sided failure, and, in rare instances, the right side fails without significant failure of the left side. Therefore, we need to discuss the special features of unilateral heart failure.

When the left side of the heart fails without concomitant failure of the right side, blood continues to be pumped into the lungs with usual right heart vigor, whereas it is not pumped adequately out of the lungs by the left heart into the systemic circulation. As a result, the *mean pulmonary filling pressure* rises because of shift of large volumes of blood from the systemic circulation into the pulmonary circulation.

As the volume of blood in the lungs increases, the pulmonary capillary pressure increases, and if this rises above a value approximately equal to the colloid osmotic pressure of the plasma, about 28 mm Hg, fluid begins to filter out of the capillaries into the lung interstitial spaces and alveoli, resulting in pulmonary edema.

Thus, among the most important problems of left heart failure are *pulmonary vascular congestion* and *pulmonary edema.* In severe, acute left heart failure, pulmonary edema occasionally occurs so rapidly that it can cause death by suffocation in 20 to 30 minutes, which we discuss later in the chapter.

Low-Output Cardiac Failure—Cardiogenic Shock

In many instances after acute heart attacks and often after prolonged periods of slow progressive cardiac deterioration, the heart becomes incapable of pumping even the minimal amount of blood flow required to keep the body alive. Consequently, the body tissues begin to suffer and even to deteriorate, often leading to death within a few hours to a few days. The picture then is one of circulatory shock, as explained in Chapter 24. Even the cardiovascular system suffers from lack of nutrition, and it, too (along with the remainder of the body), deteriorates, thus hastening death. This circulatory shock syndrome caused by inadequate cardiac pumping is called *cardiogenic shock* or simply *cardiac shock.* Once a person develops cardiogenic shock, the survival rate is often less than 30 percent even with appropriate medical care.

Vicious Circle of Cardiac Deterioration in Cardiogenic Shock. The discussion of circulatory shock in Chapter 24 emphasizes the tendency for the heart to become progressively more damaged when its coronary blood supply is reduced during the course of the shock. That is, the low arterial pressure that occurs during shock reduces the coronary blood supply even more. This makes the heart still weaker, which makes the arterial pressure fall still more, which makes the shock progressively worse, the process eventually becoming a vicious circle of cardiac deterioration. In cardiogenic shock caused by myocardial infarction, this problem is greatly compounded by already existing coronary vessel blockage. For instance, in a healthy heart, the arterial pressure usually must be reduced below about 45 mm Hg before cardiac deterioration sets in. However, in a heart that already has a blocked major coronary vessel, deterioration begins when the coronary arterial pressure falls below 80 to 90 mm Hg. In other words, even a small decrease in arterial pressure can now set off a vicious circle of cardiac deterioration. For this reason, in treating myocardial infarction, it is extremely important to prevent even short periods of hypotension.

Physiology of Treatment. Often a patient dies of cardiogenic shock before the various compensatory processes can return the cardiac output (and arterial pressure) to a life-sustaining level. Therefore, treatment of this condition is one of the most important problems in the management of acute heart attacks.

Immediate administration of digitalis is often used for strengthening the heart if the ventricular muscle shows signs of deterioration. Also, infusion of whole blood, plasma, or a blood pressure–raising drug is used to sustain the arterial pressure. If the arterial pressure can be elevated high enough, the coronary blood flow often will increase enough to prevent the vicious circle of deterioration. And this allows enough time for appropriate compensatory mechanisms in circulatory system to correct the shock.

Some success has also been achieved in saving the lives of patients in cardiogenic shock by using one of the following procedures: (1) surgically removing the clot in the coronary artery, often in combination with coronary bypass graft, or (2) catheterizing the blocked coronary artery and infusing either *streptokinase* or *tissue-type plasminogen activator* enzymes that cause dissolution of the clot. The results are occasionally astounding when one of these procedures is instituted within the first hour of cardiogenic shock but of little, if any, benefit after 3 hours.

Edema in Patients with Cardiac Failure

Inability of Acute Cardiac Failure to Cause *Peripheral* Edema. Acute *left* heart failure can cause rapid congestion of the lungs, with development of *pulmonary edema* and even death within minutes to hours.

However, either left or right heart failure is very slow to cause *peripheral edema.* This can best be explained by referring to Figure 22-3. When a previously healthy heart acutely fails as a pump, the aortic pressure falls and the right atrial pressure rises. As the cardiac output approaches zero, these two pressures approach each other at an equilibrium value of about 13 mm Hg.

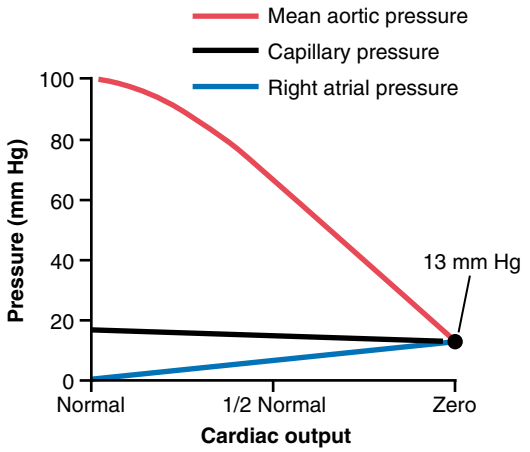


Figure 22-3 Progressive changes in mean aortic pressure, peripheral tissue capillary pressure, and right atrial pressure as the cardiac output falls from normal to zero.

Capillary pressure also falls from its normal value of 17 mm Hg to the new equilibrium pressure of 13 mm Hg. Thus, *severe acute cardiac failure often causes a fall in peripheral capillary pressure rather than a rise.* Therefore, animal experiments, as well as experience in humans, show that acute cardiac failure almost never causes immediate development of peripheral edema.

Long-Term Fluid Retention by the Kidneys—the Cause of Peripheral Edema in Persisting Heart Failure

After the first day or so of overall heart failure or of right-ventricular heart failure, peripheral edema does begin to occur principally *because of fluid retention by the kidneys*. The retention of fluid increases the mean systemic filling pressure, resulting in increased tendency for blood to return to the heart. This elevates the right atrial pressure to a still higher value and returns the arterial pressure back toward normal. Therefore, *the capillary pressure now also rises markedly*, thus causing loss of fluid into the tissues and development of severe edema.

There are several known causes of the reduced renal output of urine during cardiac failure.

1. **Decreased glomerular filtration rate.** A decrease in cardiac output has a tendency to reduce the glomerular pressure in the kidneys because of (1) *reduced arterial pressure* and (2) *intense sympathetic constriction of the afferent arterioles of the kidney.* As a consequence, except in the mildest degrees of heart failure, the glomerular filtration rate becomes less than normal. It is clear from the discussion of kidney function in Chapters 26 through 29 that *even a slight decrease in glomerular filtration often markedly decreases urine output.* When the cardiac output falls to about one-half normal, this can result in almost complete anuria.
2. **Activation of the renin-angiotensin system and increased reabsorption of water and salt by the renal tubules.** The reduced blood flow to the kidneys causes marked increase in *renin secretion* by the kidneys, and this in turn increases the *formation of angiotensin II,* as described in Chapter 19. The angiotensin in turn has a direct effect on the arterioles of the kidneys to decrease further the blood flow through the kidneys, which reduces the pressure in the peritubular capillaries surrounding the renal tubules, promoting greatly increased reabsorption of both water and salt from the tubules. Angiotensin also acts directly on the renal tubular epithelial cells to stimulate reabsorption of salt and water. Therefore, loss of water and salt into the urine decreases greatly, and large quantities of salt and water accumulate in the blood and interstitial fluids everywhere in the body.
3. **Increased aldosterone secretion.** In the chronic stage of heart failure, large quantities of aldosterone are secreted by the adrenal cortex. This results mainly from the effect of angiotensin to stimulate aldosterone secretion by the adrenal cortex. But some of the increase in aldosterone secretion often results from increased plasma potassium. Excess potassium is one of the most powerful stimuli known for aldosterone secretion, and the potassium concentration rises in response to reduced renal function in cardiac failure.

   The elevated aldosterone level further increases the reabsorption of sodium from the renal tubules. This in turn leads to a secondary increase in water reabsorption for two reasons: First, as the sodium is reabsorbed, it reduces the osmotic pressure in the tubules but increases the osmotic pressure in the renal interstitial fluids; these changes promote osmosis of water into the blood. Second, the absorbed sodium and anions that go with the sodium, mainly chloride ions, increase the osmotic concentration of the extracellular fluid everywhere in the body. This elicits *antidiuretic hormone* secretion by the hypothalamic-posterior pituitary gland system (discussed in Chapter 29). The antidiuretic hormone in turn promotes still greater increase in tubular reabsorption of water.
4. **Activation of the sympathetic nervous system.** As discussed previously, heart failure causes marked activation of the sympathetic nervous system, which in turn has several effects that lead to salt and water retention by the kidneys: (1) constriction of renal afferent arterioles, which reduces glomerular filtration rate; (2) stimulation of renal tubular reabsorption of salt and water by activation of alpha-adrenergic receptors on tubular epithelial cells; (3) stimulation of renin release and angiotensin II formation, which increases renal tubular reabsorption; and (4) stimulation of antidiuretic hormone release from the posterior pituitary, which then increases water reabsorption by the renal tubules. These effects of sympathetic stimulation are discussed in more detail in Chapters 26 and 27.

Role of Atrial Natriuretic Peptide to Delay Onset of Cardiac Decompensation. *Atrial natriuretic peptide*

(ANP) is a hormone released by the atrial walls of the heart when they become stretched. Because heart failure almost always increases both the right and left atrial pressures that stretch the atrial walls, the circulating levels of ANP in the blood may increase 5- to 10-fold in severe heart failure. The ANP in turn has a direct effect on the kidneys to increase greatly their excretion of salt and water. Therefore, ANP plays a natural role to help prevent extreme congestive symptoms during cardiac failure. The renal effects of ANP are discussed in Chapter 29.

Acute Pulmonary Edema in Late-Stage Heart Failure—Another Lethal Vicious Circle

A frequent cause of death in heart failure is *acute pulmonary edema* occurring in patients who have already had chronic heart failure for a long time. When this occurs in a person without new cardiac damage, it usually is set off by some temporary overload of the heart, such as might result from a bout of heavy exercise, some emotional experience, or even a severe cold. The acute pulmonary edema is believed to result from the following vicious circle:

1. A temporarily increased load on the already weak left ventricle initiates the vicious circle. Because of limited pumping capacity of the left heart, blood begins to dam up in the lungs.
2. The increased blood in the lungs elevates the pulmonary capillary pressure, and a small amount of fluid begins to transude into the lung tissues and alveoli.
3. The increased fluid in the lungs diminishes the degree of oxygenation of the blood.
4. The decreased oxygen in the blood further weakens the heart and also weakens the arterioles everywhere in the body, thus causing peripheral vasodilation.
5. The peripheral vasodilation increases venous return of blood from the peripheral circulation still more.
6. The increased venous return further increases the damming of the blood in the lungs, leading to still more transudation of fluid, more arterial oxygen desaturation, more venous return, and so forth. Thus, a vicious circle has been established.

Once this vicious circle has proceeded beyond a certain critical point, it will continue until death of the patient unless heroic therapeutic measures are used within minutes. The types of heroic therapeutic measures that can reverse the process and save the patient's life include the following:

1. Putting tourniquets on both arms and legs to sequester much of the blood in the veins and, therefore, decrease the workload on the left side of the heart
2. Giving a rapidly acting diuretic, such as furosemide, to cause rapid loss of fluid from the body
3. Giving the patient pure oxygen to breathe to reverse the blood oxygen desaturation, the heart deterioration, and the peripheral vasodilation
4. Giving the patient a rapidly acting cardiotonic drug, such as digitalis, to strengthen the heart

This vicious circle of acute pulmonary edema can proceed so rapidly that death can occur in 20 minutes to 1 hour. Therefore, any procedure that is to be successful must be instituted immediately.

Cardiac Reserve

The maximum percentage that the cardiac output can increase above normal is called the *cardiac reserve*. Thus, in the healthy young adult, the cardiac reserve is 300 to 400 percent. In athletically trained persons, it is 500 to 600 percent or more. But in heart failure, there is no cardiac reserve. As an example of normal reserve, during severe exercise the cardiac output of a healthy young adult can rise to about five times normal; this is an increase above normal of 400 percent—that is, *a cardiac reserve of 400 percent*.

Any factor that prevents the heart from pumping blood satisfactorily will decrease the cardiac reserve. This can result from ischemic heart disease, primary myocardial disease, vitamin deficiency that affects cardiac muscle, physical damage to the myocardium, valvular heart disease, and many other factors, some of which are shown in Figure 22-4.

Diagnosis of Low Cardiac Reserve—Exercise Test. As long as persons with low cardiac reserve remain in a state of rest, they usually will not experience major symptoms of heart disease. However, a diagnosis of low cardiac reserve usually can be easily made by requiring the person to exercise either on a treadmill or by walking up and down steps, either of which requires greatly increased cardiac output. The increased load on the heart rapidly uses up the small amount of reserve that is available, and the cardiac output soon fails to rise high enough to sustain the body's new level of activity. The acute effects are as follows:

1. Immediate and sometimes extreme shortness of breath (dyspnea) resulting from failure of the heart to pump

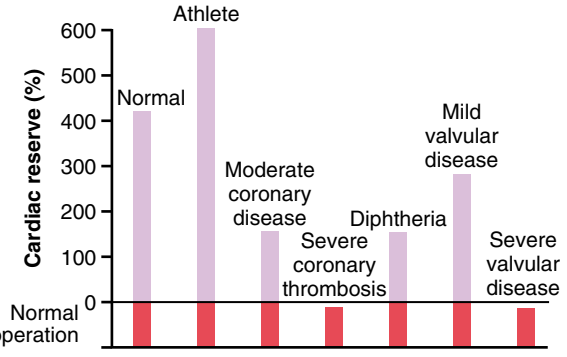


Figure 22-4 Cardiac reserve in different conditions, showing less than zero reserve for two of the conditions.

sufficient blood to the tissues, thereby causing tissue ischemia and creating a sensation of air hunger

2. Extreme muscle fatigue resulting from muscle ischemia, thus limiting the person's ability to continue with the exercise
3. Excessive increase in heart rate because the nervous reflexes to the heart overreact in an attempt to overcome the inadequate cardiac output

Exercise tests are part of the armamentarium of the cardiologist. These tests take the place of cardiac output measurements that cannot be made with ease in most clinical settings.

Quantitative Graphical Method for Analysis of Cardiac Failure

Although it is possible to understand most general principles of cardiac failure using mainly qualitative logic, as we have done thus far in this chapter, one can grasp the importance of the different factors in cardiac failure with far greater depth by using more quantitative approaches. One such approach is the graphical method for analysis of cardiac output regulation introduced in Chapter 20. In the remaining sections of this chapter, we analyze several aspects of cardiac failure, using this graphical technique.

Graphical Analysis of Acute Heart Failure and Chronic Compensation

Figure 22-5 shows *cardiac output* and *venous return curves* for different states of the heart and peripheral circulation. The two curves passing through Point A are (1) the *normal cardiac output curve* and (2) the *normal venous return curve.* As pointed out in Chapter 20, there is only one point on each of these two curves at which the circulatory system can operate—point A where the two curves cross. Therefore, the normal state of the circulation is a cardiac output and venous return of 5 L/min and a right atrial pressure of 0 mm Hg.

Effect of Acute Heart Attack. During the first few seconds after a moderately severe heart attack, the cardiac output curve falls to the *lowermost curve.* During these few seconds, the venous return curve still has not changed because the peripheral circulatory system is still operating normally. Therefore, the new state of the circulation is depicted by point B, where the new cardiac output curve crosses the normal venous return curve. Thus, the right atrial pressure rises immediately to 4 mm Hg, whereas the cardiac output falls to 2 L/min.

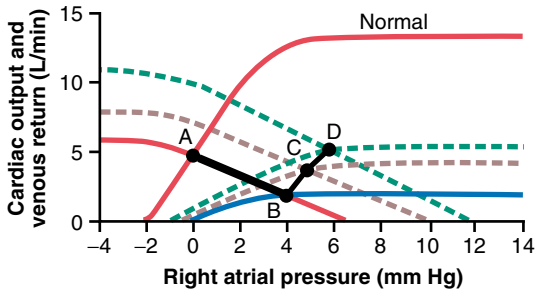


Figure 22-5 Progressive changes in cardiac output and right atrial pressure during different stages of cardiac failure.

Effect of Sympathetic Reflexes. Within the next 30 seconds, the sympathetic reflexes become very active. They raise both the cardiac output and the venous return curves. Sympathetic stimulation can increase the plateau level of the cardiac output curve as much as 30 to 100 percent. It can also increase the mean systemic filling pressure (depicted by the point where the venous return curve crosses the zero venous return axis) by several millimeters of mercury—in this figure, from a normal value of 7 mm Hg up to 10 mm Hg. This increase in mean systemic filling pressure shifts the entire venous return curve to the right and upward. The new cardiac output and venous return curves now equilibrate at point C, that is, at a right atrial pressure of +5 mm Hg and a cardiac output of 4 L/min.

Compensation During the Next Few Days. During the ensuing week, the cardiac output and venous return curves rise further because of (1) some recovery of the heart and (2) renal retention of salt and water, which raises the mean systemic filling pressure still further—this time up to +12 mm Hg. The two new curves now equilibrate at point D. Thus, the cardiac output has now returned to normal. The right atrial pressure, however, has risen still further to +6 mm Hg. Because the cardiac output is now normal, renal output is also normal, so a new state of equilibrated fluid balance has been achieved. The circulatory system will continue to function at point D and remain stable, with a normal cardiac output and an elevated right atrial pressure, until some additional extrinsic factor changes either the cardiac output curve or the venous return curve.

Using this technique for analysis, one can see especially the importance of moderate fluid retention and how it eventually leads to a new stable state of the circulation in mild to moderate heart failure. And one can also see the interrelation between mean systemic filling pressure and cardiac pumping at various degrees of heart failure.

Note that the events described in Figure 22-5 are the same as those presented in Figure 22-1, but in Figure 22-5, they are presented in a more quantitative manner.

Graphical Analysis of "Decompensated" Cardiac Failure

The black cardiac output curve in Figure 22-6 is the same as the curve shown in Figure 22-2, a greatly depressed curve that has already reached a degree of recovery as great as this heart can achieve. In this figure, we have added venous return curves that occur during successive days after the acute fall of the cardiac output curve to this low level. At point A, the curve at time zero equates with the normal venous return curve to give a cardiac output of about 3 L/min. However, stimulation of the sympathetic nervous system, caused by this low cardiac output, increases the mean systemic filling pressure within 30 seconds from 7 to 10.5 mm Hg. This shifts the venous

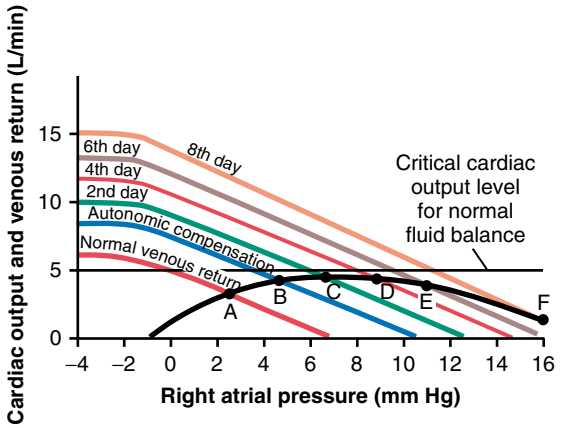


Figure 22-6 Graphical analysis of decompensated heart disease showing progressive shift of the venous return curve to the right as a result of continued fluid retention.

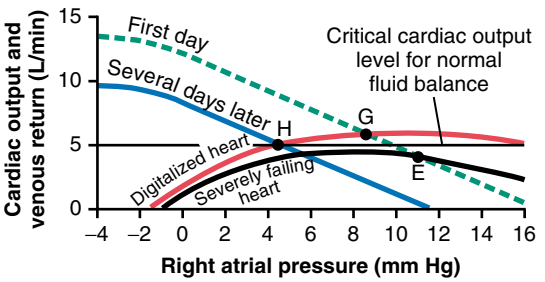


Figure 22-7 Treatment of decompensated heart disease showing the effect of digitalis in elevating the cardiac output curve, this in turn causing increased urine output and progressive shift of the venous return curve to the left.

return curve upward and to the right to produce the curve labeled "autonomic compensation." Thus, the new venous return curve equates with the cardiac output curve at point B. The cardiac output has been improved to a level of 4 L/min but at the expense of an additional rise in right atrial pressure to 5 mm Hg.

The cardiac output of 4 L/min is still too low to cause the kidneys to function normally. Therefore, fluid continues to be retained, and the mean systemic filling pressure rises from 10.5 to almost 13 mm Hg. Now the venous return curve becomes that labeled "2nd day" and equilibrates with the cardiac output curve at point C. The cardiac output rises to 4.2 L/min and the right atrial pressure to 7 mm Hg.

During the succeeding days, the cardiac output never rises quite high enough to re-establish normal renal function. Fluid continues to be retained, the mean systemic filling pressure continues to rise, the venous return curve continues to shift to the right, and the equilibrium point between the venous return curve and the cardiac output curve also shifts progressively to point D, to point E, and, finally, to point F. The equilibration process is now on the down slope of the cardiac output curve, so further retention of fluid causes even more severe cardiac edema and a detrimental effect on cardiac output. The condition accelerates downhill until death occurs.

Thus, "decompensation" results from the fact that the cardiac output curve never rises to the critical level of 5 L/min needed to re-establish normal kidney excretion of fluid that would be required to cause balance between fluid input and output.

