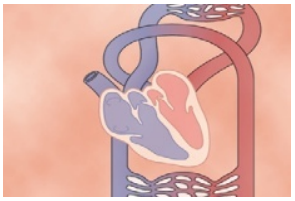
Overview of the Circulation; Biophysics of Pressure, Flow, and Resistance



The function of the circulation is to service the needs of the body tissues—to transport nutrients to the body tissues, to transport waste products away, to transport hormones from one part of the body to another, and, in general, to maintain an appropriate environment in all the tissue fluids of the body for optimal survival and function of the cells.

The rate of blood flow through many tissues is controlled mainly in response to tissue need for nutrients. In some organs, such as the kidneys, the circulation serves additional functions. Blood flow to the kidney, for example, is far in excess of its metabolic requirements and is related to its excretory function, which demands that a large volume of blood be filtered each minute.

The heart and blood vessels, in turn, are controlled to provide the necessary cardiac output and arterial pressure to cause the needed tissue blood flow. What are the mechanisms for controlling blood volume and blood flow, and how does this relate to all the other functions of the circulation? These are some of the topics and questions that we discuss in this section on the circulation.

Physical Characteristics of the Circulation

The circulation, shown in Figure 14-1, is divided into the *systemic circulation* and the *pulmonary circulation.* Because the systemic circulation supplies blood flow to all the tissues of the body except the lungs, it is also called the *greater circulation* or *peripheral circulation.*

Functional Parts of the Circulation. Before discussing the details of circulatory function, it is important to understand the role of each part of the circulation.

The function of the *arteries* is to transport blood *under high pressure* to the tissues. For this reason, the arteries have strong vascular walls, and blood flows at a high velocity in the arteries.

The *arterioles* are the last small branches of the arterial system; they act as *control conduits* through which blood is released into the capillaries. Arterioles have strong muscular walls that can close the arterioles completely or can, by relaxing, dilate the vessels severalfold, thus having the capability of vastly altering blood flow in each tissue in response to its needs.

The function of the *capillaries* is to exchange fluid, nutrients, electrolytes, hormones, and other substances between the blood and the interstitial fluid. To serve this role, the capillary walls are very thin and have numerous minute *capillary pores* permeable to water and other small molecular substances.

The *venules* collect blood from the capillaries and gradually coalesce into progressively larger veins.

The *veins* function as conduits for transport of blood from the venules back to the heart; equally important, they serve as a major reservoir of extra blood. Because the pressure in the venous system is very low, the venous walls are thin. Even so, they are muscular enough to contract or expand and thereby act as a controllable reservoir for the extra blood, either a small or a large amount, depending on the needs of the circulation.

Volumes of Blood in the Different Parts of the Circulation. Figure 14-1 gives an overview of the circulation and lists the percentage of the total blood volume in major segments of the circulation. For instance, about 84 percent of the entire blood volume of the body is in the systemic circulation and 16 percent is in the heart and lungs. Of the 84 percent in the systemic circulation, 64 percent is in the veins, 13 percent in the arteries, and 7 percent in the systemic arterioles and capillaries. The heart contains 7 percent of the blood, and the pulmonary vessels, 9 percent.

Most surprising is the low blood volume in the capillaries. It is here, however, that the most important function of the circulation occurs, diffusion of substances back and forth between the blood and the tissues. This function is discussed in detail in Chapter 16.

Cross-Sectional Areas and Velocities of Blood Flow. If all the *systemic vessels* of each type were put side by side, their approximate total cross-sectional areas for the average human being would be as follows:

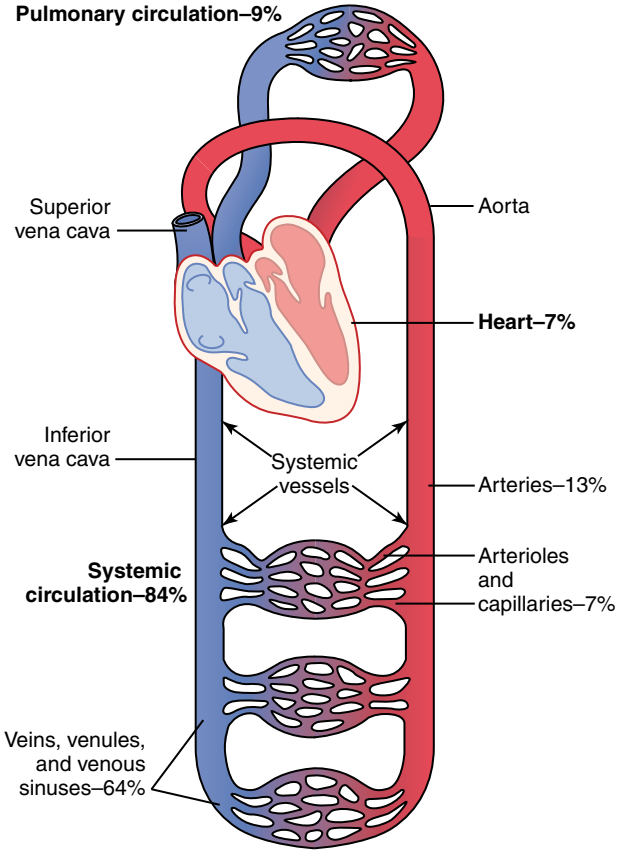


Figure 14-1 Distribution of blood (in percentage of total blood) in the different parts of the circulatory system.

Vessel	Cross-Sectional Area (cm^2)
Aorta	2.5
Small arteries	20
Arterioles	40
Capillaries	2500
Venules	250
Small veins	80
Venae cavae	8

Note particularly the much larger cross-sectional areas of the veins than of the arteries, averaging about four times those of the corresponding arteries. This explains the large blood storage capacity of the venous system in comparison with the arterial system.

Because the same volume of blood flow (F) must pass through each segment of the circulation each minute, the velocity of blood flow (v) is inversely proportional to vascular cross-sectional area (A):

$$v = F/A$$

Thus, under resting conditions, the velocity averages about 33 cm/sec in the aorta but only 1/1000 as rapidly in the capillaries, about 0.3 mm/sec. However, because the capillaries have a typical length of only 0.3 to 1 millimeter, the blood remains in the capillaries for only 1 to 3 seconds. This short time is surprising because all diffusion of nutrient food substances and electrolytes that occurs through the capillary walls must do so in this short time.

Pressures in the Various Portions of the Circulation. Because the heart pumps blood continually into the aorta, the mean pressure in the aorta is high, averaging about 100 mm Hg. Also, because heart pumping is pulsatile, the arterial pressure alternates between a *systolic pressure level* of 120 mm Hg and a *diastolic pressure level* of 80 mm Hg, as shown on the left side of Figure 14-2.

As the blood flows through the *systemic circulation,* its mean pressure falls progressively to about 0 mm Hg by the time it reaches the termination of the venae cavae where they empty into the right atrium of the heart.

The pressure in the systemic capillaries varies from as high as 35 mm Hg near the arteriolar ends to as low as 10 mm Hg near the venous ends, but their average "functional" pressure in most vascular beds is about 17 mm Hg, a pressure low enough that little of the plasma leaks through the minute *pores* of the capillary walls, even though nutrients can *diffuse* easily through these same pores to the outlying tissue cells.