Treatment of Decompensated Heart Disease with Digitalis. Let us assume that the stage of decompensation has already reached point E in Figure 22-6, and let us proceed to the same point E in Figure 22-7. At this time, digitalis is given to strengthen the heart. This raises the cardiac output curve to the level shown in Figure 22-7, but there is not an immediate change in the venous return curve. Therefore, the new cardiac output curve equates with the venous return curve at point G. The cardiac output is now 5.7 L/min, a value greater than the critical level of 5 liters required to make the kidneys excrete normal amounts of urine. Therefore, the kidneys eliminate much more fluid than normally, causing *diuresis,* a well-known therapeutic effect of digitalis.

The progressive loss of fluid over a period of several days reduces the mean systemic filling pressure back down to 11.5 mm Hg, and the new venous return curve becomes the curve labeled "Several days later." This curve equates with the cardiac output curve of the digitalized heart at point H, at an output of 5 L/min and a right atrial pressure of 4.6 mm Hg. This cardiac output is precisely that required for normal fluid balance. Therefore, no additional fluid will be lost and none will be gained. Consequently, the circulatory system has now stabilized, or in other words, the decompensation of the heart failure has been "compensated." And to state this another way, the final steady-state condition of the circulation is defined by the crossing point of three curves: the cardiac output curve, the venous return curve, and the critical level for normal fluid balance. The compensatory mechanisms automatically stabilize the circulation when all three curves cross at the same point.

Graphical Analysis of High-Output Cardiac Failure

Figure 22-8 gives an analysis of two types of high-output cardiac failure. One of these is caused by an *arteriovenous fistula* that overloads the heart because of excessive venous return, even though the pumping capability of the heart is not depressed. The other is caused by *beriberi,* in which the venous return is greatly increased because of diminished systemic vascular resistance, but at the same time, the pumping capability of the heart is depressed.

Arteriovenous Fistula. The "normal" curves of Figure 22-8 depict the normal cardiac output and normal venous return curves. These equate with each other at point A, which depicts a normal cardiac output of 5 L/min and a normal right atrial pressure of 0 mm Hg.

Now let us assume that the systemic vascular resistance (the *total peripheral vascular resistance*) becomes greatly decreased because of opening a large arteriovenous fistula (a direct opening between a large artery and a large vein). The venous return curve rotates upward to give the curve

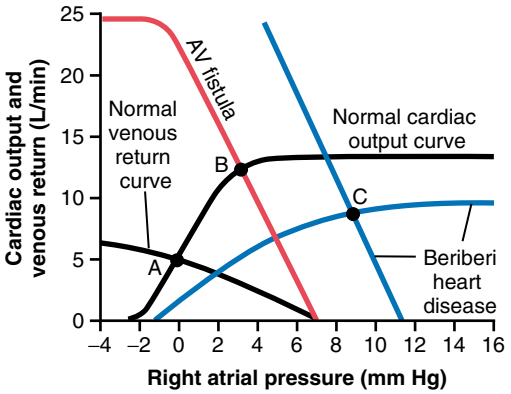


Figure 22-8 Graphical analysis of two types of conditions that can cause high-output cardiac failure: (1) arteriovenous (AV) fistula and (2) beriberi heart disease.

labeled "AV fistula." This venous return curve equates with the normal cardiac output curve at point B, with a cardiac output of 12.5 L/min and a right atrial pressure of 3 mm Hg. Thus, the cardiac output has become greatly elevated, the right atrial pressure is slightly elevated, and there are mild signs of peripheral congestion. If the person attempts to exercise, he or she will have little cardiac reserve because the heart is already at near-maximum capacity to pump the extra blood through the arteriovenous fistula. This condition resembles a failure condition and is called "high-output failure," but in reality, the heart is overloaded by excess venous return.

Beriberi. Figure 22-8 shows the approximate changes in the cardiac output and venous return curves caused by *beriberi.* The decreased level of the cardiac output curve is caused by weakening of the heart because of the avitaminosis (mainly lack of thiamine) that causes the beriberi syndrome. The weakening of the heart has decreased the blood flow to the kidneys. Therefore, the kidneys have retained a large amount of extra body fluid, which in turn has increased the mean systemic filling pressure (represented by the point where the venous return curve now intersects the zero cardiac output level) from the normal value of 7 mm Hg up to 11 mm Hg. This has shifted the venous return curve to the right. Finally, the venous return curve has rotated upward from the normal curve because the avitaminosis has dilated the peripheral blood vessels, as explained in Chapter 17.

The two blue curves (cardiac output curve and venous return curve) intersect with each other at point C, which describes the circulatory condition in beriberi, with a right atrial pressure in this instance of 9 mm Hg and a cardiac output about 65 percent above normal; this high cardiac output occurs despite the weak heart, as demonstrated by the depressed plateau level of the cardiac output curve.

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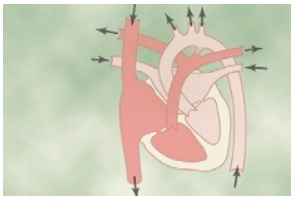
Heart Valves and Heart Sounds; Valvular and Congenital Heart Defects



Function of the heart valves was discussed in Chapter 9, where it was pointed out that *closing* of the valves causes audible sounds. Ordinarily, no audible sounds occur when the valves open. In this chapter, we first discuss the factors that cause the sounds in the heart under normal and abnormal conditions. Then we discuss the overall circulatory changes that occur when valvular or congenital heart defects are present.

Heart Sounds

Normal Heart Sounds

Listening with a stethoscope to a normal heart, one hears a sound usually described as "lub, dub, lub, dub." The "lub" is associated with closure of the atrioventricular (A-V) valves at the beginning of systole, and the "dub" is associated with closure of the semilunar (aortic and pulmonary) valves at the end of systole. The "lub" sound is called the *first heart sound,* and the "dub" is called the *second heart sound,* because the normal pumping cycle of the heart is considered to start when the A-V valves close at the onset of ventricular systole.

Causes of the First and Second Heart Sounds. The earliest explanation for the cause of the heart sounds was that the "slapping" together of the valve leaflets sets up vibrations. However, this has been shown to cause little, if any, of the sound, because the blood between the leaflets cushions the slapping effect and prevents significant sound. Instead, the cause is *vibration of the taut valves immediately after closure,* along with *vibration of the adjacent walls of the heart and major vessels around the heart.* That is, in generating the first heart sound, contraction of the ventricles first causes sudden backflow of blood against the A-V valves (the tricuspid and mitral valves), causing them to close and bulge toward the atria until the chordae tendineae abruptly stop the back bulging. The elastic tautness of the chordae tendineae and of the valves then causes the back-surging blood to bounce forward again into each respective ventricle. This causes the blood and the ventricular walls, as well as the taut valves, to vibrate and causes vibrating turbulence in the blood. The vibrations travel through the adjacent tissues to the chest wall, where they can be heard as sound by using the stethoscope.

The second heart sound results from sudden closure of the semilunar valves at the end of systole. When the semilunar valves close, they bulge backward toward the ventricles and their elastic stretch recoils the blood back into the arteries, which causes a short period of reverberation of blood back and forth between the walls of the arteries and the semilunar valves, as well as between these valves and the ventricular walls. The vibrations occurring in the arterial walls are then transmitted mainly along the arteries. When the vibrations of the vessels or ventricles come into contact with a "sounding board," such as the chest wall, they create sound that can be heard.

Duration and Pitch of the First and Second Heart Sounds. The duration of each of the heart sounds is slightly more than 0.10 second—the first sound about 0.14 second, and the second about 0.11 second. The reason for the shorter second sound is that the semilunar valves are more taut than the A-V valves, so they vibrate for a shorter time than do the A-V valves.

The audible range of frequency (pitch) in the first and second heart sounds, as shown in Figure 23-1, begins at the lowest frequency the ear can detect, about 40 cycles/sec, and goes up above 500 cycles/sec. When special electronic apparatus is used to record these sounds, by far a larger proportion of the recorded sound is at frequencies and sound levels below the audible range, going down to 3 to 4 cycles/sec and peaking at about 20 cycles/sec, as illustrated by the lower shaded area in Figure 23-1. For this reason, major portions of the heart sounds can be recorded electronically in phonocardiograms even though they cannot be heard with a stethoscope.

The second heart sound normally has a higher frequency than the first heart sound for two reasons: (1) the tautness of the semilunar valves in comparison with the much less taut A-V valves, and (2) the greater elas-

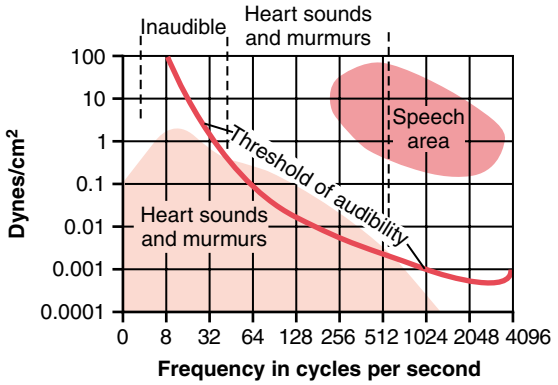


Figure 23-1 Amplitude of different-frequency vibrations in the heart sounds and heart murmurs in relation to the threshold of audibility, showing that the range of sounds that can be heard is between 40 and 520 cycles/sec. (Modified from Butterworth JS, Chassin JL, McGrath JJ: Cardiac Auscultation, 2nd ed, New York: Grune & Stratton, 1960.)

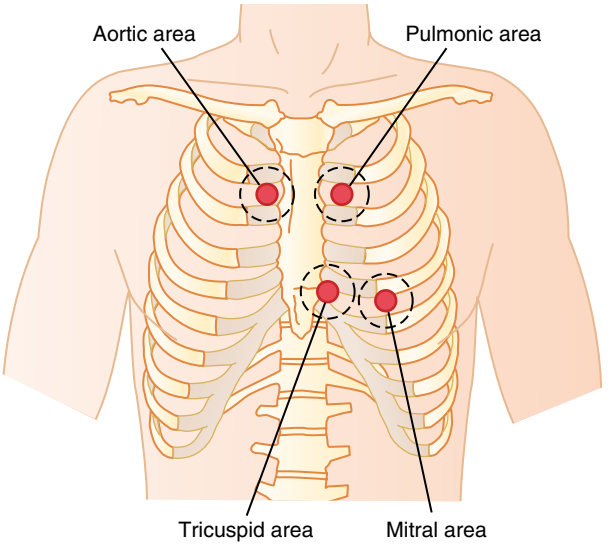


Figure 23-2 Chest areas from which sound from each valve is best heard.

tic coefficient of the taut arterial walls that provide the principal vibrating chambers for the second sound, in comparison with the much looser, less elastic ventricular chambers that provide the vibrating system for the first heart sound. The clinician uses these differences to distinguish special characteristics of the two respective sounds.

Third Heart Sound. Occasionally a weak, rumbling third heart sound is heard at the beginning of the *middle third of diastole.* A logical but unproved explanation of this sound is oscillation of blood back and forth between the walls of the ventricles initiated by inrushing blood from the atria. This is analogous to running water from a faucet into a paper sack, the inrushing water reverberating back and forth between the walls of the sack to cause vibrations in its walls. The reason the third heart sound does not occur until the middle third of diastole is believed to be that in the early part of diastole, the ventricles are not filled sufficiently to create even the small amount of elastic tension necessary for reverberation. The frequency of this sound is usually so low that the ear cannot hear it, yet it can often be recorded in the phonocardiogram.

Atrial Heart Sound (Fourth Heart Sound). An atrial heart sound can sometimes be recorded in the phonocardiogram, but it can almost never be heard with a stethoscope because of its weakness and very low frequency—usually 20 cycles/sec or less. This sound occurs when the atria contract, and presumably, it is caused by the inrush of blood into the ventricles, which initiates vibrations similar to those of the third heart sound.

Chest Surface Areas for Auscultation of Normal Heart Sounds

Listening to the sounds of the body, usually with the aid of a stethoscope, is called *auscultation.* Figure 23-2 shows the areas of the chest wall from which the different heart valvular sounds can best be distinguished. Although the sounds from all the valves can be heard from all these areas, the cardiologist distinguishes the sounds from the different valves by a process of elimination. That is, he or she moves the stethoscope from one area to another, noting the loudness of the sounds in different areas and gradually picking out the sound components from each valve.

The areas for listening to the different heart sounds are not directly over the valves themselves. The aortic area is upward along the aorta because of sound transmission up the aorta, and the pulmonic area is upward along the pulmonary artery. The tricuspid area is over the right ventricle, and the mitral area is over the apex of the left ventricle, which is the portion of the heart nearest the surface of the chest; the heart is rotated so that the remainder of the left ventricle lies more posteriorly.

Phonocardiogram

If a microphone specially designed to detect low-frequency sound is placed on the chest, the heart sounds can be amplified and recorded by a high-speed recording apparatus. The recording is called a *phonocardiogram,* and the heart sounds appear as waves, as shown schematically in Figure 23-3. Recording A is an example of normal heart sounds, showing the vibrations of the first, second, and third heart sounds and even the very weak atrial sound. Note specifically that the third and atrial heart sounds are each a very low rumble. The third heart sound can be recorded in only one third to one half of all people, and the atrial heart sound can be recorded in perhaps one fourth of all people.

Valvular Lesions

Rheumatic Valvular Lesions

By far the greatest number of valvular lesions results from *rheumatic fever.* Rheumatic fever is an autoimmune disease in which the heart valves are likely to be damaged or

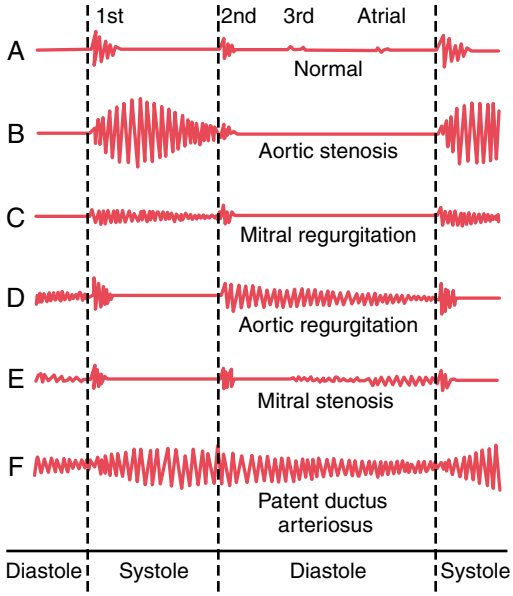


Figure 23-3 Phonocardiograms from normal and abnormal hearts.

destroyed. It is usually initiated by streptococcal toxin in the following manner.

The sequence of events almost always begins with a preliminary streptococcal infection caused specifically by group A hemolytic streptococci. These bacteria initially cause a sore throat, scarlet fever, or middle ear infection. But the streptococci also release several different proteins against which the person's reticuloendothelial system produces *antibodies.* The antibodies react not only with the streptococcal protein but also with other protein tissues of the body, often causing severe immunologic damage. These reactions continue to take place as long as the antibodies persist in the blood—1 year or more.

Rheumatic fever causes damage especially in certain susceptible areas, such as the heart valves. The degree of heart valve damage is directly correlated with the concentration and persistence of the antibodies. The principles of immunity that relate to this type of reaction are discussed in Chapter 34, and it is noted in Chapter 31 that acute glomerular nephritis of the kidneys has a similar immunologic basis.

In rheumatic fever, large hemorrhagic, fibrinous, bulbous lesions grow along the inflamed edges of the heart valves. Because the mitral valve receives more trauma during valvular action than any of the other valves, it is the one most often seriously damaged, and the aortic valve is the second most frequently damaged. The right heart valves, the tricuspid and pulmonary valves, are usually affected much less severely, probably because the low-pressure stresses that act on these valves are slight compared with the high-pressure stresses that act on the left heart valves.

Scarring of the Valves. The lesions of acute rheumatic fever frequently occur on adjacent valve leaflets simultaneously, so the edges of the leaflets become stuck together. Then, weeks, months, or years later, the lesions become scar tissue, permanently fusing portions of adjacent valve leaflets. Also, the free edges of the leaflets, which are normally filmy and free-flapping, often become solid, scarred masses.

A valve in which the leaflets adhere to one another so extensively that blood cannot flow through it normally is said to be *stenosed.* Conversely, when the valve edges are so destroyed by scar tissue that they cannot close as the ventricles contract, *regurgitation* (backflow) of blood occurs when the valve should be closed. Stenosis usually does not occur without the coexistence of at least some degree of regurgitation, and vice versa.

Other Causes of Valvular Lesions. Stenosis or lack of one or more leaflets of a valve also occurs occasionally as a *congenital defect.* Complete lack of leaflets is rare; *congenital stenosis* is more common, as is discussed later in this chapter.

Heart Murmurs Caused by Valvular Lesions

As shown by the phonocardiograms in Figure 23-3, many abnormal heart sounds, known as "heart murmurs," occur when there are abnormalities of the valves, as follows.

Systolic Murmur of Aortic Stenosis. In aortic stenosis, blood is ejected from the left ventricle through only a small fibrous opening of the aortic valve. Because of the resistance to ejection, sometimes the blood pressure in the left ventricle rises as high as 300 mm Hg, while the pressure in the aorta is still normal. Thus, a nozzle effect is created *during systole,* with blood jetting at tremendous velocity through the small opening of the valve. This causes *severe turbulence* of the blood in the root of the aorta. The turbulent blood impinging against the aortic walls causes intense vibration, and a loud murmur (see recording B, Figure 23-3) occurs during systole and is transmitted throughout the superior thoracic aorta and even into the large arteries of the neck. This sound is harsh and in severe stenosis may be so loud that it can be heard several feet away from the patient. Also, the sound vibrations can often be felt with the hand on the upper chest and lower neck, a phenomenon known as a "*thrill.*"

Diastolic Murmur of Aortic Regurgitation. In aortic regurgitation, no abnormal sound is heard during systole, but *during diastole,* blood flows backward from the high-pressure aorta into the left ventricle, causing a "blowing" murmur of relatively high pitch with a swishing quality heard maximally over the left ventricle (see recording D, Figure 23-3). This murmur results from *turbulence* of blood jetting backward into the blood already in the low-pressure diastolic left ventricle.

Systolic Murmur of Mitral Regurgitation. In mitral regurgitation, blood flows backward through the mitral valve into the left atrium *during systole.* This also causes a high-frequency "blowing," swishing sound (see recording C, Figure 23-3) similar to that of aortic regurgitation but occurring during systole rather than diastole. It is transmitted most strongly into the left atrium. However, the left atrium is so deep within the chest that it is difficult to hear this sound directly over the atrium. As a result, the sound

of mitral regurgitation is transmitted to the chest wall mainly through the left ventricle to the apex of the heart.

Diastolic Murmur of Mitral Stenosis. In mitral stenosis, blood passes with difficulty through the stenosed mitral valve from the left atrium into the left ventricle, and because the pressure in the left atrium seldom rises above 30 mm Hg, a large pressure differential forcing blood from the left atrium into the left ventricle does not develop. Consequently, the abnormal sounds heard in mitral stenosis (see recording E, Figure 23-3) are usually weak and of very low frequency, so most of the sound spectrum is below the low-frequency end of human hearing.

During the early part of diastole, a left ventricle with a stenotic mitral valve has so little blood in it and its walls are so flabby that blood does not reverberate back and forth between the walls of the ventricle. For this reason, even in severe mitral stenosis, no murmur may be heard during the first third of diastole. Then, after partial filling, the ventricle has stretched enough for blood to reverberate and a low rumbling murmur begins.

Phonocardiograms of Valvular Murmurs. Phonocardiograms B, C, D, and E of Figure 23-3 show, respectively, idealized records obtained from patients with aortic stenosis, mitral regurgitation, aortic regurgitation, and mitral stenosis. It is obvious from these phonocardiograms that the aortic stenotic lesion causes the loudest murmur, and the mitral stenotic lesion causes the weakest. The phonocardiograms show how the intensity of the murmurs varies during different portions of systole and diastole, and the relative timing of each murmur is also evident. Note especially that the murmurs of aortic stenosis and mitral regurgitation occur only during systole, whereas the murmurs of aortic regurgitation and mitral stenosis occur only during diastole. If the reader does not understand this timing, extra review should be undertaken until it is understood.

Abnormal Circulatory Dynamics in Valvular Heart Disease

Dynamics of the Circulation in Aortic Stenosis and Aortic Regurgitation

In *aortic stenosis,* the contracting left ventricle fails to empty adequately, whereas in *aortic regurgitation,* blood flows backward into the ventricle from the aorta after the ventricle has just pumped the blood into the aorta. Therefore, in either case, the *net stroke volume output* of the heart is reduced.

Several important compensations take place that can ameliorate the severity of the circulatory defects. Some of these compensations are the following.

Hypertrophy of the Left Ventricle. In both aortic stenosis and aortic regurgitation, the left ventricular musculature hypertrophies because of the increased ventricular workload.

In *regurgitation,* the left ventricular chamber also enlarges to hold all the regurgitant blood from the aorta. Sometimes the left ventricular muscle mass increases fourfold to fivefold, creating a tremendously large left side of the heart.

When the aortic valve is seriously *stenosed,* the hypertrophied muscle allows the left ventricle to develop as much as 400 mm Hg intraventricular pressure at systolic peak.

In severe aortic regurgitation, sometimes the hypertrophied muscle allows the left ventricle to pump a stroke volume output as great as 250 ml, although as much as three fourths of this blood returns to the ventricle during diastole, and only one fourth flows through the aorta to the body.

Increase in Blood Volume. Another effect that helps compensate for the diminished net pumping by the left ventricle is increased blood volume. This results from (1) an initial slight decrease in arterial pressure, plus (2) peripheral circulatory reflexes that the decrease in pressure induces. These together diminish renal output of urine, causing the blood volume to increase and the mean arterial pressure to return to normal. Also, red cell mass eventually increases because of a slight degree of tissue hypoxia.

The increase in blood volume tends to increase venous return to the heart. This, in turn, causes the left ventricle to pump with the extra power required to overcome the abnormal pumping dynamics.

Eventual Failure of the Left Ventricle and Development of Pulmonary Edema

In the early stages of aortic stenosis or aortic regurgitation, the intrinsic ability of the left ventricle to adapt to increasing loads prevents significant abnormalities in circulatory function in the person during rest, other than increased work output required of the left ventricle. Therefore, considerable degrees of aortic stenosis or aortic regurgitation often occur before the person knows that he or she has serious heart disease (such as a resting left ventricular systolic pressure as high as 200 mm Hg in aortic stenosis or a left ventricular stroke volume output as high as double normal in aortic regurgitation).

Beyond a critical stage in these aortic valve lesions, the left ventricle finally cannot keep up with the work demand. As a consequence, the left ventricle dilates and cardiac output begins to fall; blood simultaneously dams up in the left atrium and in the lungs behind the failing left ventricle. The left atrial pressure rises progressively, and at mean left atrial pressures above 25 to 40 mm Hg, serious edema appears in the lungs, as discussed in detail in Chapter 38.

Dynamics of Mitral Stenosis and Mitral Regurgitation

In mitral stenosis, blood flow from the left atrium into the left ventricle is impeded, and in mitral regurgitation, much of the blood that has flowed into the left ventricle

during diastole leaks back into the left atrium during systole rather than being pumped into the aorta. Therefore, either of these conditions reduces net movement of blood from the left atrium into the left ventricle.

Pulmonary Edema in Mitral Valvular Disease. The buildup of blood in the left atrium causes progressive increase in left atrial pressure, and this eventually results in development of serious pulmonary edema. Ordinarily, lethal edema does not occur until the mean left atrial pressure rises above 25 mm Hg and sometimes as high as 40 mm Hg, because the lung lymphatic vessels enlarge manyfold and can rapidly carry fluid away from the lung tissues.

Enlarged Left Atrium and Atrial Fibrillation. The high left atrial pressure in mitral valvular disease also causes progressive enlargement of the left atrium, which increases the distance that the cardiac electrical excitatory impulse must travel in the atrial wall. This pathway may eventually become so long that it predisposes to development of excitatory signal *circus movements,* as discussed in Chapter 13. Therefore, in late stages of mitral valvular disease, especially in mitral stenosis, atrial fibrillation usually occurs. This further reduces the pumping effectiveness of the heart and causes further cardiac debility.

Compensation in Early Mitral Valvular Disease. As also occurs in aortic valvular disease and in many types of congenital heart disease, the blood volume increases in mitral valvular disease principally because of diminished excretion of water and salt by the kidneys. This increased blood volume increases venous return to the heart, thereby helping to overcome the effect of the cardiac debility. Therefore, after compensation, cardiac output may fall only minimally until the late stages of mitral valvular disease, even though the left atrial pressure is rising.

As the left atrial pressure rises, blood begins to dam up in the lungs, eventually all the way back to the pulmonary artery. In addition, incipient edema of the lungs causes pulmonary arteriolar constriction. These two effects together increase systolic pulmonary arterial pressure and also right ventricular pressure, sometimes to as high as 60 mm Hg, which is more than double normal. This, in turn, causes hypertrophy of the right side of the heart, which partially compensates for its increased workload.

Circulatory Dynamics During Exercise in Patients with Valvular Lesions

During exercise, large quantities of venous blood are returned to the heart from the peripheral circulation. Therefore, all the dynamic abnormalities that occur in the different types of valvular heart disease become tremendously exacerbated. Even in mild valvular heart disease, in which the symptoms may be unrecognizable at rest, severe symptoms often develop during heavy exercise. For instance, in patients with aortic valvular lesions, exercise can cause acute left ventricular failure followed by *acute pulmonary edema.* Also, in patients with mitral disease, exercise can cause so much damming of blood in the lungs that serious or even lethal pulmonary edema may ensue in as little as 10 minutes.

Even in mild to moderate cases of valvular disease, the patient's *cardiac reserve* diminishes in proportion to the severity of the valvular dysfunction. That is, the cardiac output does not increase as much as it should during exercise. Therefore, the muscles of the body fatigue rapidly because of too little increase in muscle blood flow.

Abnormal Circulatory Dynamics in Congenital Heart Defects

Occasionally, the heart or its associated blood vessels are malformed during fetal life; the defect is called a *congenital anomaly.* There are three major types of congenital anomalies of the heart and its associated vessels: (1) *stenosis* of the channel of blood flow at some point in the heart or in a closely allied major blood vessel; (2) an anomaly that allows blood to flow backward from the left side of the heart or aorta to the right side of the heart or pulmonary artery, thus failing to flow through the systemic circulation-called a *left-to-right shunt;* and (3) an anomaly that allows blood to flow directly from the right side of the heart into the left side of the heart, thus failing to flow through the lungs—called a *right-to-left shunt.*

The effects of the different stenotic lesions are easily understood. For instance, *congenital aortic valve stenosis* results in the same dynamic effects as aortic valve stenosis caused by other valvular lesions, namely, a tendency to develop serious pulmonary edema and a reduced cardiac output.

Another type of congenital stenosis is *coarctation of the aorta,* often occurring near the level of the diaphragm. This causes the arterial pressure in the upper part of the body (above the level of the coarctation) to be much greater than the pressure in the lower body because of the great resistance to blood flow through the coarctation to the lower body; part of the blood must go around the coarctation through small collateral arteries, as discussed in Chapter 19.

Patent Ductus Arteriosus—a Left-to-Right Shunt

During fetal life, the lungs are collapsed, and the elastic compression of the lungs that keeps the alveoli collapsed keeps most of the lung blood vessels collapsed as well. Therefore, resistance to blood flow through the lungs is so great that the pulmonary arterial pressure is high in the fetus. Also, because of low resistance to blood flow from the aorta through the large vessels of the placenta, the pressure in the aorta of the fetus is lower than

normal—in fact, lower than in the pulmonary artery. This causes almost all the pulmonary arterial blood to flow through a special artery present in the fetus that connects the pulmonary artery with the aorta (Figure 23-4), called the *ductus arteriosus,* thus bypassing the lungs. This allows immediate recirculation of the blood through the systemic arteries of the fetus without the blood going through the lungs. This lack of blood flow through the lungs is not detrimental to the fetus because the blood is oxygenated by the placenta.

Closure of the Ductus Arteriosus After Birth. As soon as a baby is born and begins to breathe, the lungs inflate; not only do the alveoli fill with air, but also the resistance to blood flow through the pulmonary vascular tree decreases tremendously, allowing the pulmonary arterial pressure to fall. Simultaneously, the aortic pressure rises because of sudden cessation of blood flow from the aorta through the placenta. Thus, the pressure in the pulmonary artery falls, while that in the aorta rises. As a result, forward blood flow through the ductus arteriosus ceases suddenly at birth, and in fact, blood begins to flow backward through the ductus from the aorta into the pulmonary artery. This new state of backward blood flow causes the ductus arteriosus to become occluded within a few hours to a few days in most babies, so blood flow through the ductus does not persist. The ductus is believed to close because the oxygen concentration of the aortic blood now flowing through it is about twice as high as that of the blood flowing from the pulmonary artery into the ductus during fetal life. The oxygen presumably constricts the muscle in the ductus wall. This is discussed further in Chapter 83.

Unfortunately, in about 1 of every 5500 babies, the ductus does not close, causing the condition known as *patent ductus arteriosus,* which is shown in Figure 23-4.

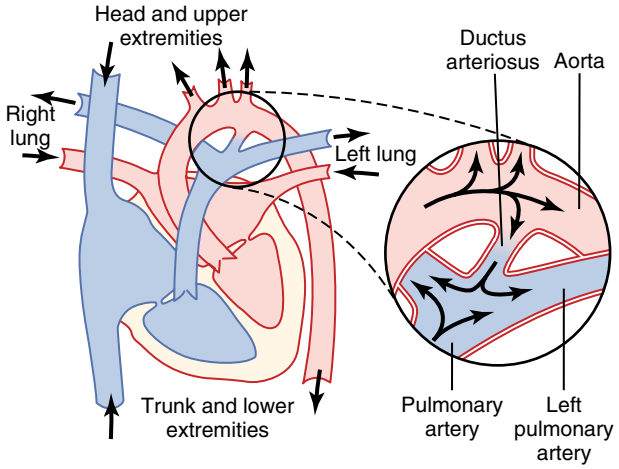


Figure 23-4 Patent ductus arteriosus, showing by the blue color that venous blood changes into oxygenated blood at different points in the circulation. The right-hand diagram shows backflow of blood from the aorta into the pulmonary artery and then through the lungs for a second time.

Dynamics of the Circulation with a Persistent Patent Ductus. During the early months of an infant's life, a patent ductus usually does not cause severely abnormal function. But as the child grows older, the differential between the high pressure in the aorta and the lower pressure in the pulmonary artery progressively increases, with corresponding increase in backward flow of blood from the aorta into the pulmonary artery. Also, the high aortic blood pressure usually causes the diameter of the partially open ductus to increase with time, making the condition even worse.

Recirculation Through the Lungs. In an older child with a patent ductus, one half to two thirds of the aortic blood flows backward through the ductus into the pulmonary artery, then through the lungs, and finally back into the left ventricle and aorta, passing through the lungs and left side of the heart two or more times for every one time that it passes through the systemic circulation. These people *do not show cyanosis until later in life, when the heart fails or the lungs become congested.* Indeed, early in life, the arterial blood is often better oxygenated than normal because of the extra times it passes through the lungs.

Diminished Cardiac and Respiratory Reserve. The major effects of patent ductus arteriosus on the patient are decreased cardiac and respiratory reserve. The left ventricle is pumping about two or more times the normal cardiac output, and the maximum that it can pump after hypertrophy of the heart has occurred is about four to seven times normal. Therefore, during exercise, the net blood flow through the remainder of the body can never increase to the levels required for strenuous activity. With even moderately strenuous exercise, the person is likely to become weak and may even faint from momentary heart failure.

The high pressures in the pulmonary vessels caused by excess flow through the lungs often lead to pulmonary congestion and pulmonary edema. As a result of the excessive load on the heart, and especially because the pulmonary congestion becomes progressively more severe with age, most patients with uncorrected patent ductus die from heart disease between ages 20 and 40 years.

Heart Sounds: Machinery Murmur. In a newborn infant with patent ductus arteriosus, occasionally no abnormal heart sounds are heard because the quantity of reverse blood flow through the ductus may be insufficient to cause a heart murmur. But as the baby grows older, reaching age 1 to 3 years, a harsh, blowing murmur begins to be heard in the pulmonary artery area of the chest, as shown in recording F, Figure 23-3. This sound is much more intense during systole when the aortic pressure is high and much less intense during diastole when the aortic pressure falls low, so that the murmur waxes and wanes with each beat of the heart, creating the so-called *machinery murmur.*

Surgical Treatment. Surgical treatment of patent ductus arteriosus is extremely simple; one need only ligate the patent ductus or divide it and then close the two ends. In fact, this was one of the first successful heart surgeries ever performed.

Tetralogy of Fallot—a Right-to-Left Shunt

Tetralogy of Fallot is shown in Figure 23-5; it is the most common cause of "blue baby." Most of the blood bypasses the lungs, so the aortic blood is mainly unoxygenated venous blood. In this condition, four abnormalities of the heart occur simultaneously:

1. The aorta originates from the right ventricle rather than the left, or it overrides a hole in the septum, as shown in Figure 23-5, receiving blood from both ventricles.
2. The pulmonary artery is stenosed, so much lower than normal amounts of blood pass from the right ventricle into the lungs; instead, most of the blood passes directly into the aorta, thus bypassing the lungs.
3. Blood from the left ventricle flows either through a ventricular septal hole into the right ventricle and then into the aorta or directly into the aorta that overrides this hole.
4. Because the right side of the heart must pump large quantities of blood against the high pressure in the aorta, its musculature is highly developed, causing an enlarged right ventricle.

Abnormal Circulatory Dynamics. It is readily apparent that the major physiological difficulty caused by tetralogy of Fallot is the shunting of blood past the lungs without its becoming oxygenated. As much as 75 percent of the venous blood returning to the heart passes directly from the right ventricle into the aorta without becoming oxygenated.

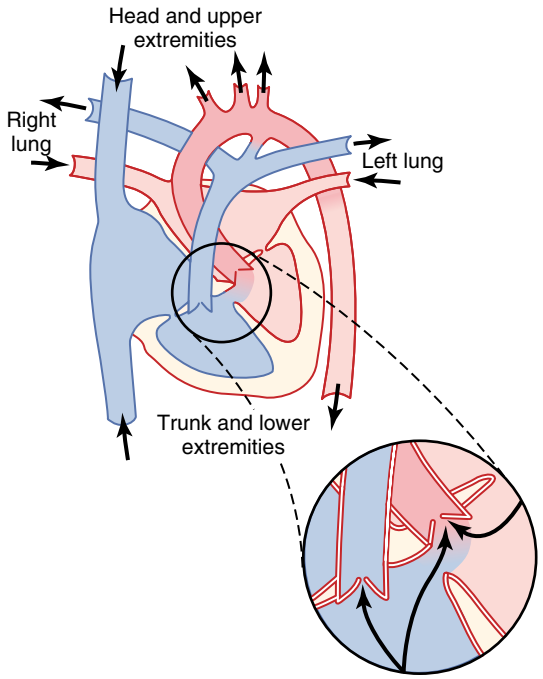


Figure 23-5 Tetralogy of Fallot, showing by the blue color that most of the venous blood is shunted from the right ventricle into the aorta without passing through the lungs.

A diagnosis of tetralogy of Fallot is usually based on (1) the fact that the baby's skin is *cyanotic* (blue); (2) measurement of high systolic pressure in the right ventricle, recorded through a catheter; (3) characteristic changes in the radiological silhouette of the heart, showing an enlarged right ventricle; and (4) angiograms (x-ray pictures) showing abnormal blood flow through the interventricular septal hole and into the overriding aorta, but much less flow through the stenosed pulmonary artery.

Surgical Treatment. Tetralogy of Fallot can usually be treated successfully by surgery. The usual operation is to open the pulmonary stenosis, close the septal defect, and reconstruct the flow pathway into the aorta. When surgery is successful, the average life expectancy increases from only 3 to 4 years to 50 or more years.

Causes of Congenital Anomalies

Congenital heart disease is not uncommon, occurring in about 8 of every 1000 live births. One of the most common causes of congenital heart defects is a viral infection in the mother during the first trimester of pregnancy when the fetal heart is being formed. Defects are particularly prone to develop when the expectant mother contracts German measles; thus, obstetricians may advise termination of pregnancy if German measles occurs in the first trimester.

Some congenital defects of the heart are hereditary because the same defect has been known to occur in identical twins, as well as in succeeding generations. Children of patients surgically treated for congenital heart disease have about a 10 times greater chance of having congenital heart disease than other children do. Congenital defects of the heart are also frequently associated with other congenital defects of the baby's body.

Use of Extracorporeal Circulation During Cardiac Surgery

It is almost impossible to repair intracardiac defects surgically while the heart is still pumping. Therefore, many types of artificial *heart-lung machines* have been developed to take the place of the heart and lungs during the course of operation. Such a system is called *extracorporeal circulation.* The system consists principally of a pump and an oxygenating device. Almost any type of pump that does not cause hemolysis of the blood seems to be suitable.

Methods used for oxygenating blood include (1) bubbling oxygen through the blood and removing the bubbles from the blood before passing it back into the patient,

(2) dripping the blood downward over the surfaces of plastic sheets in the presence of oxygen, (3) passing the blood over surfaces of rotating discs, or (4) passing the blood between thin membranes or through thin tubes that are permeable to oxygen and carbon dioxide.

The different systems have all been fraught with difficulties, including hemolysis of the blood, development of small clots in the blood, likelihood of small bubbles of oxygen or small emboli of antifoam agent passing into the arteries of the patient, necessity for large quantities of blood to prime the entire system, failure to exchange adequate quantities of oxygen, and necessity to use heparin to prevent blood coagulation in the extracorporeal system. Heparin also interferes with adequate hemostasis during the surgical procedure. Yet despite these difficulties, in the hands of experts, patients can be kept alive on artificial heart-lung machines for many hours while operations are performed on the inside of the heart.

Hypertrophy of the Heart in Valvular and Congenital Heart Disease

Hypertrophy of cardiac muscle is one of the most important mechanisms by which the heart adapts to increased workloads, whether these loads are caused by increased pressure against which the heart muscle must contract or by increased cardiac output that must be pumped. Some physicians believe that the increased strength of contraction of the heart muscle causes the hypertrophy; others believe that the increased metabolic rate of the muscle is the primary stimulus. Regardless of which of these is correct, one can calculate approximately how much hypertrophy will occur in each chamber of the heart by multiplying ventricular output by the pressure against which the ventricle must work, with emphasis on pressure. Thus, hypertrophy occurs in most types of valvular and congenital disease, sometimes causing heart weights as great as 800 grams instead of the normal 300 grams.

Detrimental Effects of Late Stages of Cardiac Hypertrophy. Although the most common cause of cardiac hypertrophy is hypertension, almost all forms of cardiac diseases including valvular and congenital disease can stimulate enlargement of the heart.

"Physiological" cardiac hypertrophy is generally considered to be a compensatory response of the heart to increased workload and is usually beneficial for maintaining cardiac output in the face of abnormalities that impair the heart's effectiveness as a pump. However, extreme degrees of hypertrophy can lead to heart failure. One of the reasons for this is that the coronary vasculature typically does not increase to the same extent as the mass of cardiac muscle increases. The second reason is that fibrosis often develops in the muscle, especially in the subendocardial muscle where the coronary blood flow is poor, with fibrous tissue replacing degenerating muscle fibers. Because of the disproportionate increase in muscle mass relative to coronary blood flow, relative ischemia may develop as the cardiac muscle hypertrophies and coronary blood flow insufficiency may ensue. Anginal pain is therefore a frequent accompaniment of cardiac hypertrophy associated with valvular and congenital heart diseases. Enlargement of the heart is also associated with greater risk for developing arrhythmias, which in turn can lead to further impairment of cardiac function and sudden death because of fibrillation.

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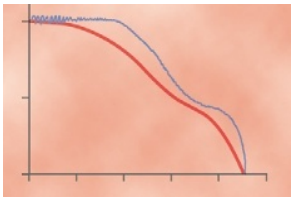
CHAPTER 24

Circulatory Shock and Its Treatment



Circulatory shock means generalized inadequate blood flow through the body, to the extent that the body tissues are damaged, especially because of too little oxygen and other nutrients delivered to the tissue cells. Even the cardiovascular system itself—the heart musculature, walls of the blood vessels, vasomotor system, and other circulatory parts—begins to deteriorate, so the shock, once begun, is prone to become progressively worse.

Physiologic Causes of Shock

Circulatory Shock Caused by Decreased Cardiac Output

Shock usually results from inadequate cardiac output. Therefore, any condition that reduces the cardiac output far below normal will likely lead to circulatory shock. Two types of factors can severely reduce cardiac output:

1. *Cardiac abnormalities that decrease the ability of the heart to pump blood.* These include especially myocardial infarction but also toxic states of the heart, severe heart valve dysfunction, heart arrhythmias, and other conditions. The circulatory shock that results from diminished cardiac pumping ability is called *cardiogenic shock.* This is discussed in detail in Chapter 22 where it is pointed out that as many as 70 percent of people who develop cardiogenic shock do not survive.
2. *Factors that decrease venous return* also decrease cardiac output because the heart cannot pump blood that does not flow into it. The most common cause of decreased venous return is *diminished blood volume*, but venous return can also be reduced as a result of *decreased vascular tone*, especially of the venous blood reservoirs, or *obstruction to blood flow* at some point in the circulation, especially in the venous return pathway to the heart.

Circulatory Shock That Occurs Without Diminished Cardiac Output

Occasionally, cardiac output is normal or even greater than normal, yet the person is in circulatory shock. This can result from (1) *excessive metabolic rate, so even a normal cardiac output is inadequate,* or (2) *abnormal tissue perfusion patterns, so most of the cardiac output is passing through blood vessels besides those that supply the local tissues with nutrition.*

The specific causes of shock are discussed later in the chapter. For the present, it is important to note that all of them lead to *inadequate delivery of nutrients to critical tissues and critical organs and also cause inadequate removal of cellular waste products from the tissues.*

What Happens to the Arterial Pressure in Circulatory Shock?

In the minds of many physicians, the arterial pressure level is the principal measure of adequacy of circulatory function. However, the arterial pressure can often be seriously misleading. At times, a person may be in severe shock and still have an almost normal arterial pressure because of powerful nervous reflexes that keep the pressure from falling. At other times, the arterial pressure can fall to half of normal, but the person still has normal tissue perfusion and is not in shock.

In most types of shock, especially shock caused by severe blood loss, the arterial blood pressure decreases at the same time the cardiac output decreases, although usually not as much.

Tissue Deterioration Is the End Result of Circulatory Shock

Once circulatory shock reaches a critical state of severity, regardless of its initiating cause, *the shock itself leads to more shock.* That is, the inadequate blood flow causes the body tissues to begin deteriorating, including the heart and circulatory system itself. This causes an even greater decrease in cardiac output, and a vicious circle ensues, with progressively increasing circulatory shock, less adequate tissue perfusion, more shock, and so forth until death. It is with this late stage of circulatory shock that we

are especially concerned, because appropriate physiologic treatment can often reverse the rapid slide to death.

Stages of Shock

Because the characteristics of circulatory shock change with different degrees of severity, shock is divided into the following three major stages:

1. A *nonprogressive stage* (sometimes called the *compensated stage*), in which the normal circulatory compensatory mechanisms eventually cause full recovery without help from outside therapy.
2. A *progressive stage,* in which, without therapy, the shock becomes steadily worse until death.
3. An *irreversible stage,* in which the shock has progressed to such an extent that all forms of known therapy are inadequate to save the person's life, even though, for the moment, the person is still alive.

Now, let us discuss the stages of circulatory shock caused by decreased blood volume, which illustrate the basic principles. Then we will consider special characteristics of shock initiated by other causes.