Note at the far right side of Figure 14-2 the respective pressures in the different parts of the *pulmonary circulation.* In the pulmonary arteries, the pressure is pulsatile, just as in the aorta, but the pressure is far less: *pulmonary artery systolic pressure* averages about 25 mm Hg and *diastolic pressure* 8 mm Hg, with a mean pulmonary arterial pressure of only 16 mm Hg. The mean pulmonary capillary pressure averages only 7 mm Hg. Yet the total blood flow through the lungs each minute is the same as through the systemic circulation. The low pressures of the pulmonary system are in accord with the needs of the lungs because all that is required is to expose the blood in the pulmonary capillaries to oxygen and other gases in the pulmonary alveoli.

Basic Principles of Circulatory Function

Although the details of circulatory function are complex, there are three basic principles that underlie all functions of the system.

1. **The rate of blood flow to each tissue of the body is almost always precisely controlled in relation to the tissue need.** When tissues are active, they need a greatly increased supply of nutrients and therefore much more blood flow than when at rest—occasionally as much as 20 to 30 times the resting level. Yet the heart normally cannot increase its cardiac output more than four to seven times greater than resting levels. Therefore, it is not possible simply to increase blood flow everywhere in the body when a particular tissue demands increased flow. Instead, the microvessels of each tissue continuously monitor tissue needs, such as the availability of oxygen and other nutrients

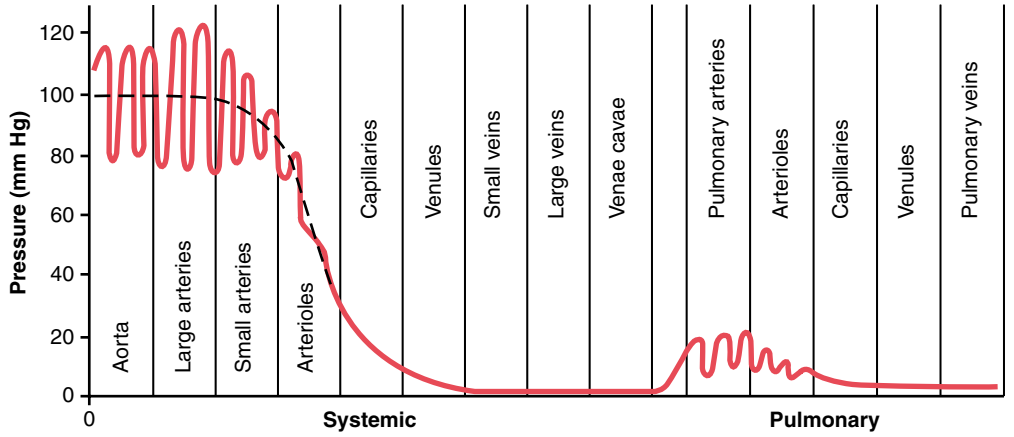


Figure 14-2 Normal blood pressures in the different portions of the circulatory system when a person is lying in the horizontal position.

and the accumulation of carbon dioxide and other tissue waste products, and these in turn act directly on the local blood vessels, dilating or constricting them, to control local blood flow precisely to that level required for the tissue activity. Also, nervous control of the circulation from the central nervous system and hormones provide additional help in controlling tissue blood flow.

2. **The cardiac output is controlled mainly by the sum of all the local tissue flows.** When blood flows through a tissue, it immediately returns by way of the veins to the heart. The heart responds automatically to this increased inflow of blood by pumping it immediately back into the arteries. Thus, the heart acts as an automaton, responding to the demands of the tissues. The heart, however, often needs help in the form of special nerve signals to make it pump the required amounts of blood flow.
3. **Arterial pressure regulation is generally independent of either local blood flow control or cardiac output control.** The circulatory system is provided with an extensive system for controlling the arterial blood pressure. For instance, if at any time the pressure falls significantly below the normal level of about 100 mm Hg, within seconds a barrage of nervous reflexes elicits a series of circulatory changes to raise the pressure back toward normal. The nervous signals especially (a) increase the force of heart pumping, (b) cause contraction of the large venous reservoirs to provide more blood to the heart, and (c) cause generalized constriction of most of the arterioles throughout the body so that more blood accumulates in the large arteries to increase the arterial pressure. Then, over more prolonged periods, hours and days, the kidneys play an additional major role in pressure control both by secreting pressure-controlling hormones and by regulating the blood volume.

Thus, in summary, the needs of the individual tissues are served specifically by the circulation. In the remainder of this chapter, we begin to discuss the basic details of the management of tissue blood flow and control of cardiac output and arterial pressure.

Interrelationships of Pressure, Flow, and Resistance

Blood flow through a blood vessel is determined by two factors: (1) *pressure difference* of the blood between the two ends of the vessel, also sometimes called "pressure gradient" along the vessel, which is the force that pushes the blood through the vessel, and (2) the impediment to blood flow through the vessel, which is called *vascular resistance*. Figure 14-3 demonstrates these relationships, showing a blood vessel segment located anywhere in the circulatory system.

P_1 represents the pressure at the origin of the vessel; at the other end, the pressure is P_2. Resistance occurs as a result of friction between the flowing blood and the intravascular endothelium all along the inside of the vessel. The flow through the vessel can be calculated by the following formula, which is called *Ohm's law* :

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

in which F is blood flow, ΔP is the pressure difference ($P_1 - P_2$) between the two ends of the vessel, and R is the resistance. This formula states that the blood flow is directly proportional to the pressure difference but inversely proportional to the resistance.

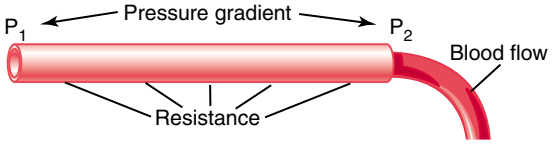


Figure 14-3 Interrelationships of pressure, resistance, and blood flow.

Note that it is the *difference* in pressure between the two ends of the vessel, not the absolute pressure in the vessel, that determines rate of flow. For example, if the pressure at both ends of a vessel is 100 mm Hg and yet no difference exists between the two ends, there will be no flow despite the presence of 100 mm Hg pressure.

Ohm's law, illustrated in Equation 1, expresses the most important of all the relations that the reader needs to understand to comprehend the hemodynamics of the circulation. Because of the extreme importance of this formula, the reader should also become familiar with its other algebraic forms:

$$\Delta P = F \times R$$

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

Blood Flow

Blood flow means the quantity of blood that passes a given point in the circulation in a given period of time. Ordinarily, blood flow is expressed in *milliliters per minute* or *liters per minute,* but it can be expressed in milliliters per second or in any other units of flow and time.

The overall blood flow in the total circulation of an adult person at rest is about 5000 ml/min. This is called the *cardiac output* because it is the amount of blood pumped into the aorta by the heart each minute.