Shock Caused by Hypovolemia—Hemorrhagic Shock

Hypovolemia means diminished blood volume. Hemorrhage is the most common cause of hypovolemic shock. Hemorrhage *decreases the filling pressure of the circulation* and, as a consequence, decreases venous return. As a result, the cardiac output falls below normal and shock may ensue.

Relationship of Bleeding Volume to Cardiac Output and Arterial Pressure

Figure 24-1 shows the approximate effects on both cardiac output and arterial pressure of removing blood from the circulatory system over a period of about 30 minutes. About 10 percent of the total blood volume can be removed with almost no effect on either arterial pressure or cardiac output, but greater blood loss usually diminishes the cardiac output first and later the arterial pressure, both of which fall to zero when about 40 to 45 percent of the total blood volume has been removed.

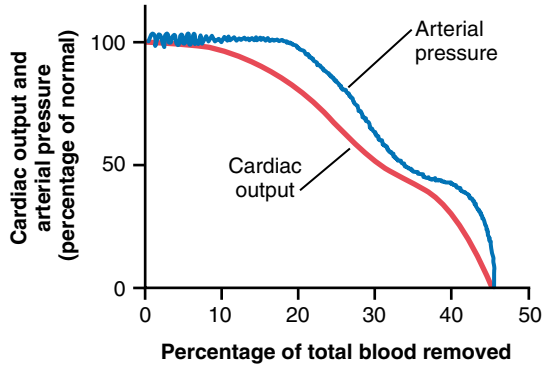


Figure 24-1 Effect of hemorrhage on cardiac output and arterial pressure.

Sympathetic Reflex Compensations in Shock—Their Special Value to Maintain Arterial Pressure. The decrease in arterial pressure after hemorrhage, as well as decreases in pressures in the pulmonary arteries and veins in the thorax, causes powerful sympathetic reflexes (initiated mainly by the arterial baroreceptors and other vascular stretch receptors, as explained in Chapter 18). These reflexes stimulate the sympathetic vasoconstrictor system in most tissues of the body, resulting in three important effects: (1) The arterioles constrict in most parts of the systemic circulation, thereby increasing the total peripheral resistance. (2) The veins and venous reservoirs constrict, thereby helping to maintain adequate venous return despite diminished blood volume. (3) Heart activity increases markedly, sometimes increasing the heart rate from the normal value of 72 beats/min to as high as 160 to 180 beats/min.

Value of the Sympathetic Nervous Reflexes. In the absence of the sympathetic reflexes, only 15 to 20 percent of the blood volume can be removed over a period of 30 minutes before a person dies; this is in contrast to a 30 to 40 percent loss of blood volume that a person can sustain when the reflexes are intact. Therefore, the reflexes extend the amount of blood loss that can occur without causing death to about twice that which is possible in their absence.

Greater Effect of the Sympathetic Nervous Reflexes in Maintaining Arterial Pressure than in Maintaining Cardiac Output. Referring again to Figure 24-1, note that the arterial pressure is maintained at or near normal levels in the hemorrhaging person longer than is the cardiac output. The reason for this is that the sympathetic reflexes are geared more for maintaining arterial pressure than for maintaining cardiac output. They increase the arterial pressure mainly by increasing the total peripheral resistance, which has no beneficial effect on cardiac output; however, the *sympathetic constriction of the veins is important to keep venous return and cardiac output from falling too much,* in addition to their role in maintaining arterial pressure.

Especially interesting is the second plateau occurring at about 50 mm Hg in the arterial pressure curve of Figure 24-1. This results from activation of the central nervous system ischemic response, which causes extreme stimulation of the sympathetic nervous system when the brain begins to suffer from lack of oxygen or from excess buildup of carbon dioxide, as discussed in Chapter 18. This effect of the central nervous system ischemic response can be called the "last-ditch stand" of the sympathetic reflexes in their attempt to keep the arterial pressure from falling too low.

Protection of Coronary and Cerebral Blood Flow by the Reflexes. A special value of the maintenance of normal arterial pressure even in the presence of decreasing

cardiac output is protection of blood flow through the coronary and cerebral circulatory systems. The sympathetic stimulation does not cause significant constriction of either the cerebral or the cardiac vessels. In addition, in both vascular beds, local blood flow autoregulation is excellent, which prevents moderate decreases in arterial pressure from significantly decreasing their blood flows. Therefore, blood flow through the heart and brain is maintained essentially at normal levels as long as the arterial pressure does not fall below about 70 mm Hg, despite the fact that blood flow in some other areas of the body might be decreased to as little as one third to one quarter normal by this time because of vasoconstriction.

Progressive and Nonprogressive Hemorrhagic Shock

Figure 24-2 shows an experiment that demonstrates the effects of different degrees of sudden acute hemorrhage on the subsequent course of arterial pressure. The animals were anesthetized and bled rapidly until their arterial pressures fell to different levels. Those animals whose pressures fell immediately to no lower than 45 mm Hg (groups I, II, and III) all eventually recovered; the recovery occurred rapidly if the pressure fell only slightly (group I) but occurred slowly if it fell almost to the 45 mm Hg level (group III). When the arterial pressure fell below 45 mm Hg (groups IV, V, and VI), all the animals died, although many of them hovered between life and death for hours before the circulatory system deteriorated to the stage of death.

This experiment demonstrates that the circulatory system can recover as long as the degree of hemorrhage is no greater than a certain critical amount. Crossing this critical threshold by even a few milliliters of blood loss makes the eventual difference between life and death. Thus, hemorrhage beyond a certain critical level causes shock to become *progressive.* That is, *the shock itself causes still more shock,* and the condition becomes a vicious circle that eventually leads to deterioration of the circulation and to death.

Nonprogressive Shock—Compensated Shock

If shock is not severe enough to cause its own progression, the person eventually recovers. Therefore, shock of this lesser degree is called *nonprogressive shock,* or *compensated shock,* meaning that the sympathetic reflexes and other factors compensate enough to prevent further deterioration of the circulation.

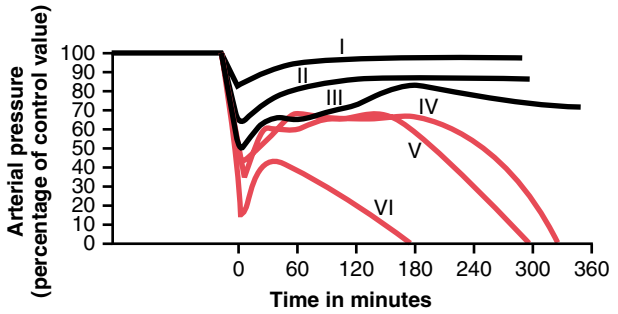


Figure 24-2 Time course of arterial pressure in dogs after different degrees of acute hemorrhage. Each curve represents average results from six dogs.

The factors that cause a person to recover from moderate degrees of shock are all the negative feedback control mechanisms of the circulation that attempt to return cardiac output and arterial pressure back to normal levels. They include the following:

1. *Baroreceptor reflexes,* which elicit powerful sympathetic stimulation of the circulation.
2. *Central nervous system ischemic response,* which elicits even more powerful sympathetic stimulation throughout the body but is not activated significantly until the arterial pressure falls below 50 mm Hg.
3. *Reverse stress-relaxation of the circulatory system,* which causes the blood vessels to contract around the diminished blood volume so that the blood volume that is available more adequately fills the circulation.
4. *Increased secretion of renin by the kidneys and formation of angiotensin II,* which constricts the peripheral arteries and also causes decreased output of water and salt by the kidneys, both of which help prevent progression of shock.
5. *Increased secretion by the posterior pituitary gland of vasopressin (antidiuretic hormone),* which constricts the peripheral arteries and veins and greatly increases water retention by the kidneys.
6. *Increased secretion by the adrenal medullae of epinephrine and norepinephrine,* which constricts the peripheral arteries and veins and increases the heart rate.
7. *Compensatory mechanisms that return the blood volume back toward normal,* including absorption of large quantities of fluid from the intestinal tract, absorption of fluid into the blood capillaries from the interstitial spaces of the body, conservation of water and salt by the kidneys, and increased thirst and increased appetite for salt, which make the person drink water and eat salty foods if able.

The sympathetic reflexes and increased secretion of catecholamines by the adrenal medullae provide rapid help toward bringing about recovery because they become maximally activated within 30 seconds to a few minutes after hemorrhage.

The angiotensin and vasopressin mechanisms, as well as the reverse stress-relaxation that causes contraction of the blood vessels and venous reservoirs, all require 10 minutes to 1 hour to respond completely, but they aid greatly in increasing the arterial pressure or increasing the circulatory filling pressure and thereby increasing the return of blood to the heart.

Finally, readjustment of blood volume by absorption of fluid from the interstitial spaces and intestinal tract, as well as oral ingestion and absorption of additional quantities of water and salt, may require from 1 to 48 hours,

but recovery eventually takes place, provided the shock does not become severe enough to enter the progressive stage.

"Progressive Shock" Is Caused by a Vicious Circle of Cardiovascular Deterioration

Figure 24-3 shows some of the positive feedbacks that further depress cardiac output in shock, thus causing the shock to become progressive. Some of the more important feedbacks are the following.

Cardiac Depression. When the arterial pressure falls low enough, *coronary blood flow decreases below that required for adequate nutrition of the myocardium.* This weakens the heart muscle and thereby decreases the cardiac output more. Thus, a positive feedback cycle has developed, whereby the shock becomes more and more severe.

Figure 24-4 shows cardiac output curves extrapolated to the human heart from studies in experimental animals, demonstrating progressive deterioration of the heart at different times after the onset of shock. An anesthetized dog was bled until the arterial pressure fell to 30 mm Hg, and the pressure was held at this level by further bleeding or retransfusion of blood as required. Note from the second curve in the figure that there was little deterioration of the heart during the first 2 hours, but by 4 hours, the heart had deteriorated about 40 percent; then, rapidly, during the last hour of the experiment (after 4 hours of low coronary blood pressure), the heart deteriorated completely.

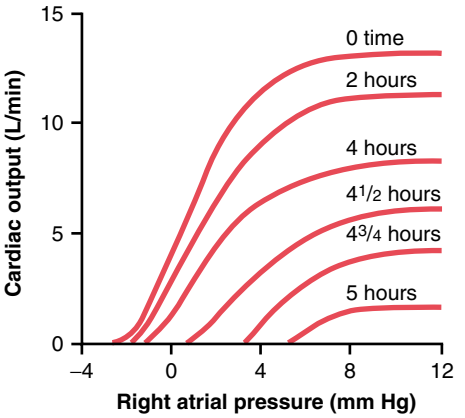


Figure 24-4 Cardiac output curves of the heart at different times after hemorrhagic shock begins. (These curves are extrapolated to the human heart from data obtained in dog experiments by Dr. J. W. Crowell.)

Thus, one of the important features of progressive shock, whether it is hemorrhagic in origin or caused in another way, is eventual progressive deterioration of the heart. In the early stages of shock, this plays very little role in the condition of the person, partly because deterioration of the heart is not severe during the first hour or so of shock, but mainly because the heart has tremendous reserve capability that normally allows it to pump 300 to 400 percent more blood than is required by the body for adequate tissue nutrition. In the latest stages of shock, however, deterioration of the heart is probably the

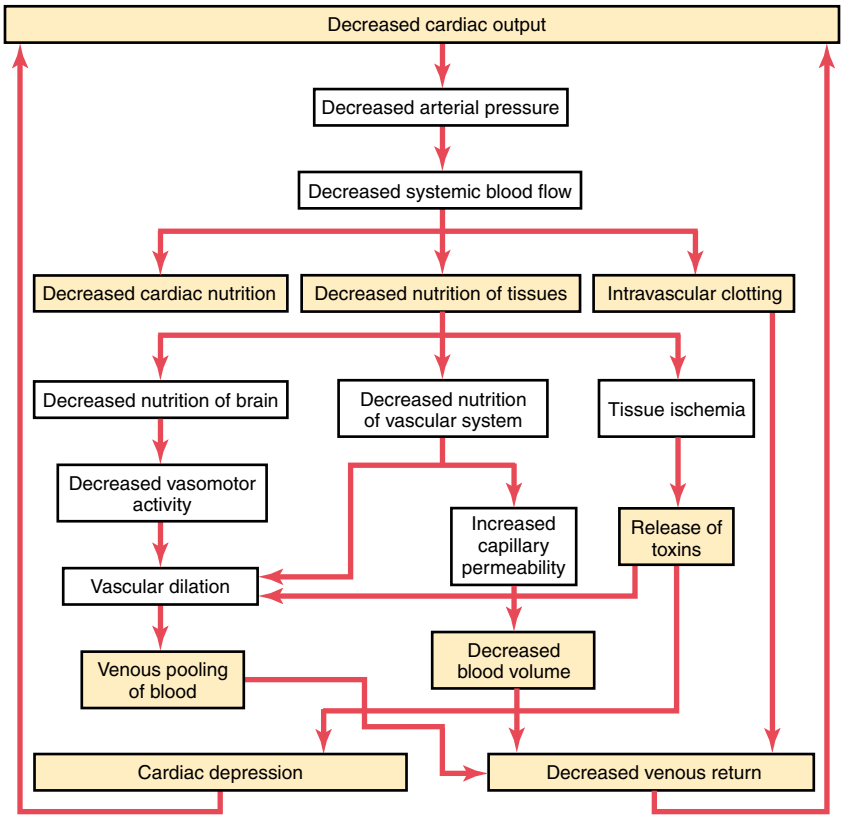


Figure 24-3 Different types of "positive feedback" that can lead to progression of shock.

most important factor in the final lethal progression of the shock.

Vasomotor Failure. In the early stages of shock, various circulatory reflexes cause intense activity of the sympathetic nervous system. This, as discussed earlier, helps delay depression of the cardiac output and especially helps prevent decreased arterial pressure. However, there comes a point when diminished blood flow to the brain's vasomotor center depresses the center so much that it, too, becomes progressively less active and finally totally inactive. For instance, *complete circulatory arrest to the brain* causes, during the first 4 to 8 minutes, the most intense of all sympathetic discharges, but by the end of 10 to 15 minutes, the vasomotor center becomes so depressed that no further evidence of sympathetic discharge can be demonstrated. Fortunately, the vasomotor center usually does not fail in the early stages of shock if the arterial pressure remains above 30 mm Hg.

Blockage of Very Small Vessels—"Sludged Blood." In time, blockage occurs in many of the very small blood vessels in the circulatory system and this also causes the shock to progress. The initiating cause of this blockage is sluggish blood flow in the microvessels. Because tissue metabolism continues despite the low flow, large amounts of acid, both carbonic acid and lactic acid, continue to empty into the local blood vessels and greatly increase the local acidity of the blood. This acid, plus other deterioration products from the ischemic tissues, causes local blood agglutination, resulting in minute blood clots, leading to very small plugs in the small vessels. Even if the vessels do not become plugged, an increased tendency for the blood cells to stick to one another makes it more difficult for blood to flow through the microvasculature, giving rise to the term *sludged blood.*

Increased Capillary Permeability. After many hours of capillary hypoxia and lack of other nutrients, the permeability of the capillaries gradually increases, and large quantities of fluid begin to transude into the tissues. This decreases the blood volume even more, with a resultant further decrease in cardiac output, making the shock still more severe. Capillary hypoxia does not cause increased capillary permeability until the late stages of prolonged shock.

Release of Toxins by Ischemic Tissue. Throughout the history of research in the field of shock, it has been suggested that shock causes tissues to release toxic substances, such as histamine, serotonin, and tissue enzymes, that cause further deterioration of the circulatory system. Experimental studies have proved the significance of at least one toxin, *endotoxin,* in some types of shock.

Cardiac Depression Caused by Endotoxin. *Endotoxin* is released from the bodies of dead gram-negative bacteria in the intestines. Diminished blood flow to the intestines often causes enhanced formation and absorption of this toxic substance. The circulating toxin then causes increased cellular metabolism despite inadequate nutrition of the cells; this has a specific effect on the heart muscle, causing *cardiac depression.* Endotoxin can play a major role in some types of shock, especially "septic shock," discussed later in the chapter.

Generalized Cellular Deterioration. As shock becomes severe, many signs of generalized cellular deterioration occur throughout the body. One organ especially affected is the *liver,* as illustrated in Figure 24-5. This occurs mainly because of lack of enough nutrients to support the normally high rate of metabolism in liver cells, but also partly because of the exposure of the liver cells to any vascular toxin or other abnormal metabolic factor occurring in shock.

Among the damaging cellular effects that are known to occur in most body tissues are the following:

1. Active transport of sodium and potassium through the cell membrane is greatly diminished. As a result, sodium and chloride accumulate in the cells and potassium is lost from the cells. In addition, the cells begin to swell.
2. Mitochondrial activity in the liver cells, as well as in many other tissues of the body, becomes severely depressed.
3. Lysosomes in the cells in widespread tissue areas begin to break open, with intracellular release of *hydrolases* that cause further intracellular deterioration.
4. Cellular metabolism of nutrients, such as glucose, eventually becomes greatly depressed in the last stages of shock. The actions of some hormones are depressed as well, including almost 100 percent depression of the action of insulin.

All these effects contribute to further deterioration of many organs of the body, including especially (1) the *liver,* with depression of its many metabolic and detoxification functions; (2) the *lungs,* with eventual development of pulmonary edema and poor ability to oxygenate the blood; and (3) the *heart,* thereby further depressing its contractility.

Tissue Necrosis in Severe Shock—Patchy Areas of Necrosis Occur Because of Patchy Blood Flows in Different Organs. Not all cells of the body are equally damaged by shock because some tissues have better blood supplies than others. For instance, the cells adjacent to the arterial ends of capillaries receive better nutrition than cells adjacent to the venous ends of the same capillaries. Therefore, more nutritive deficiency occurs around the venous ends of capillaries than elsewhere. For instance, Figure 24-5 shows necrosis in the center of a liver lobule, the portion of the lobule that is last to be exposed to the blood as it passes through the liver sinusoids.

Similar punctate lesions occur in heart muscle, although here a definite repetitive pattern, such as occurs in the liver, cannot be demonstrated. Nevertheless, the cardiac lesions play an important role in leading to the final irreversible stage of shock. Deteriorative lesions also occur in the kidneys, especially in the epithelium of the kidney tubules, leading to kidney failure and occasionally uremic death several days later. Deterioration of the lungs

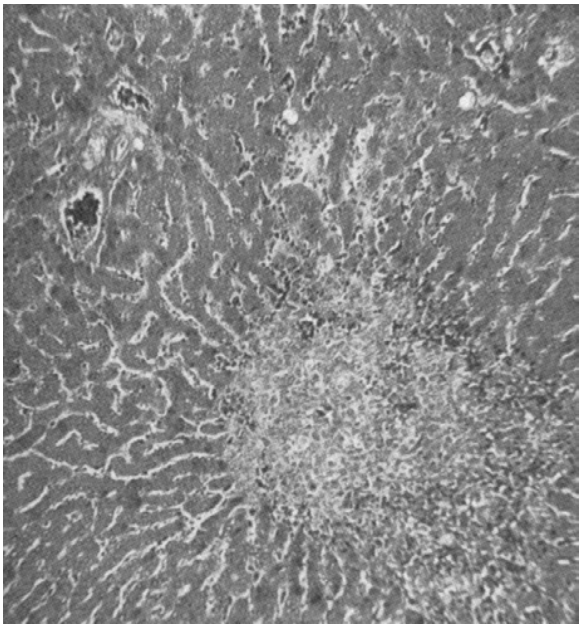


Figure 24-5 Necrosis of the central portion of a liver lobule in severe circulatory shock. (Courtesy Dr. J. W. Crowell.)

also often leads to respiratory distress and death several days later—called the *shock lung syndrome.*

Acidosis in Shock. Most metabolic derangements that occur in shocked tissue can lead to acidosis all through the body. This results from poor delivery of oxygen to the tissues, which greatly diminishes oxidative metabolism of the foodstuffs. When this occurs, the cells obtain most of their energy by the anaerobic process of glycolysis, which leads to tremendous quantities of *excess lactic acid* in the blood. In addition, poor blood flow through tissues prevents normal removal of carbon dioxide. The carbon dioxide reacts locally in the cells with water to form high concentrations of intracellular carbonic acid; this, in turn, reacts with various tissue chemicals to form still other intracellular acidic substances. Thus, another deteriorative effect of shock is both generalized and local tissue acidosis, leading to further progression of the shock itself.

Positive Feedback Deterioration of Tissues in Shock and the Vicious Circle of Progressive Shock

All the factors just discussed that can lead to further progression of shock are types of *positive feedback.* That is, each increase in the degree of shock causes a further increase in the shock.

However, positive feedback does not necessarily lead to a vicious circle. Whether a vicious circle develops depends on the intensity of the positive feedback. In mild degrees of shock, the negative feedback mechanisms of the circulation—sympathetic reflexes, reverse stress-relaxation mechanism of the blood reservoirs, absorption of fluid into the blood from the interstitial spaces, and others—can easily overcome the positive feedback influences and, therefore, cause recovery. But in severe degrees of shock, the deteriorative feedback mechanisms become more and more powerful, leading to such rapid deterioration of the circulation that all the normal negative feedback systems of circulatory control acting together cannot return the cardiac output to normal.

Considering once again the principles of positive feedback and vicious circle discussed in Chapter 1, one can readily understand why there is a critical cardiac output level above which a person in shock recovers and below which a person enters a vicious circle of circulatory deterioration that proceeds until death.

Irreversible Shock

After shock has progressed to a certain stage, transfusion or any other type of therapy becomes incapable of saving the person's life. The person is then said to be in the *irreversible stage of shock.* Ironically, even in this irreversible stage, therapy can, on rare occasions, return the arterial pressure and even the cardiac output to normal or near normal for short periods, but the circulatory system nevertheless continues to deteriorate, and death ensues in another few minutes to few hours.

Figure 24-6 demonstrates this effect, showing that transfusion during the irreversible stage can sometimes cause the cardiac output (as well as the arterial pressure) to return to nearly normal. However, the cardiac output soon begins to fall again, and subsequent transfusions have less and less effect. By this time, multiple deteriorative changes have occurred in the muscle cells of the heart that may not necessarily affect the heart's *immediate* ability to pump blood but, over a long period, depress heart pumping enough to cause death. Beyond a certain point, so much tissue damage has occurred, so many destructive enzymes have been released into the body fluids, so much acidosis has developed, and so many other destructive factors are now in progress that even a normal cardiac output for a few minutes cannot reverse the continuing deterioration. Therefore, in severe shock, a stage is eventually reached at which the person will die even though vigorous therapy might still return the cardiac output to normal for short periods.

Depletion of Cellular High-Energy Phosphate Reserves in Irreversible Shock. The high-energy phosphate reserves in the tissues of the body, especially in the liver and the heart, are greatly diminished in severe degrees

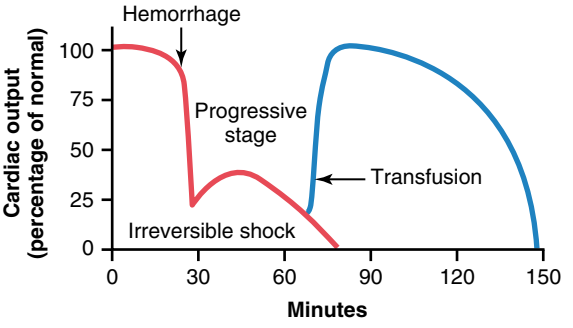


Figure 24-6 Failure of transfusion to prevent death in irreversible shock.

of shock. Essentially all the *creatine phosphate* has been degraded, and almost all the *adenosine triphosphate* has downgraded to *adenosine diphosphate, adenosine monophosphate,* and, eventually, *adenosine.* Then much of this adenosine diffuses out of the cells into the circulating blood and is converted into uric acid, a substance that cannot re-enter the cells to reconstitute the adenosine phosphate system. New adenosine can be synthesized at a rate of only about 2 percent of the normal cellular amount an hour, meaning that once the high-energy phosphate stores of the cells are depleted, they are difficult to replenish.

Thus, one of the most devastating end results of deterioration in shock, and the one that is perhaps most significant for development of the final state of irreversibility, is this cellular depletion of these high-energy compounds.

Hypovolemic Shock Caused by Plasma Loss

Loss of plasma from the circulatory system, even without loss of red blood cells, can sometimes be severe enough to reduce the total blood volume markedly, causing typical hypovolemic shock similar in almost all details to that caused by hemorrhage. Severe plasma loss occurs in the following conditions:

1. *Intestinal obstruction* may cause severely reduced plasma volume. Distention of the intestine in intestinal obstruction partly blocks venous blood flow in the intestinal walls, which increases intestinal capillary pressure. This in turn causes fluid to leak from the capillaries into the intestinal walls and also into the intestinal lumen. Because the lost fluid has high protein content, the result is reduced total blood plasma protein, as well as reduced plasma volume.
2. In almost all patients who have *severe burns* or other denuding conditions of the skin, so much plasma is lost through the denuded skin areas that the plasma volume becomes markedly reduced.

The hypovolemic shock that results from plasma loss has almost the same characteristics as the shock caused by hemorrhage, except for one additional complicating factor: the blood viscosity increases greatly as a result of increased red blood cell concentration in the remaining blood, and this exacerbates the sluggishness of blood flow.

Loss of fluid from all fluid compartments of the body is called *dehydration;* this, too, can reduce the blood volume and cause hypovolemic shock similar to that resulting from hemorrhage. Some of the causes of this type of shock are (1) excessive sweating, (2) fluid loss in severe diarrhea or vomiting, (3) excess loss of fluid by the kidneys, (4) inadequate intake of fluid and electrolytes, or (5) destruction of the adrenal cortices, with loss of aldosterone secretion and consequent failure of the kidneys to reabsorb sodium, chloride, and water, which occurs in the absence of the adrenocortical hormone aldosterone.

Hypovolemic Shock Caused by Trauma

One of the most common causes of circulatory shock is trauma to the body. Often the shock results simply from hemorrhage caused by the trauma, but it can also occur even without hemorrhage, because extensive contusion of the body can damage the capillaries sufficiently to allow excessive loss of plasma into the tissues. This results in greatly reduced plasma volume, with resultant hypovolemic shock.

Various attempts have been made to implicate toxic factors released by the traumatized tissues as one of the causes of shock after trauma. However, cross-transfusion experiments into normal animals have failed to show significant toxic elements.

In summary, traumatic shock seems to result mainly from hypovolemia, although there might also be a moderate degree of concomitant neurogenic shock caused by loss of vasomotor tone, as discussed next.

Neurogenic Shock—Increased Vascular Capacity

Shock occasionally results without any loss of blood volume. Instead, the *vascular capacity* increases so much that even the normal amount of blood becomes incapable of filling the circulatory system adequately. One of the major causes of this is *sudden loss of vasomotor tone* throughout the body, resulting especially in massive dilation of the veins. The resulting condition is known as *neurogenic shock.*

The role of vascular capacity in helping to regulate circulatory function was discussed in Chapter 15, where it was pointed out that either an increase in vascular capacity or a decrease in blood volume *reduces the mean systemic filling pressure,* which reduces venous return to the heart. Diminished venous return caused by vascular dilation is called *venous pooling* of blood.

Causes of Neurogenic Shock. Some neurogenic factors that can cause loss of vasomotor tone include the following:

1. *Deep general anesthesia* often depresses the vasomotor center enough to cause vasomotor paralysis, with resulting neurogenic shock.
2. *Spinal anesthesia,* especially when this extends all the way up the spinal cord, blocks the sympathetic nervous outflow from the nervous system and can be a potent cause of neurogenic shock.
3. *Brain damage* is often a cause of vasomotor paralysis. Many patients who have had brain concussion or contusion of the basal regions of the brain develop profound neurogenic shock. Also, even though brain ischemia for a few minutes almost always causes extreme vasomotor stimulation, prolonged ischemia (lasting longer than 5 to 10 minutes) can cause the opposite effect—

total inactivation of the vasomotor neurons in the brain stem, with consequent development of severe neurogenic shock.

Anaphylactic Shock and Histamine Shock

Anaphylaxis is an allergic condition in which the cardiac output and arterial pressure often decrease drastically. This is discussed in Chapter 34. It results primarily from an antigen-antibody reaction that rapidly occurs after an antigen to which the person is sensitive enters the circulation. One of the principal effects is to cause the *basophils* in the blood and *mast* cells in the pericapillary tissues to release *histamine* or a *histamine-like substance.* The histamine causes (1) an increase in vascular capacity because of venous dilation, thus causing a marked decrease in venous return; (2) dilation of the arterioles, resulting in greatly reduced arterial pressure; and (3) greatly increased capillary permeability, with rapid loss of fluid and protein into the tissue spaces. The net effect is a great reduction in venous return and sometimes such serious shock that the person dies within minutes.

Intravenous injection of large amounts of histamine causes "histamine shock," which has characteristics almost identical to those of anaphylactic shock.

Septic Shock

A condition that was formerly known by the popular name "blood poisoning" is now called *septic shock* by most clinicians. This refers to a bacterial infection widely disseminated to many areas of the body, with the infection being borne through the blood from one tissue to another and causing extensive damage. There are many varieties of septic shock because of the many types of bacterial infections that can cause it and because infection in different parts of the body produces different effects.

Septic shock is extremely important to the clinician because other than cardiogenic shock, septic shock is the most frequent cause of shock-related death in the modern hospital.

Some of the typical causes of septic shock include the following:

1. Peritonitis caused by spread of infection from the uterus and fallopian tubes, sometimes resulting from instrumental abortion performed under unsterile conditions.
2. Peritonitis resulting from rupture of the gastrointestinal system, sometimes caused by intestinal disease and sometimes by wounds.
3. Generalized bodily infection resulting from spread of a skin infection such as streptococcal or staphylococcal infection.
4. Generalized gangrenous infection resulting specifically from gas gangrene bacilli, spreading first through peripheral tissues and finally by way of the blood to the internal organs, especially the liver.
5. Infection spreading into the blood from the kidney or urinary tract, often caused by colon bacilli.

Special Features of Septic Shock. Because of the multiple types of septic shock, it is difficult to categorize this condition. Some features often observed are:

1. High fever.
2. Often marked vasodilation throughout the body, especially in the infected tissues.
3. High cardiac output in perhaps half of patients, caused by arteriolar dilation in the infected tissues and by high metabolic rate and vasodilation elsewhere in the body, resulting from bacterial toxin stimulation of cellular metabolism and from high body temperature.
4. Sludging of the blood, caused by red cell agglutination in response to degenerating tissues.
5. Development of micro-blood clots in widespread areas of the body, a condition called *disseminated intravascular coagulation.* Also, this causes the blood clotting factors to be used up, so hemorrhaging occurs in many tissues, especially in the gut wall of the intestinal tract.

In early stages of septic shock, the patient usually does not have signs of circulatory collapse but only signs of the bacterial infection. As the infection becomes more severe, the circulatory system usually becomes involved either because of direct extension of the infection or secondarily as a result of toxins from the bacteria, with resultant loss of plasma into the infected tissues through deteriorating blood capillary walls. There finally comes a point at which deterioration of the circulation becomes progressive in the same way that progression occurs in all other types of shock. The end stages of septic shock are not greatly different from the end stages of hemorrhagic shock, even though the initiating factors are markedly different in the two conditions.

Physiology of Treatment in Shock

Replacement Therapy

Blood and Plasma Transfusion. If a person is in shock caused by hemorrhage, the best possible therapy is usually transfusion of whole blood. If the shock is caused by plasma loss, the best therapy is administration of plasma; when dehydration is the cause, administration of an appropriate electrolyte solution can correct the shock.

Whole blood is not always available, such as under battlefield conditions. Plasma can usually substitute adequately for whole blood because it increases the blood volume and restores normal hemodynamics. Plasma cannot

restore a normal hematocrit, but the human body can usually stand a decrease in hematocrit to about half of normal before serious consequences result, if cardiac output is adequate. Therefore, in emergency conditions, it is reasonable to use plasma in place of whole blood for treatment of hemorrhagic or most other types of hypovolemic shock.

Sometimes plasma is unavailable. In these instances, various *plasma substitutes* have been developed that perform almost exactly the same hemodynamic functions as plasma. One of these is dextran solution.

Dextran Solution as a Plasma Substitute. The principal requirement of a truly effective plasma substitute is that it remain in the circulatory system—that is, does not filter through the capillary pores into the tissue spaces. In addition, the solution must be nontoxic and must contain appropriate electrolytes to prevent derangement of the body's extracellular fluid electrolytes on administration.

To remain in the circulation, the plasma substitute must contain some substance that has a large enough molecular size to exert colloid osmotic pressure. One substance developed for this purpose is *dextran,* a large polysaccharide polymer of glucose. Certain bacteria secrete dextran as a by-product of their growth, and commercial dextran can be manufactured using a bacterial culture procedure. By varying the growth conditions of the bacteria, the molecular weight of the dextran can be controlled to the desired value. Dextrans of appropriate molecular size do not pass through the capillary pores and, therefore, can replace plasma proteins as colloid osmotic agents.

Few toxic reactions have been observed when using purified dextran to provide colloid osmotic pressure; therefore, solutions containing this substance have proved to be a satisfactory substitute for plasma in most fluid replacement therapy.

Treatment of Shock with Sympathomimetic Drugs—Sometimes Useful, Sometimes Not

A *sympathomimetic drug* is a drug that mimics sympathetic stimulation. These drugs include *norepinephrine, epinephrine,* and a large number of long-acting drugs that have the same effect as epinephrine and norepinephrine.

In two types of shock, sympathomimetic drugs have proved to be especially beneficial. The first of these is *neurogenic shock,* in which the sympathetic nervous system is severely depressed. Administering a sympathomimetic drug takes the place of the diminished sympathetic actions and can often restore full circulatory function.

The second type of shock in which sympathomimetic drugs are valuable is *anaphylactic shock,* in which excess histamine plays a prominent role. The sympathomimetic drugs have a vasoconstrictor effect that opposes the vasodilating effect of histamine. Therefore, epinephrine, norepinephrine, or other sympathomimetic drugs are often lifesaving.

Sympathomimetic drugs have not proved to be very valuable in hemorrhagic shock. The reason is that in this type of shock, the sympathetic nervous system is almost always maximally activated by the circulatory reflexes already; so much norepinephrine and epinephrine are already circulating in the blood that sympathomimetic drugs have essentially no additional beneficial effect.

Other Therapy

Treatment by the Head-Down Position. When the pressure falls too low in most types of shock, especially in hemorrhagic and neurogenic shock, placing the patient with the head at least 12 inches lower than the feet helps in promoting venous return, thereby also increasing cardiac output. This head-down position is the first essential step in the treatment of many types of shock.

Oxygen Therapy. Because the major deleterious effect of most types of shock is too little delivery of oxygen to the tissues, giving the patient oxygen to breathe can be of benefit in some instances. However, this frequently is far less beneficial than one might expect, because the problem in most types of shock is not inadequate oxygenation of the blood by the lungs but inadequate transport of the blood after it is oxygenated.

Treatment with Glucocorticoids (Adrenal Cortex Hormones That Control Glucose Metabolism). Glucocorticoids are frequently given to patients in severe shock for several reasons: (1) experiments have shown empirically that glucocorticoids frequently increase the strength of the heart in the late stages of shock; (2) glucocorticoids stabilize lysosomes in tissue cells and thereby prevent release of lysosomal enzymes into the cytoplasm of the cells, thus preventing deterioration from this source; and (3) glucocorticoids might aid in the metabolism of glucose by the severely damaged cells.

Circulatory Arrest

A condition closely allied to circulatory shock is circulatory arrest, in which all blood flow stops. This occurs frequently on the surgical operating table as a result of *cardiac arrest* or *ventricular fibrillation.*

Ventricular fibrillation can usually be stopped by strong electroshock of the heart, the basic principles of which are described in Chapter 13.

Cardiac arrest may result from too little oxygen in the anesthetic gaseous mixture or from a depressant effect of the anesthesia itself. A normal cardiac rhythm can usually be restored by removing the anesthetic and immediately applying cardiopulmonary resuscitation procedures, while at the same time supplying the patient's lungs with adequate quantities of ventilatory oxygen.

Effect of Circulatory Arrest on the Brain

A special problem in circulatory arrest is to prevent detrimental effects in the brain as a result of the arrest. In general, more than 5 to 8 minutes of total circulatory arrest can cause at least some degree of permanent brain damage in more than half of patients. Circulatory arrest for as long as 10 to 15 minutes almost always permanently destroys significant amounts of mental power.

For many years, it was taught that this detrimental effect on the brain was caused by the acute cerebral hypoxia that occurs during circulatory arrest. However, experiments have shown that if blood clots are prevented from occurring in the blood vessels of the brain, this will also prevent much of the early deterioration of the brain during circulatory arrest. For instance, in animal experiments, all the blood was removed from the animal's blood vessels at the beginning of circulatory arrest and then replaced at the end of circulatory arrest so that no intravascular blood clotting could occur. In this experiment, the brain was usually able to withstand up to 30 minutes of circulatory arrest without permanent brain damage. Also, administration of heparin or streptokinase (to prevent blood coagulation) before cardiac arrest was shown to increase the survivability of the brain up to two to four times longer than usual.

It is likely that the severe brain damage that occurs from circulatory arrest is caused mainly by permanent blockage of many small blood vessels by blood clots, thus leading to prolonged ischemia and eventual death of the neurons.

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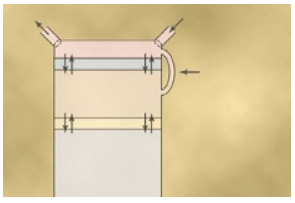
The Body Fluid Compartments: Extracellular and Intracellular Fluids; Edema



The maintenance of a relatively constant volume and a stable composition of the body fluids is essential for homeostasis, as discussed in Chapter 1. Some of the most common and important problems in clinical medicine arise because of abnormalities in the control systems that maintain this constancy of the body fluids. In this chapter and in the following chapters on the kidneys, we discuss the overall regulation of body fluid volume, constituents of the extracellular fluid, acid-base balance, and control of fluid exchange between extracellular and intracellular compartments.

Fluid Intake and Output Are Balanced During Steady-State Conditions

The relative constancy of the body fluids is remarkable because there is continuous exchange of fluid and solutes with the external environment, as well as within the different compartments of the body. For example, there is a highly variable fluid intake that must be carefully matched by equal output of water from the body to prevent body fluid volumes from increasing or decreasing.

Daily Intake of Water

Water is added to the body by two major sources: (1) It is ingested in the form of liquids or water in the food, which together normally add about 2100 ml/day to the body fluids, and (2) it is synthesized in the body as a result of oxidation of carbohydrates, adding about 200 ml/day. This provides a total water intake of about 2300 ml/day (Table 25-1). Intake of water, however, is highly variable among different people and even within the same person on different days, depending on climate, habits, and level of physical activity.

Daily Loss of Body Water

Insensible Water Loss. Some of the water losses cannot be precisely regulated. For example, there is a continuous loss of water by evaporation from the respiratory tract and diffusion through the skin, which together account for about 700 ml/day of water loss under normal conditions. This is termed *insensible water loss* because we are not consciously aware of it, even though it occurs continually in all living humans.

The insensible water loss through the skin occurs independently of sweating and is present even in people who are born without sweat glands; the average water loss by diffusion through the skin is about 300 to 400 ml/day. This loss is minimized by the cholesterol-filled cornified layer of the skin, which provides a barrier against excessive loss by diffusion. When the cornified layer becomes denuded, as occurs with extensive burns, the rate of evaporation can increase as much as 10-fold, to 3 to 5 L/day. For this reason, burn victims must be given large amounts of fluid, usually intravenously, to balance fluid loss.

Insensible water loss through the respiratory tract averages about 300 to 400 ml/day. As air enters the respiratory tract, it becomes saturated with moisture, to a vapor pressure of about 47 mm Hg, before it is expelled. Because the vapor pressure of the inspired air is usually less than 47 mm Hg, water is continuously lost through the lungs with respiration. In cold weather, the atmospheric vapor pressure decreases to nearly 0, causing an even greater loss of water from the lungs as the temperature decreases. This explains the dry feeling in the respiratory passages in cold weather.

Fluid Loss in Sweat. The amount of water lost by sweating is highly variable, depending on physical activity and environmental temperature. The volume of sweat normally is about 100 ml/day, but in very hot weather or during heavy exercise water loss in sweat occasionally increases to 1 to 2 L/hour. This would rapidly deplete the body fluids if intake were not also increased by activating the thirst mechanism discussed in Chapter 29.

Water Loss in Feces. Only a small amount of water (100 ml/day) normally is lost in the feces. This can increase to several liters a day in people with severe diarrhea. For this reason, severe diarrhea can be life threatening if not corrected within a few days.

Table 25-1 Daily Intake and Output of Water (ml/day)

	Normal	Prolonged, Heavy Exercise
Intake		
Fluids ingested	2100	?
From metabolism	200	200
Total intake	2300	?
Output		
Insensible—skin	350	350
Insensible—lungs	350	650
Sweat	100	5000
Feces	100	100
Urine	1400	500
Total output	2300	6600

Water Loss by the Kidneys. The remaining water loss from the body occurs in the urine excreted by the kidneys. There are multiple mechanisms that control the rate of urine excretion. In fact, the most important means by which the body maintains a balance between water intake and output, as well as a balance between intake and output of most electrolytes in the body, is by controlling the rates at which the kidneys excrete these substances. For example, urine volume can be as low as 0.5 L/day in a dehydrated person or as high as 20 L/day in a person who has been drinking tremendous amounts of water.

This variability of intake is also true for most of the electrolytes of the body, such as sodium, chloride, and potassium. In some people, sodium intake may be as low as 20 mEq/day, whereas in others, sodium intake may be as high as 300 to 500 mEq/day. The kidneys are faced with the task of adjusting the excretion rate of water and electrolytes to match precisely the intake of these substances, as well as compensating for excessive losses of fluids and electrolytes that occur in certain disease states. In Chapters 26 through 30, we discuss the mechanisms that allow the kidneys to perform these remarkable tasks.

Body Fluid Compartments

The total body fluid is distributed mainly between two compartments: the *extracellular fluid* and the *intracellular fluid* (Figure 25-1). The extracellular fluid is divided into the *interstitial fluid* and the blood *plasma.*

There is another small compartment of fluid that is referred to as *transcellular fluid.* This compartment includes fluid in the synovial, peritoneal, pericardial, and intraocular spaces, as well as the cerebrospinal fluid; it is usually considered to be a specialized type of extracellular fluid, although in some cases its composition may differ markedly from that of the plasma or interstitial fluid. All the transcellular fluids together constitute about 1 to 2 liters.

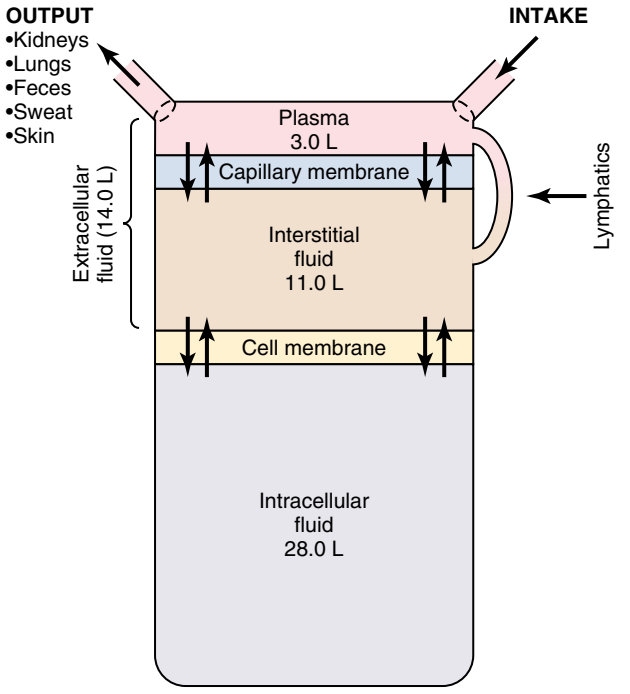


Figure 25-1 Summary of body fluid regulation, including the major body fluid compartments and the membranes that separate these compartments. The values shown are for an average 70-kilogram person.