Methods for Measuring Blood Flow. Many mechanical and mechanoelectrical devices can be inserted in series with a blood vessel or, in some instances, applied to the outside of the vessel to measure flow. They are called *flowmeters.*

Electromagnetic Flowmeter. One of the most important devices for measuring blood flow without opening the vessel is the electromagnetic flowmeter, the principles of which are illustrated in Figure 14-4. Figure 14-4*A* shows the generation of electromotive force (electrical voltage) in a wire that is moved rapidly in a cross-wise direction through a magnetic field. This is the well-known principle for production of electricity by the electric generator. Figure 14-4*B* shows that the same principle applies for generation of electromotive force in blood that is moving through a magnetic field. In this case, a blood vessel is placed between the poles of a strong magnet, and electrodes are placed on the two sides of the vessel perpendicular to the magnetic lines of force. When blood flows through the vessel, an electrical voltage proportional to the rate of blood flow is generated between the two electrodes, and this is recorded using an appropriate voltmeter or electronic recording apparatus. Figure 14-4*C* shows an actual "probe" that is placed on a large blood vessel to record its blood flow. The probe contains both the strong magnet and the electrodes.

A special advantage of the electromagnetic flowmeter is that it can record changes in flow in less than 1/100 of a second, allowing accurate recording of pulsatile changes in flow, as well as steady flow.

Ultrasonic Doppler Flowmeter. Another type of flowmeter that can be applied to the outside of the vessel and that has many of the same advantages as the electromagnetic flowmeter is the *ultrasonic Doppler flowmeter,* shown in Figure 14-5. A minute piezoelectric crystal is mounted at one end in the wall of the device. This crystal, when energized with an appropriate electronic apparatus, transmits ultrasound at a frequency of several hundred thousand cycles per second downstream along the flowing

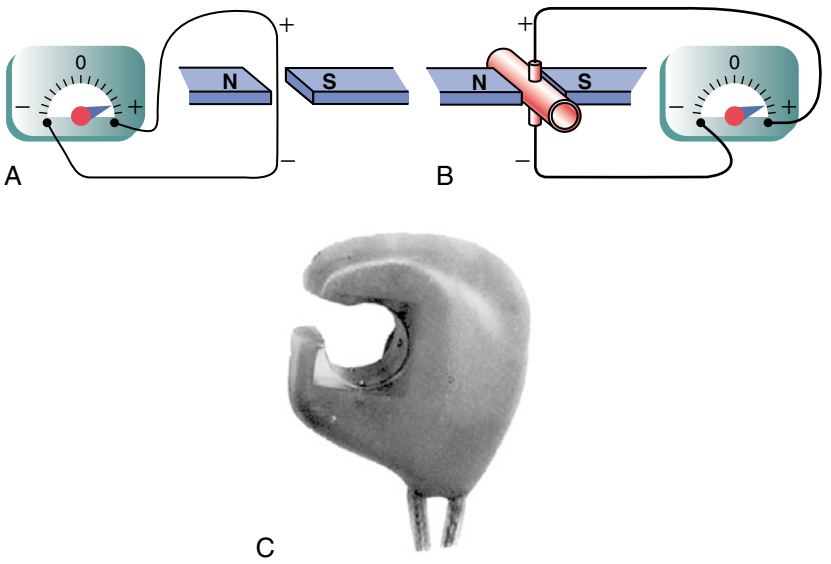


Figure 14-4 Flowmeter of the electromagnetic type, showing generation of an electrical voltage in a wire as it passes through an electromagnetic field (*A*); generation of an electrical voltage in electrodes on a blood vessel when the vessel is placed in a strong magnetic field and blood flows through the vessel (*B*); and a modern electromagnetic flowmeter probe for chronic implantation around blood vessels (*C*).

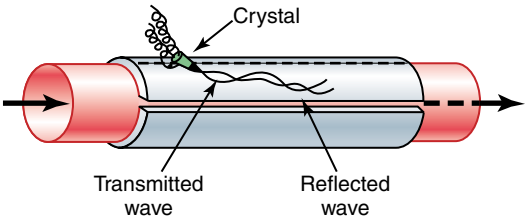


Figure 14-5 Ultrasonic Doppler flowmeter.

blood. A portion of the sound is reflected by the red blood cells in the flowing blood. The reflected ultrasound waves then travel backward from the blood cells toward the crystal. These reflected waves have a lower frequency than the transmitted wave because the red cells are moving away from the transmitter crystal. This is called the *Doppler effect.* (It is the same effect that one experiences when a train approaches and passes by while blowing its whistle. Once the whistle has passed by the person, the pitch of the sound from the whistle suddenly becomes much lower than when the train is approaching.)

For the flowmeter shown in Figure 14-5, the high-frequency ultrasound wave is intermittently cut off, and the reflected wave is received back onto the crystal and amplified greatly by the electronic apparatus. Another portion of the electronic apparatus determines the frequency difference between the transmitted wave and the reflected wave, thus determining the velocity of blood flow. As long as diameter of a blood vessel does not change, changes in blood flow in the vessel are directly related to changes in flow velocity.

Like the electromagnetic flowmeter, the ultrasonic Doppler flowmeter is capable of recording rapid, pulsatile changes in flow, as well as steady flow.

Laminar Flow of Blood in Vessels. When blood flows at a steady rate through a long, smooth blood vessel, it flows in *streamlines,* with each layer of blood remaining the same distance from the vessel wall. Also, the centralmost portion of the blood stays in the center of the vessel. This type of flow is called *laminar flow* or *streamline flow,* and it is the opposite of *turbulent flow,* which is blood flowing in all directions in the vessel and continually mixing within the vessel, as discussed subsequently.

Parabolic Velocity Profile during Laminar Flow. When laminar flow occurs, the velocity of flow in the center of the vessel is far greater than that toward the outer edges. This is demonstrated in Figure 14-6. In Figure 14-6*A*, a vessel contains two fluids, the one at the left colored by a dye and the one at the right a clear fluid, but there is no flow in the vessel. When the fluids are made to flow, a parabolic interface develops between them, as shown 1 second later in Figure 14-6*B*; the portion of fluid adjacent to the vessel wall has hardly moved, the portion slightly away from the wall has moved a small distance, and the portion in the center of the vessel has moved a long distance. This effect is called the "parabolic profile for velocity of blood flow."

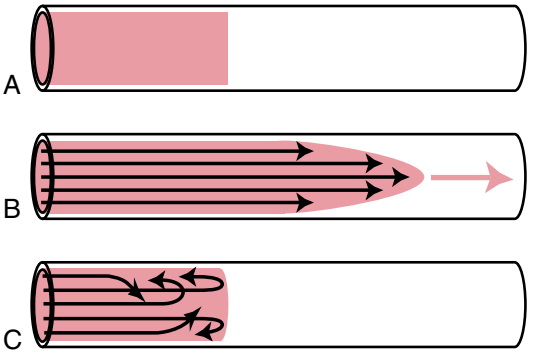


Figure 14-6 *A*, Two fluids (one dyed red, and the other clear) before flow begins; *B*, the same fluids 1 second after flow begins; *C*, turbulent flow, with elements of the fluid moving in a disorderly pattern.

The cause of the parabolic profile is the following: The fluid molecules touching the wall move slowly because of adherence to the vessel wall. The next layer of molecules slips over these, the third layer over the second, the fourth layer over the third, and so forth. Therefore, the fluid in the middle of the vessel can move rapidly because many layers of slipping molecules exist between the middle of the vessel and the vessel wall; thus, each layer toward the center flows progressively more rapidly than the outer layers.