In the average 70-kilogram adult man, the total body water is about 60 percent of the body weight, or about 42 liters. This percentage can change, depending on age, gender, and degree of obesity. As a person grows older, the percentage of total body weight that is fluid gradually decreases. This is due in part to the fact that aging is usually associated with an increased percentage of the body weight being fat, which decreases the percentage of water in the body.

Because women normally have more body fat than men, their total body water averages about 50 percent of the body weight. In premature and newborn babies, the total body water ranges from 70 to 75 percent of body weight. Therefore, when discussing the "average" body fluid compartments, we should realize that variations exist, depending on age, gender, and percentage of body fat.

Intracellular Fluid Compartment

About 28 of the 42 liters of fluid in the body are inside the 100 trillion cells and are collectively called the *intracellular fluid.* Thus, the intracellular fluid constitutes about 40 percent of the total body weight in an "average" person.

The fluid of each cell contains its individual mixture of different constituents, but the concentrations of these substances are similar from one cell to another. In fact, the composition of cell fluids is remarkably similar even in different animals, ranging from the most primitive microorganisms to humans. For this reason, the intracellular fluid of all the different cells together is considered to be one large fluid compartment.

Extracellular Fluid Compartment

All the fluids outside the cells are collectively called the *extracellular fluid.* Together these fluids account for about 20 percent of the body weight, or about 14 liters in a normal 70-kilogram man. The two largest compartments of the extracellular fluid are the *interstitial fluid,* which makes up more than three fourths (11 liters) of the extracellular fluid, and the *plasma,* which makes up almost one fourth of the extracellular fluid, or about 3 liters. The plasma is the noncellular part of the blood; it exchanges substances continuously with the interstitial fluid through the pores of the capillary membranes. These pores are highly permeable to almost all solutes in the extracellular fluid except the proteins. Therefore, the extracellular fluids are constantly mixing, so the plasma and interstitial fluids have about the same composition except for proteins, which have a higher concentration in the plasma.

Blood Volume

Blood contains both extracellular fluid (the fluid in plasma) and intracellular fluid (the fluid in the red blood cells). However, blood is considered to be a separate fluid compartment because it is contained in a chamber of its own, the circulatory system. The blood volume is especially important in the control of cardiovascular dynamics.

The average blood volume of adults is about 7 percent of body weight, or about 5 liters. About 60 percent of the blood is plasma and 40 percent is red blood cells, but these percentages can vary considerably in different people, depending on gender, weight, and other factors.

Hematocrit (Packed Red Cell Volume). The hematocrit is the fraction of the blood composed of red blood cells, as determined by centrifuging blood in a "hematocrit tube" until the cells become tightly packed in the bottom of the tube. It is impossible to completely pack the red cells together; therefore, about 3 to 4 percent of the plasma remains entrapped among the cells, and the true hematocrit is only about 96 percent of the measured hematocrit.

In men, the measured hematocrit is normally about 0.40, and in women, it is about 0.36. In severe *anemia,* the hematocrit may fall as low as 0.10, a value that is barely sufficient to sustain life. Conversely, there are some conditions in which there is excessive production of red blood cells, resulting in *polycythemia.* In these conditions, the hematocrit can rise to 0.65.

Constituents of Extracellular and Intracellular Fluids

Comparisons of the composition of the extracellular fluid, including the plasma and interstitial fluid, and the intracellular fluid are shown in Figures 25-2 and 25-3 and in Table 25-2.

Ionic Composition of Plasma and Interstitial Fluid Is Similar

Because the plasma and interstitial fluid are separated only by highly permeable capillary membranes, their ionic composition is similar. The most important difference between these two compartments is the higher concentration of protein in the plasma; because the capillaries have a low permeability to the plasma proteins, only small amounts of proteins are leaked into the interstitial spaces in most tissues.

Because of the *Donnan effect,* the concentration of positively charged ions (cations) is slightly greater (≈2 percent) in the plasma than in the interstitial fluid. The plasma proteins have a net negative charge and, therefore, tend to bind cations, such as sodium and potassium ions, thus holding extra amounts of these cations in the plasma along with the plasma proteins. Conversely, negatively charged ions (anions) tend to have a slightly higher concentration in the interstitial fluid compared with the plasma, because the negative charges of the plasma proteins repel the negatively charged anions. For practical purposes, however, the concentration of ions in the interstitial fluid and in the plasma is considered to be about equal.

Referring again to Figure 25-2, one can see that the extracellular fluid, including the plasma and the interstitial fluid, contains large amounts of sodium and chloride ions, reasonably large amounts of bicarbonate ions, but only small quantities of potassium, calcium, magnesium, phosphate, and organic acid ions.

The composition of extracellular fluid is carefully regulated by various mechanisms, but especially by the kidneys, as discussed later. This allows the cells to remain continually bathed in a fluid that contains the proper concentration of electrolytes and nutrients for optimal cell function.

Intracellular Fluid Constituents

The intracellular fluid is separated from the extracellular fluid by a cell membrane that is highly permeable to water but not to most of the electrolytes in the body.

In contrast to the extracellular fluid, the intracellular fluid contains only small quantities of sodium and chloride ions and almost no calcium ions. Instead, it contains large amounts of potassium and phosphate ions plus moderate quantities of magnesium and sulfate ions, all of which have low concentrations in the extracellular fluid. Also, cells contain large amounts of protein, almost four times as much as in the plasma.

Measurement of Fluid Volumes in the Different Body Fluid Compartments—the Indicator-Dilution Principle

The volume of a fluid compartment in the body can be measured by placing an indicator substance in the compartment, allowing it to disperse evenly throughout the compartment's fluid, and then analyzing the extent to which the

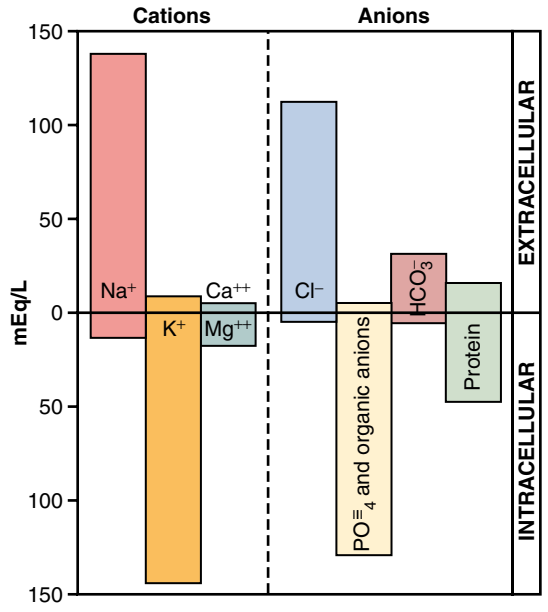


Figure 25-2 Major cations and anions of the intracellular and extracellular fluids. The concentrations of Ca^{++} and Mg^{++} represent the sum of these two ions. The concentrations shown represent the total of free ions and complexed ions.

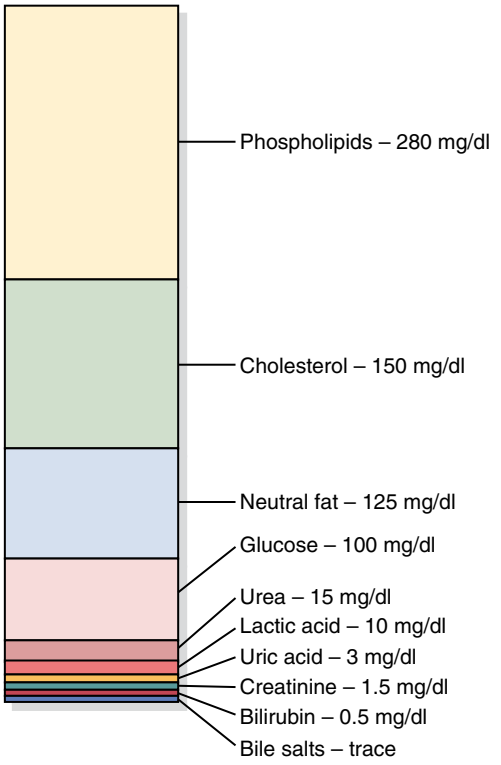


Figure 25-3 Nonelectrolytes of the plasma.

Table 25-2 Osmolar Substances in Extracellular and Intracellular Fluids

	Plasma (mOsm/L H_2O)	Interstitial (mOsm/L H_2O)	Intracellular (mOsm/L H_2O)
Na^+	142	139	14
K^+	4.2	4.0	140
Ca^{++}	1.3	1.2	0
Mg^{++}	0.8	0.7	20
Cl^-	108	108	4
HCO_3^-	24	28.3	10
$HPO_4^=$, $H_2PO_4^-$	2	2	11
$SO_4^=$	0.5	0.5	1
Phosphocreatine			45
Carnosine			14
Amino acids	2	2	8
Creatine	0.2	0.2	9
Lactate	1.2	1.2	1.5
Adenosine triphosphate			5
Hexose monophosphate			3.7
Glucose	5.6	5.6	
Protein	1.2	0.2	4
Urea	4	4	4
Others	4.8	3.9	10
Total mOsm/L	301.8	300.8	301.2
Corrected osmolar activity (mOsm/L)	282.0	281.0	281.0
Total osmotic pressure at 37°C (mm Hg)	5443	5423	5423

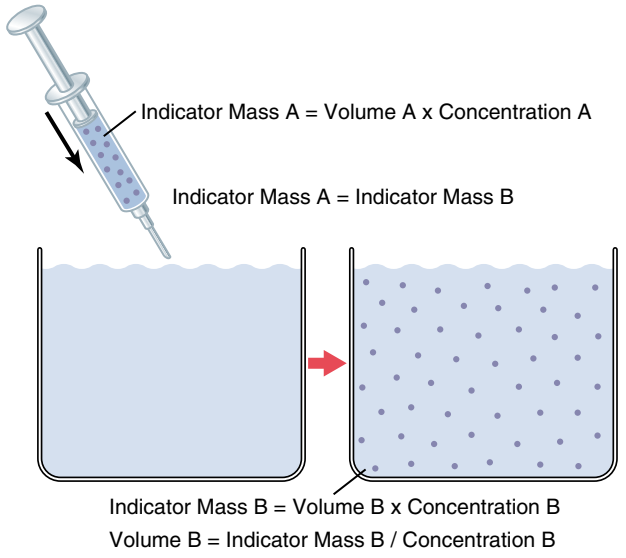


Figure 25-4 Indicator-dilution method for measuring fluid volumes.

substance becomes diluted. Figure 25-4 shows this "indicator-dilution" method of measuring the volume of a fluid compartment. This method is based on the conservation of mass principle, which means that the total mass of a substance after dispersion in the fluid compartment will be the same as the total mass injected into the compartment.

In the example shown in Figure 25-4, a small amount of dye or other substance contained in the syringe is injected into a chamber and the substance is allowed to disperse throughout the chamber until it becomes mixed in equal concentrations in all areas. Then a sample of fluid containing the dispersed substance is removed and the concentration is analyzed chemically, photoelectrically, or by other means. If none of the substance leaks out of the compartment, the total mass of substance in the compartment (Volume B × Concentration B) will equal the total mass of the substance injected (Volume A × Concentration A). By simple rearrangement of the equation, one can calculate the unknown volume of chamber B as

$$\text{Volume B} = \frac{\text{Volume A} \times \text{Concentration A}}{\text{Concentration B}}$$

Note that all one needs to know for this calculation is (1) the total amount of substance injected into the chamber (the numerator of the equation) and (2) the concentration of the fluid in the chamber after the substance has been dispersed (the denominator).

For example, if 1 milliliter of a solution containing 10 mg/ml of dye is dispersed into chamber B and the final concentration in the chamber is 0.01 milligram for each milliliter of fluid, the unknown volume of the chamber can be calculated as follows:

$$\text{Volume B} = \frac{1\ \text{ml} \times 10\ \text{mg/ml}}{0.01\ \text{mg/ml}} = 1000\ \text{ml}$$

This method can be used to measure the volume of virtually any compartment in the body as long as (1) the indicator disperses evenly throughout the compartment, (2) the indicator disperses only in the compartment that is being measured, and (3) the indicator is not metabolized or excreted. Several substances can be used to measure the volume of each of the different body fluids.

Determination of Volumes of Specific Body Fluid Compartments

Measurement of Total Body Water. Radioactive water (tritium, $^{3}H_2O$) or heavy water (deuterium, $^{2}H_2O$) can be used to measure total body water. These forms of water mix with the total body water within a few hours after being injected into the blood, and the dilution principle can be used to calculate total body water (Table 25-3). Another substance that has been used to measure total body water is *antipyrine,* which is very lipid soluble and can rapidly penetrate cell membranes and distribute itself uniformly throughout the intracellular and extracellular compartments.

Measurement of Extracellular Fluid Volume. The volume of extracellular fluid can be estimated using any of several substances that disperse in the plasma and interstitial fluid but do not readily permeate the cell membrane. They include radioactive sodium, radioactive chloride, radioactive iothalamate, thiosulfate ion, and inulin. When any one of these substances is injected into the blood, it usually disperses almost completely throughout the extracellular fluid within 30 to 60 minutes. Some of these substances, however, such as radioactive sodium, may diffuse into the cells in small amounts. Therefore, one frequently speaks of the *sodium space* or the *inulin space,* instead of calling the measurement the true extracellular fluid volume.

Table 25-3 Measurement of Body Fluid Volumes

Volume	Indicators
Total body water	$^{3}H_2O$, $^{2}H_2O$, antipyrine
Extracellular fluid	^{22}Na, ^{125}I-iothalamate, thiosulfate, inulin
Intracellular fluid	(Calculated as total body water – Extracellular fluid volume)
Plasma volume	^{125}I-albumin, Evans blue dye (T-1824)
Blood volume	^{51}Cr-labeled red blood cells, or calculated as blood volume = Plasma volume/(1 – Hematocrit)
Interstitial fluid	(Calculated as extracellular fluid volume – Plasma volume)

Calculation of Intracellular Volume. The intracellular volume cannot be measured directly. However, it can be calculated as

Intracellular volume = Total body water – Extracellular volume

Measurement of Plasma Volume. To measure plasma volume, a substance must be used that does not readily penetrate capillary membranes but remains in the vascular system after injection. One of the most commonly used substances for measuring plasma volume is serum albumin labeled with radioactive iodine (^{125}I-albumin). Also, dyes that avidly bind to the plasma proteins, such as *Evans blue dye* (also called *T-1824*), can be used to measure plasma volume.

Calculation of Interstitial Fluid Volume. Interstitial fluid volume cannot be measured directly, but it can be calculated as

Interstitial fluid volume = Extracellular fluid volume – Plasma volume

Measurement of Blood Volume. If one measures plasma volume using the methods described earlier, blood volume can also be calculated if one knows the *hematocrit* (the fraction of the total blood volume composed of cells), using the following equation:

$$\text{Total blood volume} = \frac{\text{Plasma volume}}{1 - \text{Hematocrit}}$$

For example, if plasma volume is 3 liters and hematocrit is 0.40, total blood volume would be calculated as

$$\frac{3 \text{ liters}}{1 - 0.4} = 5 \text{ liters}$$

Another way to measure blood volume is to inject into the circulation red blood cells that have been labeled with radioactive material. After these mix in the circulation, the radioactivity of a mixed blood sample can be measured and the total blood volume can be calculated using the indicator-dilution principle. A substance frequently used to label the red blood cells is radioactive chromium (^{51}Cr), which binds tightly with the red blood cells.

Regulation of Fluid Exchange and Osmotic Equilibrium Between Intracellular and Extracellular Fluid

A frequent problem in treating seriously ill patients is maintaining adequate fluids in one or both of the intracellular and extracellular compartments. As discussed in Chapter 16 and later in this chapter, the relative amounts of extracellular fluid distributed between the plasma and interstitial spaces are determined mainly by the balance of hydrostatic and colloid osmotic forces across the capillary membranes.

The distribution of fluid between intracellular and extracellular compartments, in contrast, is determined mainly by the osmotic effect of the smaller solutes—especially sodium, chloride, and other electrolytes—acting across the cell membrane. The reason for this is that the cell membranes are highly permeable to water but relatively impermeable to even small ions such as sodium and chloride. Therefore, water moves across the cell membrane rapidly and the intracellular fluid remains isotonic with the extracellular fluid.

In the next section, we discuss the interrelations between intracellular and extracellular fluid volumes and the osmotic factors that can cause shifts of fluid between these two compartments.

Basic Principles of Osmosis and Osmotic Pressure

The basic principles of osmosis and osmotic pressure were presented in Chapter 4. Therefore, we review here only the most important aspects of these principles as they apply to volume regulation.

Osmosis is the net diffusion of water across a selectively permeable membrane from a region of high water concentration to one that has a lower water concentration. When a solute is added to pure water, this reduces the concentration of water in the mixture. Thus, the higher the solute concentration in a solution, the lower the water concentration. Further, water diffuses from a region of low solute concentration (high water concentration) to one with a high solute concentration (low water concentration).

Because cell membranes are relatively impermeable to most solutes but highly permeable to water (i.e., selectively permeable), whenever there is a higher concentration of solute on one side of the cell membrane, water diffuses across the membrane toward the region of higher solute concentration. Thus, if a solute such as sodium chloride is added to the extracellular fluid, water rapidly diffuses from the cells through the cell membranes into the extracellular fluid until the water concentration on both sides of the membrane becomes equal. Conversely, if a solute such as sodium chloride is removed from the extracellular fluid, water diffuses from the extracellular fluid through the cell membranes and into the cells. The rate of diffusion of water is called the *rate of osmosis.*

Relation Between Moles and Osmoles. Because the water concentration of a solution depends on the number of solute particles in the solution, a concentration term is necessary to describe the total concentration of solute particles, regardless of their exact composition. The total number of particles in a solution is measured in *osmoles.* One osmole (osm) is equal to 1 mole (mol) (6.02×10^{23})

of solute particles. Therefore, a solution containing 1 mole of glucose in each liter has a concentration of 1 osm/L. If a molecule dissociates into two ions (giving two particles), such as sodium chloride ionizing to give chloride and sodium ions, then a solution containing 1 mol/L will have an osmolar concentration of 2 osm/L. Likewise, a solution that contains 1 mole of a molecule that dissociates into three ions, such as sodium sulfate (Na_2SO_4), will contain 3 osm/L. Thus, the term *osmole* refers to the number of osmotically active particles in a solution rather than to the molar concentration.

In general, the osmole is too large a unit for expressing osmotic activity of solutes in the body fluids.

The term *milliosmole* (mOsm), which equals 1/1000 osmole, is commonly used.

Osmolality and Osmolarity. The osmolal concentration of a solution is called *osmolality* when the concentration is expressed as *osmoles per kilogram of water;* it is called *osmolarity* when it is expressed as *osmoles per liter of solution.* In dilute solutions such as the body fluids, these two terms can be used almost synonymously because the differences are small. In most cases, it is easier to express body fluid quantities in liters of fluid rather than in kilograms of water. Therefore, most of the calculations used clinically and the calculations expressed in the next several chapters are based on osmolarities rather than osmolalities.

Calculation of the Osmolarity and Osmotic Pressure of a Solution. Using van't Hoff's law, one can calculate the potential osmotic pressure of a solution, assuming that the cell membrane is impermeable to the solute.

For example, the osmotic pressure of a 0.9 percent sodium chloride solution is calculated as follows: A 0.9 percent solution means that there is 0.9 gram of sodium chloride per 100 milliliters of solution, or 9 g/L. Because the molecular weight of sodium chloride is 58.5 g/mol, the molarity of the solution is 9 g/L divided by 58.5 g/mol, or about 0.154 mol/L. Because each molecule of sodium chloride is equal to 2 osmoles, the osmolarity of the solution is 0.154 × 2, or 0.308 osm/L. Therefore, the osmolarity of this solution is 308 mOsm/L. The potential osmotic pressure of this solution would therefore be 308 mOsm/L × 19.3 mm Hg/mOsm/L, or 5944 mm Hg.

This calculation is only an approximation because sodium and chloride ions do not behave entirely independently in solution because of interionic attraction between them. One can correct for these deviations from the predictions of van't Hoff's law by using a correction factor called the *osmotic coefficient.* For sodium chloride, the osmotic coefficient is about 0.93. Therefore, the actual osmolarity of a 0.9 percent sodium chloride solution is 308 × 0.93, or about 286 mOsm/L. For practical reasons, the osmotic coefficients of different solutes are sometimes neglected in determining the osmolarity and osmotic pressures of physiologic solutions.

Osmolarity of the Body Fluids. Turning back to Table 25-2, note the approximate osmolarity of the various osmotically active substances in plasma, interstitial fluid, and intracellular fluid. Note that about 80 percent of the total osmolarity of the interstitial fluid and plasma is due to sodium and chloride ions, whereas for intracellular fluid, almost half the osmolarity is due to potassium ions and the remainder is divided among many other intracellular substances.

As shown in Table 25-2, the total osmolarity of each of the three compartments is about 300 mOsm/L, with the plasma being about 1 mOsm/L greater than that of the interstitial and intracellular fluids. The slight difference between plasma and interstitial fluid is caused by the osmotic effects of the plasma proteins, which maintain about 20 mm Hg greater pressure in the capillaries than in the surrounding interstitial spaces, as discussed in Chapter 16.

Corrected Osmolar Activity of the Body Fluids. At the bottom of Table 25-2 are shown *corrected osmolar activities* of plasma, interstitial fluid, and intracellular fluid. The reason for these corrections is that cations and anions exert interionic attraction, which can cause a slight decrease in the osmotic "activity" of the dissolved substance.