Turbulent Flow of Blood under Some Conditions. When the rate of blood flow becomes too great, when it passes by an obstruction in a vessel, when it makes a sharp turn, or when it passes over a rough surface, the flow may then become *turbulent,* or disorderly, rather than streamlined (see Figure 14-6*C*). Turbulent flow means that the blood flows crosswise in the vessel and along the vessel, usually forming whorls in the blood, called *eddy currents.* These are similar to the whirlpools that one frequently sees in a rapidly flowing river at a point of obstruction.

When eddy currents are present, the blood flows with much greater resistance than when the flow is streamlined, because eddies add tremendously to the overall friction of flow in the vessel.

The tendency for turbulent flow increases in direct proportion to the velocity of blood flow, the diameter of the blood vessel, and the density of the blood and is inversely proportional to the viscosity of the blood, in accordance with the following equation:

$$Re = \frac{v \cdot d \cdot \rho}{\eta}$$

where Re is *Reynolds' number* and is the measure of the tendency for turbulence to occur, v is the mean velocity of blood flow (in centimeters/second), d is the vessel diameter (in centimeters), ρ is density, and η is the viscosity (in poise). The viscosity of blood is normally about ⅓₀ poise, and the density is only slightly greater than 1. When Reynolds' number rises above 200 to 400, turbulent

flow will occur at some branches of vessels but will die out along the smooth portions of the vessels. However, when Reynolds' number rises above approximately 2000, turbulence will usually occur even in a straight, smooth vessel.

Reynolds' number for flow in the vascular system even normally rises to 200 to 400 in large arteries; as a result there is almost always some turbulence of flow at the branches of these vessels. In the proximal portions of the aorta and pulmonary artery, Reynolds' number can rise to several thousand during the rapid phase of ejection by the ventricles; this causes considerable turbulence in the proximal aorta and pulmonary artery where many conditions are appropriate for turbulence: (1) high velocity of blood flow, (2) pulsatile nature of the flow, (3) sudden change in vessel diameter, and (4) large vessel diameter. However, in small vessels, Reynolds' number is almost never high enough to cause turbulence.

Blood Pressure

Standard Units of Pressure. Blood pressure almost always is measured in millimeters of mercury (mm Hg) because the mercury manometer has been used as the standard reference for measuring pressure since its invention in 1846 by Poiseuille. Actually, blood pressure means the *force exerted by the blood against any unit area of the vessel wall*. When one says that the pressure in a vessel is 50 mm Hg, this means that the force exerted is sufficient to push a column of mercury against gravity up to a level 50 millimeters high. If the pressure is 100 mm Hg, it will push the column of mercury up to 100 millimeters.

Occasionally, pressure is measured in *centimeters of water (cm H_2O)*. A pressure of 10 cm H_2O means a pressure sufficient to raise a column of water against gravity to a height of 10 centimeters. *One millimeter of mercury pressure equals 1.36 cm water pressure* because the specific gravity of mercury is 13.6 times that of water, and 1 centimeter is 10 times as great as 1 millimeter.

High-Fidelity Methods for Measuring Blood Pressure. The mercury in a manometer has so much inertia that it cannot rise and fall rapidly. For this reason, the mercury manometer, although excellent for recording steady pressures, cannot respond to pressure changes that occur more rapidly than about one cycle every 2 to 3 seconds. Whenever it is desired to record rapidly changing pressures, some other type of pressure recorder is necessary. Figure 14-7 demonstrates the basic principles of three electronic pressure *transducers* commonly used for converting blood pressure and/or rapid changes in pressure into electrical signals and then recording the electrical signals on a high-speed electrical recorder. Each of these transducers uses a very thin, highly stretched metal membrane that forms one wall of the fluid chamber. The fluid chamber in turn is connected through a needle or catheter inserted into the blood vessel in which the pressure is to be measured. When the pressure is high, the membrane bulges slightly, and when it is low, it returns toward its resting position.

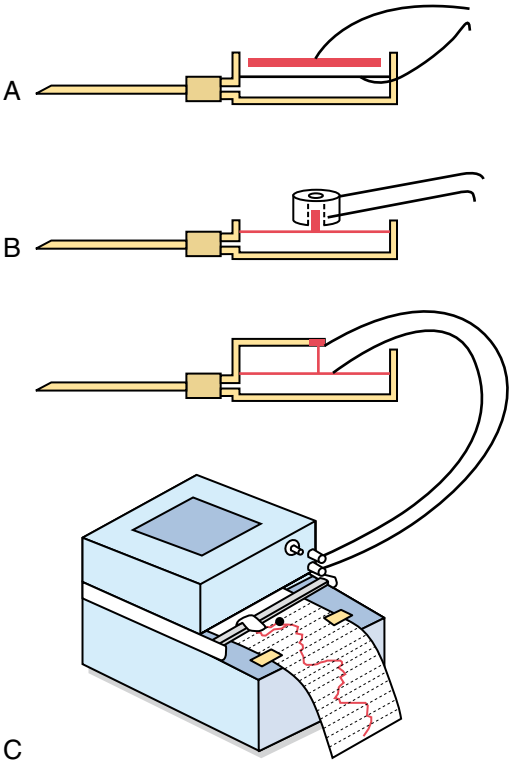


Figure 14-7 Principles of three types of electronic transducers for recording rapidly changing blood pressures (explained in the text).

In Figure 14-7*A*, a simple metal plate is placed a few hundredths of a centimeter above the membrane. When the membrane bulges, the membrane comes closer to the plate, which increases the *electrical capacitance* between these two, and this change in capacitance can be recorded using an appropriate electronic system.

In Figure 14-7*B*, a small iron slug rests on the membrane, and this can be displaced upward into a center space inside an electrical wire coil. Movement of the iron into the coil increases the *inductance* of the coil, and this, too, can be recorded electronically.

Finally, in Figure 14-7*C*, a very thin, stretched resistance wire is connected to the membrane. When this wire is stretched greatly, its resistance increases; when it is stretched less, its resistance decreases. These changes, too, can be recorded by an electronic system.

The electrical signals from the transducer are sent to an amplifier and then to an appropriate recording device. With some of these high-fidelity types of recording systems, pressure cycles up to 500 cycles per second have been recorded accurately. In common use are recorders capable of registering pressure changes that occur as rapidly as 20 to 100 cycles per second, in the manner shown on the recording paper in Figure 14-7*C*.

Resistance to Blood Flow

Units of Resistance. Resistance is the impediment to blood flow in a vessel, but it cannot be measured by any direct means. Instead, resistance must be calculated from measurements of blood flow and pressure

difference between two points in the vessel. If the pressure difference between two points is 1 mm Hg and the flow is 1 ml/sec, the resistance is said to be 1 *peripheral resistance unit,* usually abbreviated *PRU*.

Expression of Resistance in CGS Units. Occasionally, a basic physical unit called the CGS (centimeters, grams, seconds) unit is used to express resistance. This unit is dyne sec/cm^5. Resistance in these units can be calculated by the following formula:

$$R\left(\text{in}\ \frac{\text{dyne sec}}{\text{cm}^5}\right) = \frac{1333 \times \text{mm Hg}}{\text{ml/sec}}$$

Total Peripheral Vascular Resistance and Total Pulmonary Vascular Resistance. The rate of blood flow through the entire circulatory system is equal to the rate of blood pumping by the heart—that is, it is equal to the cardiac output. In the adult human being, this is approximately 100 ml/sec. The pressure difference from the systemic arteries to the systemic veins is about 100 mm Hg. Therefore, the resistance of the entire systemic circulation, called the *total peripheral resistance,* is about 100/100, or 1 peripheral resistance unit (PRU).

In conditions in which all the blood vessels throughout the body become strongly constricted, the total peripheral resistance occasionally rises to as high as 4 PRU. Conversely, when the vessels become greatly dilated, the resistance can fall to as little as 0.2 PRU.

In the pulmonary system, the mean pulmonary arterial pressure averages 16 mm Hg and the mean left atrial pressure averages 2 mm Hg, giving a net pressure difference of 14 mm. Therefore, when the cardiac output is normal at about 100 ml/sec, the *total pulmonary vascular resistance* calculates to be about 0.14 PRU (about one seventh that in the systemic circulation).

"Conductance" of Blood in a Vessel and Its Relation to Resistance. Conductance is a measure of the blood flow through a vessel for a given pressure difference. This is generally expressed in terms of milliliters per second per millimeter of mercury pressure, but it can also be expressed in terms of liters per second per millimeter of mercury or in any other units of blood flow and pressure.

It is evident that conductance is the exact reciprocal of resistance in accord with the following equation:

$$\text{Conductance} = \frac{1}{\text{Resistance}}$$

Very Slight Changes in Diameter of a Vessel Can Change Its Conductance Tremendously! Slight changes in the diameter of a vessel cause tremendous changes in the vessel's ability to conduct blood when the blood flow is streamlined. This is demonstrated by the experiment illustrated in Figure 14-8*A*, which shows three vessels with relative diameters of 1, 2, and 4 but with the same pressure difference of 100 mm Hg between the two ends of the vessels. Although the diameters of these vessels increase only fourfold, the respective flows are 1, 16, and 256 ml/min, which is a 256-fold increase in flow. Thus, the conductance of the vessel increases in proportion to the *fourth power of the diameter,* in accordance with the following formula:

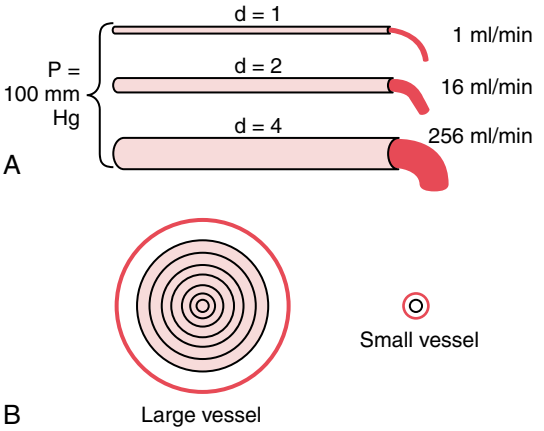


Figure 14-8 *A*, Demonstration of the effect of vessel diameter on blood flow. *B*, Concentric rings of blood flowing at different velocities; the farther away from the vessel wall, the faster the flow.

$$\text{Conductance} \propto \text{Diameter}^4$$

Poiseuille's Law. The cause of this great increase in conductance when the diameter increases can be explained by referring to Figure 14-8*B*, which shows cross sections of a large and a small vessel. The concentric rings inside the vessels indicate that the velocity of flow in each ring is different from that in the adjacent rings because of *laminar* flow, which was discussed earlier in the chapter. That is, the blood in the ring touching the wall of the vessel is barely flowing because of its adherence to the vascular endothelium. The next ring of blood toward the center of the vessel slips past the first ring and, therefore, flows more rapidly. The third, fourth, fifth, and sixth rings likewise flow at progressively increasing velocities. Thus, the blood that is near the wall of the vessel flows slowly, whereas that in the middle of the vessel flows much more rapidly.

In the small vessel, essentially all the blood is near the wall, so the extremely rapidly flowing central stream of blood simply does not exist. By integrating the velocities of all the concentric rings of flowing blood and multiplying them by the areas of the rings, one can derive the following formula, known as Poiseuille's law:

$$F = \frac{\pi \Delta P r^4}{8 \eta l}$$

in which F is the rate of blood flow, ΔP is the pressure difference between the ends of the vessel, r is the radius of the vessel, l is length of the vessel, and η is viscosity of the blood.

Note particularly in this equation that the rate of blood flow is directly proportional to the *fourth power of the radius* of the vessel, which demonstrates once again that the diameter of a blood vessel (which is equal to twice the radius) plays by far the greatest role of all factors in determining the rate of blood flow through a vessel.

Importance of the Vessel Diameter "Fourth Power Law" in Determining Arteriolar Resistance. In the systemic circulation, about two thirds of the total systemic resistance to blood flow is arteriolar resistance in the small arterioles. The internal diameters of the arterioles range from as little as 4 micrometers to as great as 25 micrometers. However, their strong vascular walls allow the internal diameters to change tremendously, often as much as fourfold. From the fourth power law discussed earlier that relates blood flow to diameter of the vessel, one can see that a fourfold increase in vessel diameter can increase the flow as much as 256-fold. Thus, this fourth power law makes it possible for the arterioles, responding with only small changes in diameter to nervous signals or local tissue chemical signals, either to turn off almost completely the blood flow to the tissue or at the other extreme to cause a vast increase in flow. Indeed, ranges of blood flow of more than 100-fold in separate tissue areas have been recorded between the limits of maximum arteriolar constriction and maximum arteriolar dilatation.

Resistance to Blood Flow in Series and Parallel Vascular Circuits. Blood pumped by the heart flows from the high-pressure part of the systemic circulation (i.e., aorta) to the low-pressure side (i.e., vena cava) through many miles of blood vessels arranged in series and in parallel. The arteries, arterioles, capillaries, venules, and veins are collectively arranged in series. When blood vessels are arranged in series, flow through each blood vessel is the same and the total resistance to blood flow (R_{total}) is equal to the sum of the resistances of each vessel:

$$R_{total} = R_1 + R_2 + R_3 + R_4 \ldots$$

The total peripheral vascular resistance is therefore equal to the sum of resistances of the arteries, arterioles, capillaries, venules, and veins. In the example shown in Figure 14-9*A*, the total vascular resistance is equal to the sum of R_1 and R_2.

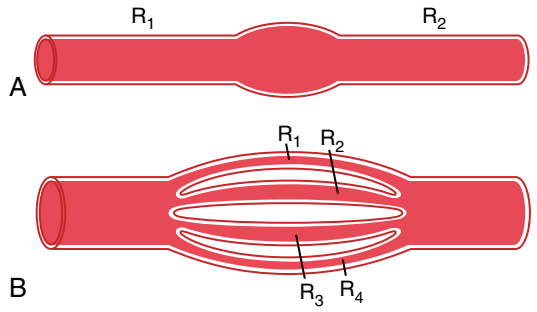


Figure 14-9 Vascular resistances: *A*, in series and *B*, in parallel.