Osmotic Equilibrium Is Maintained Between Intracellular and Extracellular Fluids

Large osmotic pressures can develop across the cell membrane with relatively small changes in the concentrations of solutes in the extracellular fluid. As discussed earlier, for each milliosmole concentration gradient of an *impermeant solute* (one that will not permeate the cell membrane), about 19.3 mm Hg osmotic pressure is exerted across the cell membrane. If the cell membrane is exposed to pure water and the osmolarity of intracellular fluid is 282 mOsm/L, the potential osmotic pressure that can develop across the cell membrane is more than 5400 mm Hg. This demonstrates the large force that can move water across the cell membrane when the intracellular and extracellular fluids are not in osmotic equilibrium. As a result of these forces, relatively small changes in the concentration of impermeant solutes in the extracellular fluid can cause large changes in cell volume.

Isotonic, Hypotonic, and Hypertonic Fluids. The effects of different concentrations of impermeant solutes in the extracellular fluid on cell volume are shown in Figure 25-5. If a cell is placed in a solution of impermeant solutes having an osmolarity of 282 mOsm/L, the cells

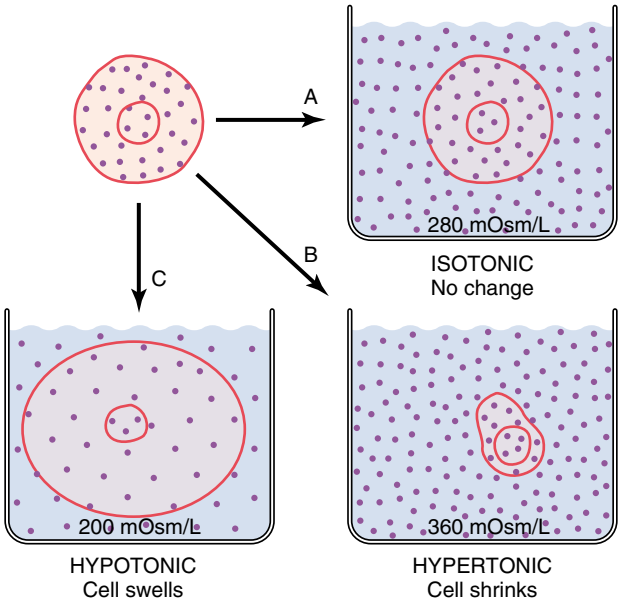


Figure 25-5 Effects of isotonic (*A*), hypertonic (*B*), and hypotonic (*C*) solutions on cell volume.

will not shrink or swell because the water concentration in the intracellular and extracellular fluids is equal and the solutes cannot enter or leave the cell. Such a solution is said to be *isotonic* because it neither shrinks nor swells the cells. Examples of isotonic solutions include a 0.9 percent solution of sodium chloride or a 5 percent glucose solution. These solutions are important in clinical medicine because they can be infused into the blood without the danger of upsetting osmotic equilibrium between the intracellular and extracellular fluids.

If a cell is placed into a *hypotonic* solution that has a lower concentration of impermeant solutes (<282 mOsm/L), water will diffuse into the cell, causing it to swell; water will continue to diffuse into the cell, diluting the intracellular fluid while also concentrating the extracellular fluid until both solutions have about the same osmolarity. Solutions of sodium chloride with a concentration of less than 0.9 percent are hypotonic and cause cells to swell.

If a cell is placed in a *hypertonic* solution having a higher concentration of impermeant solutes, water will flow out of the cell into the extracellular fluid, concentrating the intracellular fluid and diluting the extracellular fluid. In this case, the cell will shrink until the two concentrations become equal. Sodium chloride solutions of greater than 0.9 percent are hypertonic.

Isosmotic, Hyperosmotic, and Hypo-osmotic Fluids. The terms *isotonic, hypotonic,* and *hypertonic* refer to whether solutions will cause a change in cell volume. The tonicity of solutions depends on the concentration of impermeant solutes. Some solutes, however, can permeate the cell membrane. Solutions with an osmolarity the same as the cell are called *isosmotic,* regardless of whether the solute can penetrate the cell membrane.

The terms *hyperosmotic* and *hypo-osmotic* refer to solutions that have a higher or lower osmolarity, respectively, compared with the normal extracellular fluid, without regard for whether the solute permeates the cell membrane. Highly permeating substances, such as urea, can cause transient shifts in fluid volume between the intracellular and extracellular fluids, but given enough time, the concentrations of these substances eventually become equal in the two compartments and have little effect on intracellular volume under steady-state conditions.

Osmotic Equilibrium Between Intracellular and Extracellular Fluids Is Rapidly Attained. The transfer of fluid across the cell membrane occurs so rapidly that any differences in osmolarities between these two compartments are usually corrected within seconds or, at the most, minutes. This rapid movement of water across the cell membrane does not mean that complete equilibrium occurs between the intracellular and extracellular compartments throughout the whole body within the same short period. The reason for this is that fluid usually enters the body through the gut and must be transported by the blood to all tissues before complete osmotic equilibrium can occur. It usually takes about 30 minutes to achieve osmotic equilibrium everywhere in the body after drinking water.

Volume and Osmolality of Extracellular and Intracellular Fluids in Abnormal States

Some of the different factors that can cause extracellular and intracellular volumes to change markedly are ingestion of water, dehydration, intravenous infusion of different types of solutions, loss of large amounts of fluid from the gastrointestinal tract, and loss of abnormal amounts of fluid by sweating or through the kidneys.

One can calculate both the changes in intracellular and extracellular fluid volumes and the types of therapy that should be instituted if the following basic principles are kept in mind:

1. *Water moves rapidly across cell membranes;* therefore, the osmolarities of intracellular and extracellular fluids remain almost exactly equal to each other except for a few minutes after a change in one of the compartments.
2. *Cell membranes are almost completely impermeable to many solutes;* therefore, the number of osmoles in the extracellular or intracellular fluid generally remains constant unless solutes are added to or lost from the extracellular compartment.

With these basic principles in mind, we can analyze the effects of different abnormal fluid conditions on extracellular and intracellular fluid volumes and osmolarities.

Effect of Adding Saline Solution to the Extracellular Fluid

If an *isotonic* saline solution is added to the extracellular fluid compartment, the osmolarity of the extracellular fluid does not change; therefore, no osmosis occurs through the cell membranes. The only effect is an increase in extracellular fluid volume (Figure 25-6*A*). The sodium and chloride largely remain in the extracellular fluid because the cell membrane behaves as though it were virtually impermeable to the sodium chloride.

If a *hypertonic* solution is added to the extracellular fluid, the extracellular osmolarity increases and causes osmosis of water out of the cells into the extracellular compartment (see Figure 25-6*B*). Again, almost all the added sodium chloride remains in the extracellular compartment and fluid diffuses from the cells into the extracellular space to achieve osmotic equilibrium. The net effect is an increase in extracellular volume (greater than the volume of fluid added), a decrease in intracellular volume, and a rise in osmolarity in both compartments.

If a *hypotonic* solution is added to the extracellular fluid, the osmolarity of the extracellular fluid decreases and some of the extracellular water diffuses into the cells until the intracellular and extracellular compartments have the same osmolarity (see Figure 25-6*C*). Both the intracellular and the extracellular volumes are increased by the addition of hypotonic fluid, although the intracellular volume increases to a greater extent.

Calculation of Fluid Shifts and Osmolarities After Infusion of Hypertonic Saline. We can calculate the sequential effects of infusing different solutions on extracellular and intracellular fluid volumes and osmolarities. For example, if 2 liters of a hypertonic 3.0 percent sodium chloride solution are infused into the extracellular fluid compartment of a 70-kilogram patient whose initial plasma osmolarity is 280 mOsm/L, what would be the intracellular and extracellular fluid volumes and osmolarities after osmotic equilibrium?

The first step is to calculate the initial conditions, including the volume, concentration, and total milliosmoles in each compartment. Assuming that extracellular fluid volume is 20 percent of body weight and intracellular fluid volume is 40 percent of body weight, the following volumes and concentrations can be calculated.

Step 1. Initial Conditions

	Volume (Liters)	Concentration (mOsm/L)	Total (mOsm)
Extracellular fluid	14	280	3,920
Intracellular fluid	28	280	7,840
Total body fluid	42	280	11,760

Next, we calculate the total milliosmoles added to the extracellular fluid in 2 liters of 3.0 percent sodium chloride. A 3.0 percent solution means that there are 3.0 g/100 ml, or 30 grams of sodium chloride per liter. Because the molecular weight of sodium chloride is about 58.5 g/mol, this means that there is about 0.513 mole of sodium chloride per liter of solution. For 2 liters of solution, this would be 1.026 mole of sodium chloride. Because 1 mole of sodium chloride is about equal to 2 osmoles (sodium chloride has two osmotically active particles per

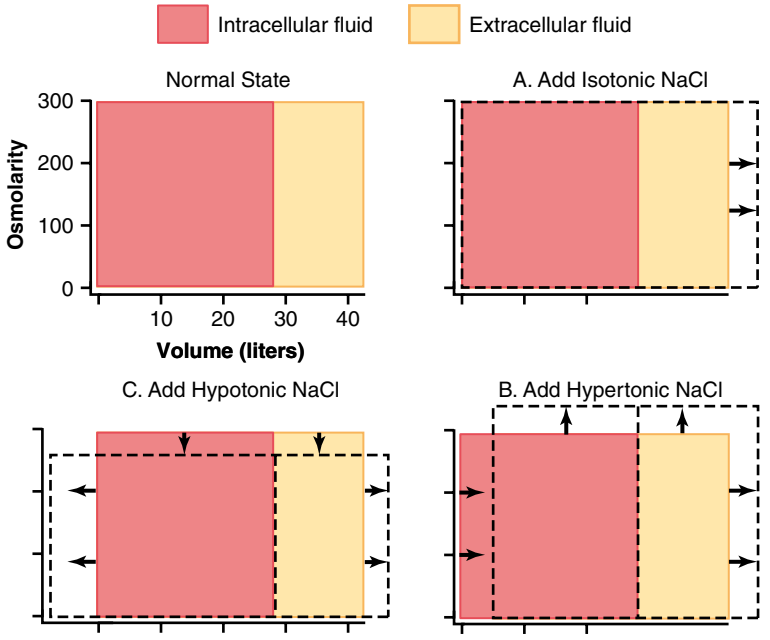


Figure 25-6 Effect of adding isotonic, hypertonic, and hypotonic solutions to the extracellular fluid after osmotic equilibrium. The normal state is indicated by the solid lines, and the shifts from normal are shown by the shaded areas. The volumes of intracellular and extracellular fluid compartments are shown in the abscissa of each diagram, and the osmolarities of these compartments are shown on the ordinates.

mole), the net effect of adding 2 liters of this solution is to add 2051 milliosmoles of sodium chloride to the extracellular fluid.

In Step 2, we calculate the instantaneous effect of adding 2051 milliosmoles of sodium chloride to the extracellular fluid along with 2 liters of volume. There would be no change in the *intracellular fluid* concentration or volume, and there would be no osmotic equilibrium. In the *extracellular fluid,* however, there would be an additional 2051 milliosmoles of total solute, yielding a total of 5791 milliosmoles. Because the extracellular compartment now has 16 liters of volume, the concentration can be calculated by dividing 5791 milliosmoles by 16 liters to yield a concentration of 373 mOsm/L. Thus, the following values would occur instantly after adding the solution.

Step 2. Instantaneous Effect of Adding 2 Liters of 3.0 Percent Sodium Chloride

	Volume (Liters)	Concentration (mOsm/L)	Total (mOsm)
Extracellular fluid	16	373	5,971
Intracellular fluid	28	280	7,840
Total body fluid	44	No equilibrium	13,811

In the third step, we calculate the volumes and concentrations that would occur within a few minutes after osmotic equilibrium develops. In this case, the concentrations in the intracellular and extracellular fluid compartments would be equal and can be calculated by dividing the total milliosmoles in the body, 13,811, by the total volume, which is now 44 liters. This yields a concentration of 313.9 mOsm/L. Therefore, all the body fluid compartments will have this same concentration after osmotic equilibrium. Assuming that no solute or water has been lost from the body and that there is no movement of sodium chloride into or out of the cells, we then calculate the volumes of the intracellular and extracellular compartments. The intracellular fluid volume is calculated by dividing the total milliosmoles in the intracellular fluid (7840) by the concentration (313.9 mOsm/L), to yield a volume of 24.98 liters. Extracellular fluid volume is calculated by dividing the total milliosmoles in extracellular fluid (5971) by the concentration (313.9 mOsm/L), to yield a volume of 19.02 liters. Again, these calculations are based on the assumption that the sodium chloride added to the extracellular fluid remains there and does not move into the cells.

Step 3. Effect of Adding 2 Liters of 3.0 Percent Sodium Chloride After Osmotic Equilibrium

	Volume (Liters)	Concentration (mOsm/L)	Total (mOsm)
Extracellular fluid	19.02	313.9	5,971
Intracellular fluid	24.98	313.9	7,840
Total body fluid	44.0	313.9	13,811

Thus, one can see from this example that adding 2 liters of a hypertonic sodium chloride solution causes more than a 5-liter increase in extracellular fluid volume while decreasing intracellular fluid volume by almost 3 liters.

This method of calculating changes in intracellular and extracellular fluid volumes and osmolarities can be applied to virtually any clinical problem of fluid volume regulation. The reader should be familiar with such calculations because an understanding of the mathematical aspects of osmotic equilibrium between intracellular and extracellular fluid compartments is essential for understanding almost all fluid abnormalities of the body and their treatment.

Glucose and Other Solutions Administered for Nutritive Purposes

Many types of solutions are administered intravenously to provide nutrition to people who cannot otherwise take adequate amounts of nutrition. Glucose solutions are widely used, and amino acid and homogenized fat solutions are used to a lesser extent. When these solutions are administered, their concentrations of osmotically active substances are usually adjusted nearly to isotonicity, or they are given slowly enough that they do not upset the osmotic equilibrium of the body fluids. After the glucose or other nutrients are metabolized, an excess of water often remains, especially if additional fluid is ingested. Ordinarily, the kidneys excrete this in the form of a very dilute urine. The net result, therefore, is the addition of only nutrients to the body.

Clinical Abnormalities of Fluid Volume Regulation: Hyponatremia and Hypernatremia

The primary measurement that is readily available to the clinician for evaluating a patient's fluid status is the plasma sodium concentration. Plasma osmolarity is not routinely measured, but because sodium and its associated anions (mainly chloride) account for more than 90 percent of the solute in the extracellular fluid, plasma sodium concentration is a reasonable indicator of plasma osmolarity under many conditions. When plasma sodium concentration is reduced more than a few milliequivalents below normal (about 142 mEq/L), a person is said to have *hyponatremia.* When plasma sodium concentration is elevated above normal, a person is said to have *hypernatremia.*

Causes of Hyponatremia: Excess Water or Loss of Sodium

Decreased plasma sodium concentration can result from loss of sodium chloride from the extracellular fluid or addition of excess water to the extracellular fluid (Table 25-4).

Table 25-4 Abnormalities of Body Fluid Volume Regulation: Hyponatremia and Hypernatremia

Abnormality	Cause	Plasma Na^+ Concentration	Extracellular Fluid Volume	Intracellular Fluid Volume
Hyponatremia—dehydration	Adrenal insufficiency; overuse of diuretics	↓	↓	↑
Hyponatremia—overhydration	Excess ADH (SIADH); bronchogenic tumors	↓	↑	↑
Hypernatremia—dehydration	Diabetes insipidus; excessive sweating	↑	↓	↓
Hypernatremia—overhydration	Cushing's disease; primary aldosteronism	↑	↑	↓

ADH, antidiuretic hormone; SIADH, syndrome of inappropriate ADH.

A primary loss of sodium chloride usually results in *hyponatremia—dehydration* and is associated with decreased extracellular fluid volume. Conditions that can cause hyponatremia owing to loss of sodium chloride include *diarrhea* and *vomiting*. *Overuse of diuretics* that inhibit the ability of the kidneys to conserve sodium and certain types of sodium-wasting kidney diseases can also cause modest degrees of hyponatremia. Finally, *Addison's disease,* which results from decreased secretion of the hormone aldosterone, impairs the ability of the kidneys to reabsorb sodium and can cause a modest degree of hyponatremia.

Hyponatremia can also be associated with excess water retention, which dilutes the sodium in the extracellular fluid, a condition that is referred to as *hyponatremia—overhydration.* For example, *excessive secretion of antidiuretic hormone,* which causes the kidney tubules to reabsorb more water, can lead to hyponatremia and overhydration.

Consequences of Hyponatremia: Cell Swelling

Rapid changes in cell volume as a result of hyponatremia can have profound effects on tissue and organ function, especially the brain. A rapid reduction in plasma sodium concentration, for example, can cause brain cell edema and neurological symptoms, including headache, nausea, lethargy, and disorientation. If plasma sodium concentration rapidly falls below 115 to 120 mmol/L, brain swelling may lead to seizures, coma, permanent brain damage, and death. Because the skull is rigid, the brain cannot increase its volume by more than about 10 percent without it being forced down the neck *(herniation),* which can lead to permanent brain injury and death.

When hyponatremia evolves more slowly over several days, the brain and other tissues respond by transporting sodium, chloride, potassium, and organic solutes, such as glutamate, from the cells into the extracellular compartment. This attenuates osmotic flow of water into the cells and swelling of the tissues (Figure 25-7).

Transport of solutes from the cells during slowly developing hyponatremia, however, can make the brain vulnerable to injury if the hyponatremia is corrected too rapidly. When hypertonic solutions are added too rapidly to correct hyponatremia, this can outpace the brain's ability to recapture the solutes lost from the cells and may lead to osmotic injury of the neurons that is associated with *demyelination,* a loss of the myelin sheath from nerves. This osmotic-mediated demyelination of neurons can be avoided by limiting the correction of chronic hyponatremia to less than 10 to 12 mmol/L in 24 hours and to less than 18 mmol/L in 48 hours. This slow rate of correction permits the brain to recover the lost osmoles that have occurred as a result of adaptation to chronic hyponatremia.

Hyponatremia is the most common electrolyte disorder encountered in clinical practice and may occur in up to 15% to 25% of hospitalized patients.

Causes of Hypernatremia: Water Loss or Excess Sodium

Increased plasma sodium concentration, which also causes increased osmolarity, can be due to either loss of water from the extracellular fluid, which concentrates the sodium ions, or excess sodium in the extracellular fluid. When there is primary loss of water from the extracellular fluid, this results in *hypernatremia—dehydration.* This condition can occur from an inability to secrete antidiuretic hormone, which is needed for the kidneys to conserve water. As a result of lack of antidiuretic hormone, the kidneys excrete large amounts of dilute urine (a disorder referred to as *diabetes insipidus*), causing dehydration and increased concentration of sodium chloride in the extracellular fluid. In certain types of renal diseases, the kidneys cannot respond to antidiuretic hormone, also causing a type of *nephrogenic diabetes insipidus.* A more common cause of hypernatremia associated with decreased extracellular fluid volume is *dehydration* caused by water intake that is less than water loss, as can occur with sweating during prolonged, heavy exercise.

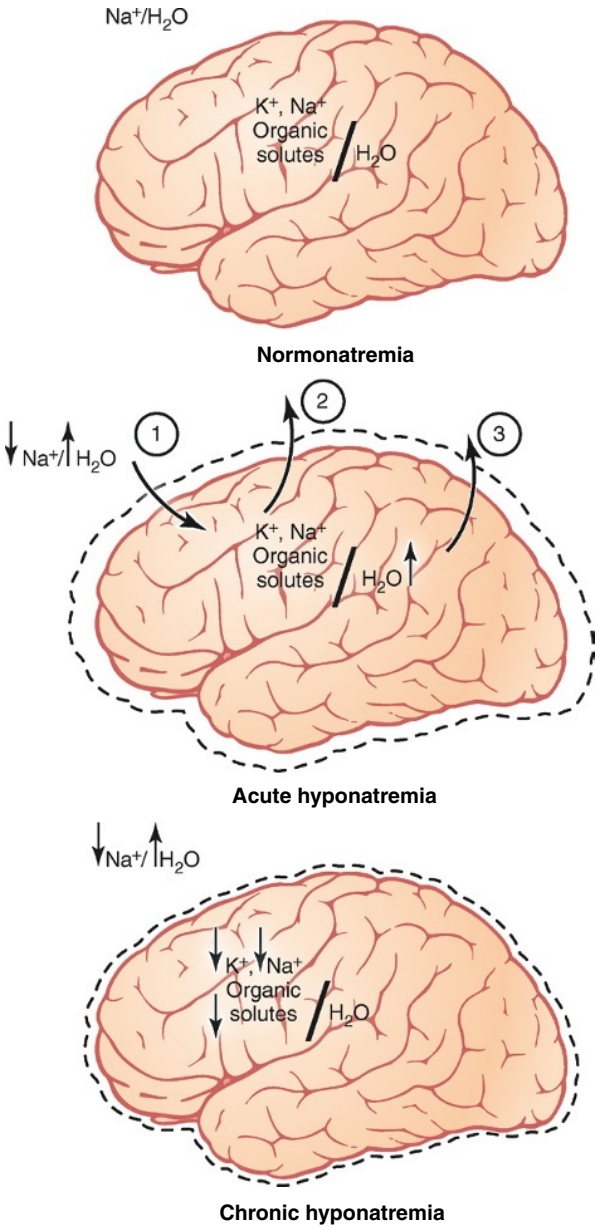


Figure 25-7 Brain cell volume regulation during hyponatremia. During acute hyponatremia, caused by loss of Na^+ or excess H_2O, there is diffusion of H_2O into the cells (*1*) and swelling of the brain tissue. This stimulates transport of Na^+, K^+, and organic solutes out of the cells (*2*), which then cause water diffusion out of the cells (*3*). With chronic hyponatremia, the brain swelling is attenuated by the transport of solutes from the cells.