Blood vessels branch extensively to form parallel circuits that supply blood to the many organs and tissues of the body. This parallel arrangement permits each tissue to regulate its own blood flow, to a great extent, independently of flow to other tissues.

For blood vessels arranged in parallel (Figure 14-9*B*), the total resistance to blood flow is expressed as:

$$\frac{1}{R_{total}} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \frac{1}{R_4} \ldots$$

It is obvious that for a given pressure gradient, far greater amounts of blood will flow through this parallel system than through any of the individual blood vessels. Therefore, the total resistance is far less than the resistance of any single blood vessel. Flow through each of the parallel vessels in Figure 14-9*B* is determined by the pressure gradient and its own resistance, not the resistance of the other parallel blood vessels. However, increasing the resistance of any of the blood vessels increases the total vascular resistance.

It may seem paradoxical that adding more blood vessels to a circuit reduces the total vascular resistance. Many parallel blood vessels, however, make it easier for blood to flow through the circuit because each parallel vessel provides another pathway, or *conductance,* for blood flow. The total conductance (C_{total}) for blood flow is the sum of the conductance of each parallel pathway:

$$C_{total} = C_1 + C_2 + C_3 + C_4 \ldots$$

For example, brain, kidney, muscle, gastrointestinal, skin, and coronary circulations are arranged in parallel, and each tissue contributes to the overall conductance of the systemic circulation. Blood flow through each tissue is a fraction of the total blood flow (cardiac output) and is determined by the resistance (the reciprocal of conductance) for blood flow in the tissue, as well as the pressure gradient. Therefore, amputation of a limb or surgical removal of a kidney also removes a parallel circuit and reduces the total vascular conductance and total blood flow (i.e., cardiac output) while increasing total peripheral vascular resistance.

Effect of Blood Hematocrit and Blood Viscosity on Vascular Resistance and Blood Flow

Note especially that another of the important factors in Poiseuille's equation is the viscosity of the blood. The greater the viscosity, the less the flow in a vessel if all other factors are constant. Furthermore, *the viscosity of normal blood is about three times as great as the viscosity of water.*

But what makes the blood so viscous? It is mainly the large numbers of suspended red cells in the blood, each of which exerts frictional drag against adjacent cells and against the wall of the blood vessel.

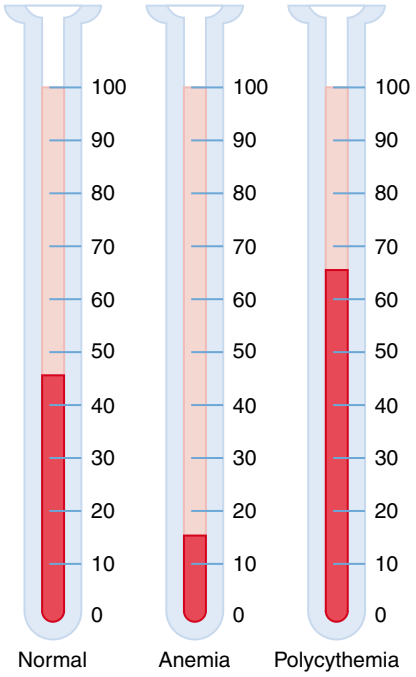


Figure 14-10 Hematocrits in a healthy (normal) person and in patients with anemia and polycythemia.

Hematocrit. The proportion of the blood that is red blood cells is called the *hematocrit.* Thus, if a person has a hematocrit of 40, this means that 40 percent of the blood volume is cells and the remainder is plasma. The hematocrit of adult men averages about 42, while that of women averages about 38. These values vary tremendously, depending on whether the person has anemia, on the degree of bodily activity, and on the altitude at which the person resides. These changes in hematocrit are discussed in relation to the red blood cells and their oxygen transport function in Chapter 32.

Hematocrit is determined by centrifuging blood in a calibrated tube, as shown in Figure 14-10. The calibration allows direct reading of the percentage of cells.

Effect of Hematocrit on Blood Viscosity. The viscosity of blood increases drastically as the hematocrit increases, as shown in Figure 14-11. The viscosity of whole blood at normal hematocrit is about 3; this means that three times as much pressure is required to force whole blood as to force water through the same blood vessel. When the hematocrit rises to 60 or 70, which it often does in *polycythemia,* the blood viscosity can become as great as 10 times that of water, and its flow through blood vessels is greatly retarded.

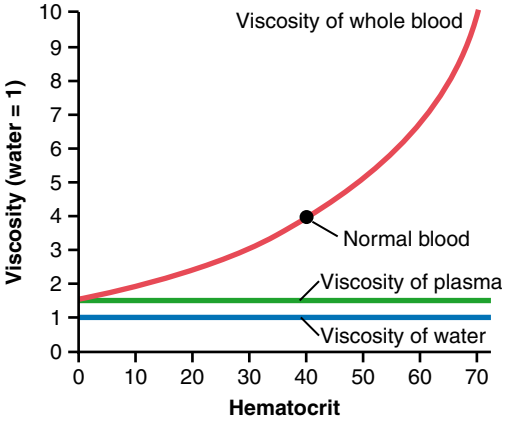


Figure 14-11 Effect of hematocrit on blood viscosity. (Water viscosity = 1.)

Other factors that affect blood viscosity are the plasma protein concentration and types of proteins in the plasma, but these effects are so much less than the effect of hematocrit that they are not significant considerations in most hemodynamic studies. The viscosity of blood plasma is about 1.5 times that of water.

Effects of Pressure on Vascular Resistance and Tissue Blood Flow

"Autoregulation" Attenuates the Effect of Arterial Pressure on Tissue Blood Flow. From the discussion thus far, one might expect an increase in arterial pressure to cause a proportionate increase in blood flow through the various tissues of the body. However, the effect of arterial pressure on blood flow in many tissues is usually far less than one would expect, as shown in Figure 14-12. The reason for this is that an increase in arterial pressure not only increases the force that pushes blood through the vessels but it also initiates compensatory increases in vascular resistance within a few seconds through activation of the local control mechanisms discussed in Chapter 17. Conversely, with reductions in arterial pressure most vascular resistance is promptly reduced in most tissues and blood flow is maintained relatively constant. The ability of each tissue to adjust its vascular resistance and to maintain normal blood flow during changes in arterial pressure between approximately 70 and 175 mm Hg is called *blood flow autoregulation.*

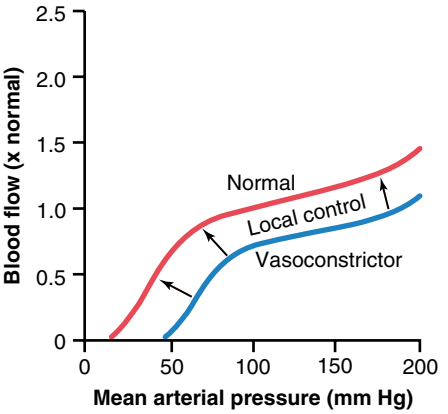


Figure 14-12 Effect of changes in arterial pressure over a period of several minutes on blood flow in a tissue such as skeletal muscle. Note that between pressure of 70 and 175 mm Hg blood flow is "autoregulated." The ***blue line*** shows the effect of sympathetic nerve stimulation or vasoconstriction by hormones such as norepinephrine, angiotensin II, vasopressin, or endothelin on this relationship. Reduced tissue blood flow is rarely maintained for more than a few hours due to activation of local autoregulatory mechanisms that eventually return blood flow toward normal.

Note in Figure 14-12 that changes in blood flow can be caused by strong sympathetic stimulation, which *constricts* the blood vessels. Likewise, hormonal vasoconstrictors, such as *norepinephrine, angiotensin II, vasopressin,* or *endothelin,* can also reduce blood flow, at least transiently.

Changes in tissue blood flow rarely last for more than a few hours even when increases in arterial pressure or increased levels of vasoconstrictors are sustained. The reason for the relative constancy of blood flow is that each tissue's local autoregulatory mechanisms eventually override most of the effects of vasoconstrictors in order to provide a blood flow that is appropriate for the needs of the tissue.

Pressure-Flow Relationship in Passive Vascular Beds. In isolated blood vessels or in tissues that do not exhibit autoregulation, changes in arterial pressure may have important effects on blood flow. In fact, the effect of pressure on blood flow may be greater than predicted by Poiseuille's equation, as shown by the upward curving lines in Figure 14-13. The reason for this is that increased arterial pressure not only increases the force that pushes blood through the vessels but it also distends the elastic vessels, actually *decreasing* vascular resistance. Conversely, decreased arterial pressure in passive blood vessels increases resistance as the elastic vessels gradually collapse due to reduced distending pressure. When pressure falls below a critical level, called the *critical closing pressure,* flow ceases as the blood vessels are completely collapsed.

Sympathetic stimulation and other vasoconstrictors can alter the passive pressure-flow relationship shown in Figure 14-13. Thus, *inhibition of* sympathetic activity

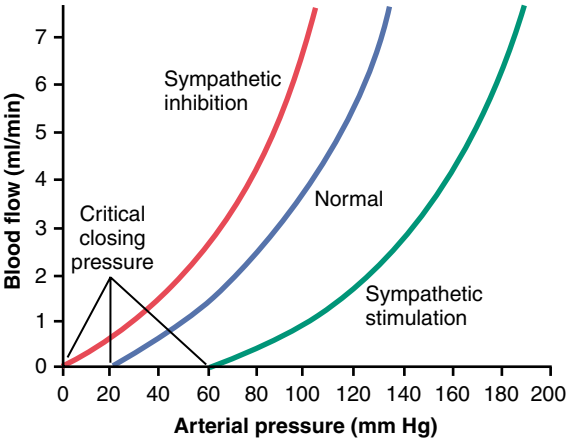


Figure 14-13 Effect of arterial pressure on blood flow through a *passive* blood vessel at different degrees of vascular tone caused by increased or decreased sympathetic stimulation of the vessel.

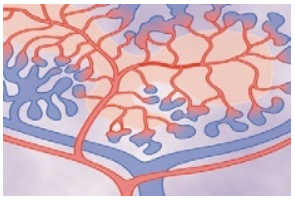
greatly dilates the vessels and can increase the blood flow twofold or more. Conversely, very strong sympathetic stimulation *can constrict* the vessels so much that blood flow occasionally decreases to as low as zero for a few seconds despite high arterial pressure.

In reality, there are few physiological conditions in which tissues display the passive pressure-flow relationship shown in Figure 14-13. Even in tissues that do not effectively autoregulate blood flow during acute changes in arterial pressure, blood flow is regulated according to the needs of the tissue when the pressure changes are sustained, as discussed in Chapter 17.

Bibliography

See bibliography for Chapter 15.

Vascular Distensibility and Functions of the Arterial and Venous Systems



Vascular Distensibility

A valuable characteristic of the vascular system is that all blood vessels are *distensible.* The distensible nature of the arteries allows them to accommodate the pulsatile output of the heart and to average out the pressure pulsations. This provides smooth, continuous flow of blood through the very small blood vessels of the tissues.

The most distensible by far of all the vessels are the veins. Even slight increases in venous pressure cause the veins to store 0.5 to 1.0 liter of extra blood. Therefore, the veins provide a *reservoir function* for storing large quantities of extra blood that can be called into use whenever required elsewhere in the circulation.

Units of Vascular Distensibility. Vascular distensibility normally is expressed as the fractional increase in volume for each millimeter of mercury rise in pressure, in accordance with the following formula:

$$\text{Vascular distensibility} = \frac{\text{Increase in volume}}{\text{Increase in pressure} \times \text{Original volume}}$$

That is, if 1 mm Hg causes a vessel that originally contained 10 millimeters of blood to increase its volume by 1 milliliter, the distensibility would be 0.1 per mm Hg, or 10 percent per mm Hg.

Difference in Distensibility of the Arteries and the Veins. Anatomically, the walls of the arteries are far stronger than those of the veins. Consequently, the veins, on average, are about eight times more distensible than the arteries. That is, a given increase in pressure causes about eight times as much increase in blood in a vein as in an artery of comparable size.

In the pulmonary circulation, the pulmonary vein distensibilities are similar to those of the systemic circulation. But the pulmonary arteries normally operate under pressures about one sixth of those in the systemic arterial system, and their distensibilities are correspondingly greater, about six times the distensibility of systemic arteries.

Vascular Compliance (or Vascular Capacitance)

In hemodynamic studies, it usually is much more important to know the *total quantity of blood* that can be stored in a given portion of the circulation for each mm Hg pressure rise than to know the distensibilities of the individual vessels. This value is called the *compliance* or *capacitance* of the respective vascular bed; that is,

$$\text{Vascular compliance} = \frac{\text{Increase in volume}}{\text{Increase in pressure}}$$

Compliance and distensibility are quite different. A highly distensible vessel that has a slight volume may have far less compliance than a much less distensible vessel that has a large volume because *compliance is equal to distensibility times volume.*

The compliance of a systemic vein is about 24 times that of its corresponding artery because it is about 8 times as distensible and it has a volume about 3 times as great ($8 \times 3 = 24$).

Volume-Pressure Curves of the Arterial and Venous Circulations

A convenient method for expressing the relation of pressure to volume in a vessel or in any portion of the circulation is to use the so-called *volume-pressure curve.* The red and blue solid curves in Figure 15-1 represent, respectively, the volume-pressure curves of the normal systemic arterial system and venous system, showing that when the arterial system of the average adult person (including all the large arteries, small arteries, and arterioles) is filled with about 700 milliliters of blood, the mean arterial pressure is 100 mm Hg, but when it is filled with only 400 milliliters of blood, the pressure falls to zero.