Hypernatremia can also occur as a result of excessive sodium chloride added to the extracellular fluid. This often results in *hypernatremia—overhydration* because excess extracellular sodium chloride is usually associated with at least some degree of water retention by the kidneys as well. For example, *excessive secretion of the sodium-retaining hormone aldosterone* can cause a mild degree of hypernatremia and overhydration. The reason that the hypernatremia is not more severe is that increased aldosterone secretion causes the kidneys to reabsorb greater amounts of water, as well as sodium.

Thus, in analyzing abnormalities of plasma sodium concentration and deciding on proper therapy, one should first determine whether the abnormality is caused by a primary loss or gain of sodium or a primary loss or gain of water.

Consequences of Hypernatremia: Cell Shrinkage

Hypernatremia is much less common than hyponatremia and severe symptoms usually occur only with rapid and large increases in plasma sodium concentration above 158 to 160 mmol/L. One reason for this is that hypernatremia promotes intense thirst that protects against a large increase in plasma and extracellular fluid sodium, as discussed in Chapter 28. However, severe hypernatremia can occur in patients with hypothalamic lesions that impair their sense of thirst, in infants who may not have ready access to water, or elderly patients with altered mental status.

Correction of hypernatremia can be achieved by administering hypo-osmotic sodium chloride or dextrose solutions. However, it is prudent to correct the hypernatremia slowly in patients who have had chronic increases in plasma sodium concentration. The reason for this is that hypernatremia also activates defense mechanisms that protect the cell from changes in volume. These defense mechanisms are opposite to those that occur for hyponatremia and consist of mechanisms that increase the intracellular concentration of sodium and other solutes.

Edema: Excess Fluid in the Tissues

Edema refers to the presence of excess fluid in the body tissues. In most instances, edema occurs mainly in the extracellular fluid compartment, but it can involve intracellular fluid as well.

Intracellular Edema

Three conditions are especially prone to cause intracellular swelling: (1) hyponatremia, as discussed earlier; (2) depression of the metabolic systems of the tissues; and (3) lack of adequate nutrition to the cells. For example, when blood flow to a tissue is decreased, the delivery of oxygen and nutrients is reduced. If the blood flow becomes too low to maintain normal tissue metabolism, the cell membrane ionic pumps become depressed. When this occurs, sodium ions that normally leak into the interior of the cell can no longer be pumped out of the cells and the excess intracellular sodium ions cause osmosis of water into the cells. Sometimes this can increase intracellular volume of a tissue area—even of an entire ischemic leg, for example—to two to three times normal. When this occurs, it is usually a prelude to death of the tissue.

Intracellular edema can also occur in inflamed tissues. Inflammation usually increases cell membrane permeability, allowing sodium and other ions to diffuse into the interior of the cell, with subsequent osmosis of water into the cells.

Extracellular Edema

Extracellular fluid edema occurs when there is excess fluid accumulation in the extracellular spaces. There are two general causes of extracellular edema: (1) abnormal leakage of fluid from the plasma to the interstitial spaces across the capillaries, and (2) failure of the lymphatics to return fluid from the interstitium back into the blood, often called *lymphedema*. The most common clinical cause of interstitial fluid accumulation is excessive capillary fluid filtration.

Factors That Can Increase Capillary Filtration

To understand the causes of excessive capillary filtration, it is useful to review the determinants of capillary filtration discussed in Chapter 16. Mathematically, capillary filtration rate can be expressed as

$$\text{Filtration} = K_f \times (P_c - P_{if} - \pi_c + \pi_{if}),$$

where K_f is the capillary filtration coefficient (the product of the permeability and surface area of the capillaries), P_c is the capillary hydrostatic pressure, P_{if} is the interstitial fluid hydrostatic pressure, π_c is the capillary plasma colloid osmotic pressure, and π_{if} is the interstitial fluid colloid osmotic pressure. From this equation, one can see *that any one of the following changes can increase the capillary filtration rate:*

- Increased capillary filtration coefficient.
- Increased capillary hydrostatic pressure.
- Decreased plasma colloid osmotic pressure.

Lymphedema—Failure of the Lymph Vessels to Return Fluid and Protein to the Blood

When lymph vessel function is greatly impaired, due to blockage or loss of the lymph vessels, edema can become especially severe because plasma proteins that leak into the interstitium have no other way to be removed. The rise in protein concentration raises the colloid osmotic pressure of the interstitial fluid, which draws even more fluid out of the capillaries.

Blockage of lymph flow can be especially severe with infections of the lymph nodes, such as occurs with infection by *filaria nematodes (Wuchereria bancrofti),* which are microscopic, threadlike worms. The adult worms live in the human lymph system and are spread from person to person by mosquitoes. People with filarial infections can suffer from severe lymphedema and *elephantiasis* and in men, swelling of the scrotum, called *hydrocele*. Lymphatic filariasis affects over 120 million people in 80 countries throughout the tropics and subtropics of Asia, Africa, the Western Pacific, and parts of the Caribbean and South America.

Lymphedema can also occur in certain types of cancer or after surgery in which lymph vessels are removed or obstructed. For example, large numbers of lymph vessels are removed during radical mastectomy, impairing removal of fluid from the breast and arm areas and causing edema and swelling of the tissue spaces. A few lymph vessels eventually regrow after this type of surgery, so the interstitial edema is usually temporary.

Summary of Causes of Extracellular Edema

A large number of conditions can cause fluid accumulation in the interstitial spaces by abnormal leaking of fluid from the capillaries or by preventing the lymphatics from returning fluid from the interstitium back to the circulation. The following is a partial list of conditions that can cause extracellular edema by these two types of abnormalities:

- **I.** Increased capillary pressure
  - **A.** Excessive kidney retention of salt and water
    - **1.** Acute or chronic kidney failure
    - **2.** Mineralocorticoid excess
  - **B.** High venous pressure and venous constriction
    - **1.** Heart failure
    - **2.** Venous obstruction
    - **3.** Failure of venous pumps
      - **(a)** Paralysis of muscles
      - **(b)** Immobilization of parts of the body
      - **(c)** Failure of venous valves
  - **C.** Decreased arteriolar resistance
    - **1.** Excessive body heat
    - **2.** Insufficiency of sympathetic nervous system
    - **3.** Vasodilator drugs
- **II.** Decreased plasma proteins
  - **A.** Loss of proteins in urine (nephrotic syndrome)
  - **B.** Loss of protein from denuded skin areas
    - **1.** Burns
    - **2.** Wounds
  - **C.** Failure to produce proteins
    - **1.** Liver disease (e.g., cirrhosis)
    - **2.** Serious protein or caloric malnutrition
- **III.** Increased capillary permeability
  - **A.** Immune reactions that cause release of histamine and other immune products
  - **B.** Toxins
  - **C.** Bacterial infections
  - **D.** Vitamin deficiency, especially vitamin C
  - **E.** Prolonged ischemia
  - **F.** Burns
- **IV.** Blockage of lymph return
  - **A.** Cancer
  - **B.** Infections (e.g., filaria nematodes)
  - **C.** Surgery
  - **D.** Congenital absence or abnormality of lymphatic vessels

Edema Caused by Heart Failure. One of the most serious and most common causes of edema is heart failure. In heart failure, the heart fails to pump blood normally from the veins into the arteries; this raises venous pressure and capillary pressure, causing increased capillary filtration. In addition, the arterial pressure tends to fall, causing decreased excretion of salt and water by the kidneys, which increases blood volume and further raises capillary hydrostatic pressure to cause still more edema. Also, blood flow to the kidneys is reduced in heart failure and this stimulates secretion of renin, causing increased formation of angiotensin II and increased secretion of aldosterone, both of which cause additional salt and water retention by the kidneys. Thus, in untreated heart failure, all these factors acting together cause serious generalized extracellular edema.

In patients with left-sided heart failure but without significant failure of the right side of the heart, blood is pumped into the lungs normally by the right side of the heart but cannot escape easily from the pulmonary veins to the left side of the heart because this part of the heart has been greatly weakened. Consequently, all the pulmonary vascular pressures, including pulmonary capillary pressure, rise far above normal, causing serious and life-threatening pulmonary edema. When untreated, fluid accumulation in the lungs can rapidly progress, causing death within a few hours.

Edema Caused by Decreased Kidney Excretion of Salt and Water. As discussed earlier, most sodium chloride added to the blood remains in the extracellular compartment, and only small amounts enter the cells. Therefore, in kidney diseases that compromise urinary excretion of salt and water, large amounts of sodium chloride and water are added to the extracellular fluid. Most of this salt and water leaks from the blood into the interstitial spaces, but some remains in the blood. The main effects of this are to cause (1) widespread increases in interstitial fluid volume (extracellular edema) and (2) hypertension because of the increase in blood volume, as explained in Chapter 19. As an example, children who develop acute glomerulonephritis, in which the renal glomeruli are injured by inflammation and therefore fail to filter adequate amounts of fluid, also develop serious extracellular fluid edema in the entire body; along with the edema, these children usually develop severe hypertension.

Edema Caused by Decreased Plasma Proteins. A reduction in plasma concentration of proteins because of either failure to produce normal amounts of proteins or leakage of proteins from the plasma causes the plasma colloid osmotic pressure to fall. This leads to increased capillary filtration throughout the body and extracellular edema.

One of the most important causes of decreased plasma protein concentration is loss of proteins in the urine in certain kidney diseases, a condition referred to as *nephrotic syndrome.* Multiple types of renal diseases can damage the membranes of the renal glomeruli, causing the membranes to become leaky to the plasma proteins and often allowing large quantities of these proteins to pass into the urine. When this loss exceeds the ability of the body to synthesize proteins, a reduction in plasma protein concentration occurs. Serious generalized edema occurs when the plasma protein concentration falls below 2.5 g/100 ml.

Cirrhosis of the liver is another condition that causes a reduction in plasma protein concentration. Cirrhosis means development of large amounts of fibrous tissue among the liver parenchymal cells. One result is failure of these cells to produce sufficient plasma proteins, leading to decreased plasma colloid osmotic pressure and the generalized edema that goes with this condition.

Another way liver cirrhosis causes edema is that the liver fibrosis sometimes compresses the abdominal portal venous drainage vessels as they pass through the liver before emptying back into the general circulation. Blockage of this portal venous outflow raises capillary hydrostatic pressure throughout the gastrointestinal area and further increases filtration of fluid out of the plasma into the intra-abdominal areas. When this occurs, the combined effects of decreased plasma protein concentration and high portal capillary pressures cause transudation of large amounts of fluid and protein into the abdominal cavity, a condition referred to as *ascites.*

Safety Factors That Normally Prevent Edema

Even though many disturbances can cause edema, usually the abnormality must be severe before serious edema develops. The reason for this is that three major safety factors prevent excessive fluid accumulation in the interstitial spaces: (1) low compliance of the interstitium when interstitial fluid pressure is in the negative pressure range, (2) the ability of lymph flow to increase 10- to 50-fold, and (3) washdown of interstitial fluid protein concentration, which reduces interstitial fluid colloid osmotic pressure as capillary filtration increases.

Safety Factor Caused by Low Compliance of the Interstitium in the Negative Pressure Range

In Chapter 16, we noted that interstitial fluid hydrostatic pressure in most loose subcutaneous tissues of the body is slightly less than atmospheric pressure, averaging about −3 mm Hg. This slight suction in the tissues helps hold the tissues together. Figure 25-8 shows the approximate relations between different levels of interstitial fluid pressure and interstitial fluid volume, as extrapolated to the human being from animal studies. Note in Figure 25-8 that as long as the interstitial fluid pressure is in the negative range, small changes in interstitial fluid volume are associated with relatively large changes in interstitial fluid hydrostatic pressure. Therefore, in the negative pressure range, the *compliance* of the tissues, defined as the change in volume per millimeter of mercury pressure change, is low.

How does the low compliance of the tissues in the negative pressure range act as a safety factor against edema? To answer this question, recall the determinants of capillary

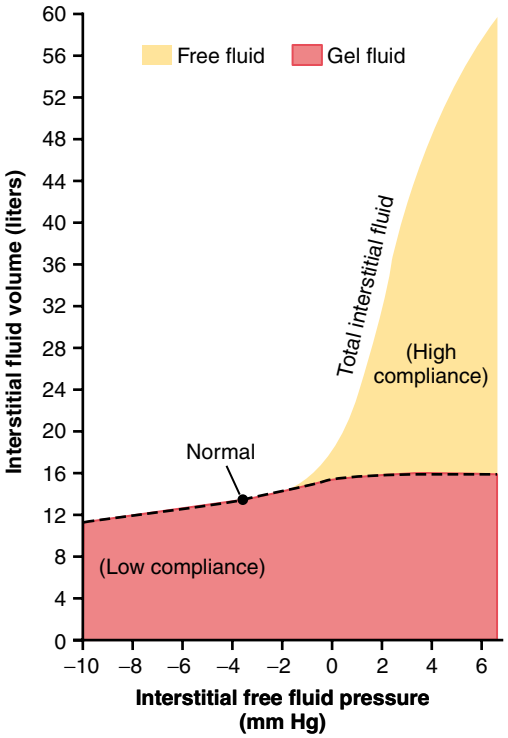


Figure 25-8 Relation between interstitial fluid hydrostatic pressure and interstitial fluid volumes, including total volume, free fluid volume, and gel fluid volume, for loose tissues such as skin. Note that significant amounts of free fluid occur only when the interstitial fluid pressure becomes positive. (Modified from Guyton AC, Granger HJ, Taylor AE: Interstitial fluid pressure. Physiol Rev 51:527, 1971.)

filtration discussed previously. When interstitial fluid hydrostatic pressure increases, this increased pressure tends to oppose further capillary filtration. Therefore, as long as the interstitial fluid hydrostatic pressure is in the negative pressure range, small increases in interstitial fluid volume cause relatively large increases in interstitial fluid hydrostatic pressure, opposing further filtration of fluid into the tissues.

Because the normal interstitial fluid hydrostatic pressure is –3 mm Hg, the interstitial fluid hydrostatic pressure must increase by about 3 mm Hg before large amounts of fluid will begin to accumulate in the tissues. Therefore, the safety factor against edema is a change of interstitial fluid pressure of about 3 mm Hg.

Once interstitial fluid pressure rises above 0 mm Hg, the compliance of the tissues increases markedly, allowing large amounts of fluid to accumulate in the tissues with relatively small additional increases in interstitial fluid hydrostatic pressure. Thus, in the positive tissue pressure range, this safety factor against edema is lost because of the large increase in compliance of the tissues.

Importance of Interstitial Gel in Preventing Fluid Accumulation in the Interstitium. Note in Figure 25-8 that in normal tissues with negative interstitial fluid pressure, virtually all the fluid in the interstitium is in gel form. That is, the fluid is bound in a proteoglycan meshwork so that there are virtually no "free" fluid spaces larger than a few hundredths of a micrometer in diameter. The importance of the gel is that it prevents fluid from *flowing* easily through the tissues because of impediment from the "brush pile" of trillions of proteoglycan filaments. Also, when the interstitial fluid pressure falls to very negative values, the gel does not contract greatly because the meshwork of proteoglycan filaments offers an elastic resistance to compression. In the negative fluid pressure range, the interstitial fluid volume does not change greatly, regardless of whether the degree of suction is only a few millimeters of mercury negative pressure or 10 to 20 mm Hg negative pressure. In other words, the compliance of the tissues is very low in the negative pressure range.

By contrast, when interstitial fluid pressure rises to the positive pressure range, there is a tremendous accumulation of *free fluid* in the tissues. In this pressure range, the tissues are compliant, allowing large amounts of fluid to accumulate with relatively small additional increases in interstitial fluid hydrostatic pressure. Most of the extra fluid that accumulates is "free fluid" because it pushes the brush pile of proteoglycan filaments apart. Therefore, the fluid can flow freely through the tissue spaces because it is not in gel form. When this occurs, the edema is said to be *pitting edema* because one can press the thumb against the tissue area and push the fluid out of the area. When the thumb is removed, a pit is left in the skin for a few seconds until the fluid flows back from the surrounding tissues. This type of edema is distinguished from *nonpitting edema,* which occurs when the tissue cells swell instead of the interstitium or when the fluid in the interstitium becomes clotted with fibrinogen so that it cannot move freely within the tissue spaces.

Importance of the Proteoglycan Filaments as a "Spacer" for the Cells and in Preventing Rapid Flow of Fluid in the Tissues. The proteoglycan filaments, along with much larger collagen fibrils in the interstitial spaces, act as a "spacer" between the cells. Nutrients and ions do not diffuse readily through cell membranes; therefore, without adequate spacing between the cells, these nutrients, electrolytes, and cell waste products could not be rapidly exchanged between the blood capillaries and cells located at a distance from one another.

The proteoglycan filaments also prevent fluid from flowing too easily through the tissue spaces. If it were not for the proteoglycan filaments, the simple act of a person standing up would cause large amounts of interstitial fluid to flow from the upper body to the lower body. When too much fluid accumulates in the interstitium, as occurs in edema, this extra fluid creates large channels that allow the fluid to flow readily through the interstitium. Therefore, when severe edema occurs in the legs, the edema fluid often can be decreased by simply elevating the legs.

Even though fluid does not *flow* easily through the tissues in the presence of the compacted proteoglycan filaments, different substances within the fluid can *diffuse* through the tissues at least 95 percent as easily as they normally diffuse. Therefore, the usual diffusion of nutrients to the cells and the removal of waste products from the cells are not compromised by the proteoglycan filaments of the interstitium.

Increased Lymph Flow as a Safety Factor Against Edema

A major function of the lymphatic system is to return to the circulation the fluid and proteins filtered from the capillaries into the interstitium. Without this continuous return of the filtered proteins and fluid to the blood, the plasma volume would be rapidly depleted, and interstitial edema would occur.

The lymphatics act as a safety factor against edema because lymph flow can increase 10- to 50-fold when fluid begins to accumulate in the tissues. This allows the lymphatics to carry away large amounts of fluid and proteins in response to increased capillary filtration, preventing the interstitial pressure from rising into the positive pressure range. The safety factor caused by increased lymph flow has been calculated to be about 7 mm Hg.

"Washdown" of the Interstitial Fluid Protein as a Safety Factor Against Edema

As increased amounts of fluid are filtered into the interstitium, the interstitial fluid pressure increases, causing increased lymph flow. In most tissues the protein concentration of the interstitium decreases as lymph flow is increased, because larger amounts of protein are carried away than can be filtered out of the capillaries; the reason for this is that the capillaries are relatively impermeable to proteins, compared with the lymph vessels. Therefore, the proteins are "washed out" of the interstitial fluid as lymph flow increases.

Because the interstitial fluid colloid osmotic pressure caused by the proteins tends to draw fluid out of the capillaries, decreasing the interstitial fluid proteins lowers the net filtration force across the capillaries and tends to prevent further accumulation of fluid. The safety factor from this effect has been calculated to be about 7 mm Hg.

Summary of Safety Factors That Prevent Edema

Putting together all the safety factors against edema, we find the following:

1. The safety factor caused by low tissue compliance in the negative pressure range is about 3 mm Hg.
2. The safety factor caused by increased lymph flow is about 7 mm Hg.
3. The safety factor caused by washdown of proteins from the interstitial spaces is about 7 mm Hg.

Therefore, the total safety factor against edema is about 17 mm Hg. This means that the capillary pressure in a peripheral tissue could theoretically rise by 17 mm Hg, or approximately double the normal value, before marked edema would occur.

Fluids in the "Potential Spaces" of the Body

Some examples of "potential spaces" are pleural cavity, pericardial cavity, peritoneal cavity, and synovial cavities, including both the joint cavities and the bursae. Virtually all these potential spaces have surfaces that almost touch each other, with only a thin layer of fluid in between, and the surfaces slide over each other. To facilitate the sliding, a viscous proteinaceous fluid lubricates the surfaces.

Fluid Is Exchanged Between the Capillaries and the Potential Spaces. The surface membrane of a potential space usually does not offer significant resistance to the passage of fluids, electrolytes, or even proteins, which all move back and forth between the space and the interstitial fluid in the surrounding tissue with relative ease. Therefore, each potential space is in reality a large tissue space. Consequently, fluid in the capillaries adjacent to the potential space diffuses not only into the interstitial fluid but also into the potential space.

Lymphatic Vessels Drain Protein from the Potential Spaces. Proteins collect in the potential spaces because of leakage out of the capillaries, similar to the collection of protein in the interstitial spaces throughout the body. The protein must be removed through lymphatics or other channels and returned to the circulation. Each potential space is either directly or indirectly connected with lymph vessels. In some cases, such as the pleural cavity and peritoneal cavity, large lymph vessels arise directly from the cavity itself.

Edema Fluid in the Potential Spaces Is Called "Effusion." When edema occurs in the subcutaneous tissues adjacent to the potential space, edema fluid usually collects in the potential space as well and this fluid is called *effusion.* Thus, lymph blockage or any of the multiple abnormalities that can cause excessive capillary filtration can cause effusion in the same way that interstitial edema is caused. The abdominal cavity is especially prone to collect effusion fluid, and in this instance, the effusion is called *ascites.* In serious cases, 20 liters or more of ascitic fluid can accumulate.

The other potential spaces, such as the pleural cavity, pericardial cavity, and joint spaces, can become seriously swollen when there is generalized edema. Also, injury or local infection in any one of the cavities often blocks the lymph drainage, causing isolated swelling in the cavity.

The dynamics of fluid exchange in the pleural cavity are discussed in detail in Chapter 38. These dynamics are mainly representative of all the other potential spaces as well. It is especially interesting that the normal fluid pressure in most or all of the potential spaces in the nonedematous state is *negative* in the same way that this pressure is negative (subatmospheric) in loose subcutaneous tissue. For instance, the interstitial fluid hydrostatic pressure is normally about −7 to −8 mm Hg in the pleural cavity, −3 to −5 mm Hg in the joint spaces, and −5 to −6 mm Hg in the pericardial cavity.

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