In the entire systemic venous system, the volume normally ranges from 2000 to 3500 milliliters, and a change of several hundred millimeters in this volume is required to change the venous pressure only 3 to 5 mm Hg. This mainly explains why as much as one half liter of blood can be

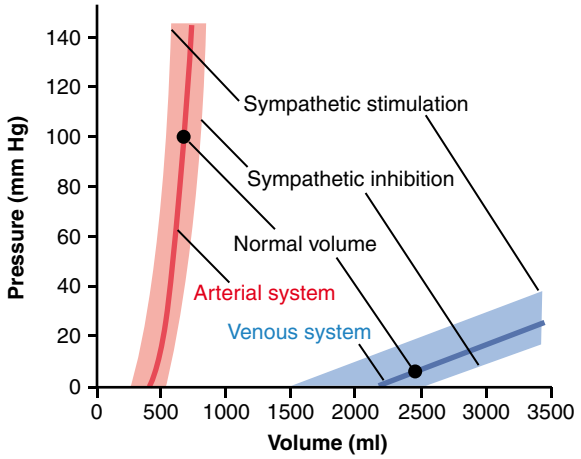


Figure 15-1 "Volume-pressure curves" of the systemic arterial and venous systems, showing the effects of stimulation or inhibition of the sympathetic nerves to the circulatory system.

transfused into a healthy person in only a few minutes without greatly altering function of the circulation.

Effect of Sympathetic Stimulation or Sympathetic Inhibition on the Volume-Pressure Relations of the Arterial and Venous Systems. Also shown in Figure 15-1 are the effects of exciting or inhibiting the vascular sympathetic nerves on the volume-pressure curves. It is evident that increase in vascular smooth muscle tone caused by sympathetic stimulation increases the pressure at each volume of the arteries or veins, whereas sympathetic inhibition decreases the pressure at each volume. Control of the vessels in this manner by the sympathetics is a valuable means for diminishing the dimensions of one segment of the circulation, thus transferring blood to other segments. For instance, an increase in vascular tone throughout the systemic circulation often causes large volumes of blood to shift into the heart, which is one of the principal methods that the body uses to increase heart pumping.

Sympathetic control of vascular capacitance is also highly important during hemorrhage. Enhancement of sympathetic tone, especially to the veins, reduces the vessel sizes enough that the circulation continues to operate almost normally even when as much as 25 percent of the total blood volume has been lost.

Delayed Compliance (Stress-Relaxation) of Vessels

The term "delayed compliance" means that a vessel exposed to increased volume at first exhibits a large increase in pressure, but progressive delayed stretching of smooth muscle in the vessel wall allows the pressure to return back toward normal over a period of minutes to hours. This effect is shown in Figure 15-2. In this figure, the pressure is recorded in a small segment of a vein that is occluded at both ends. An extra volume of blood is suddenly injected until the pressure rises from 5 to 12 mm Hg. Even though none of the blood is removed after it is injected, the pressure begins to decrease immediately and approaches about 9 mm Hg after several minutes. In other words, the volume of blood injected causes immediate

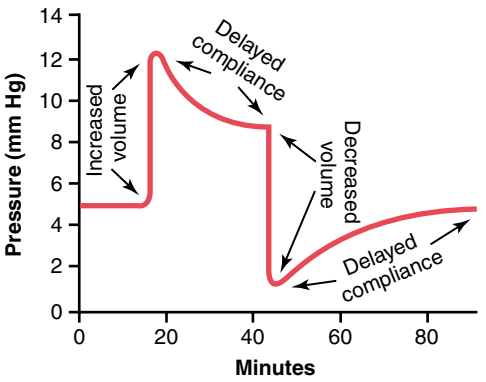


Figure 15-2 Effect on the intravascular pressure of injecting a volume of blood into a venous segment and later removing the excess blood, demonstrating the principle of delayed compliance.

elastic distention of the vein, but then the smooth muscle fibers of the vein begin to "creep" to longer lengths, and their tensions correspondingly decrease. This effect is a characteristic of all smooth muscle tissue and is called *stress-relaxation,* which was explained in Chapter 8.

Delayed compliance is a valuable mechanism by which the circulation can accommodate extra blood when necessary, such as after too large a transfusion. Delayed compliance in the reverse direction is one of the ways in which the circulation automatically adjusts itself over a period of minutes or hours to diminished blood volume after serious hemorrhage.

Arterial Pressure Pulsations

With each beat of the heart a new surge of blood fills the arteries. Were it not for distensibility of the arterial system, all of this new blood would have to flow through the peripheral blood vessels almost instantaneously, only during cardiac systole, and no flow would occur during diastole. However, the compliance of the arterial tree normally reduces the pressure pulsations to almost no pulsations by the time the blood reaches the capillaries; therefore, tissue blood flow is mainly continuous with very little pulsation.

A typical record of the *pressure pulsations* at the root of the aorta is shown in Figure 15-3. In the healthy young adult, the pressure at the top of each pulse, called the *systolic pressure,* is about 120 mm Hg. At the lowest point of each pulse, called the *diastolic pressure,* it is about 80 mm Hg. The difference between these two pressures, about 40 mm Hg, is called the *pulse pressure.*

Two major factors affect the pulse pressure: (1) the *stroke volume output* of the heart and (2) the *compliance (total distensibility)* of the arterial tree. A third, less important factor, is the character of ejection from the heart during systole.

In general, the greater the stroke volume output, the greater the amount of blood that must be accommodated in the arterial tree with each heartbeat, and, therefore, the greater the pressure rise and fall during systole and diastole, thus causing a greater pulse pressure. Conversely, the less the compliance of the arterial system, the greater the

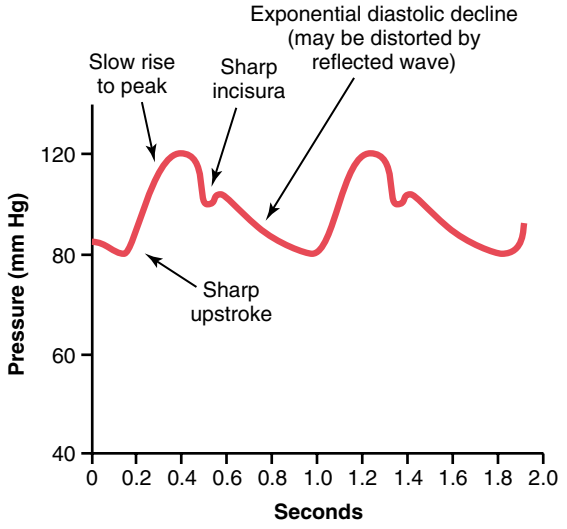


Figure 15-3 Pressure pulse contour in the ascending aorta.

rise in pressure for a given stroke volume of blood pumped into the arteries. For instance, as demonstrated by the middle top curves in Figure 15-4, the pulse pressure in old age sometimes rises to as much as twice normal, because the arteries have become hardened with *arteriosclerosis* and therefore are relatively noncompliant.

In effect, pulse pressure is determined approximately by the *ratio of stroke volume output to compliance of the arterial tree.* Any condition of the circulation that affects either of these two factors also affects the pulse pressure:

Pulse Pressure ≈ stroke volume/arterial compliance

Abnormal Pressure Pulse Contours

Some conditions of the circulation also cause *abnormal contours of the pressure pulse wave* in addition to altering the pulse pressure. Especially distinctive among these are aortic stenosis, patent ductus arteriosus, and aortic regurgitation, each of which is shown in Figure 15-4.

In *aortic valve stenosis,* the diameter of the aortic valve opening is reduced significantly, and the aortic pressure pulse is decreased significantly because of diminished blood flow outward through the stenotic valve.

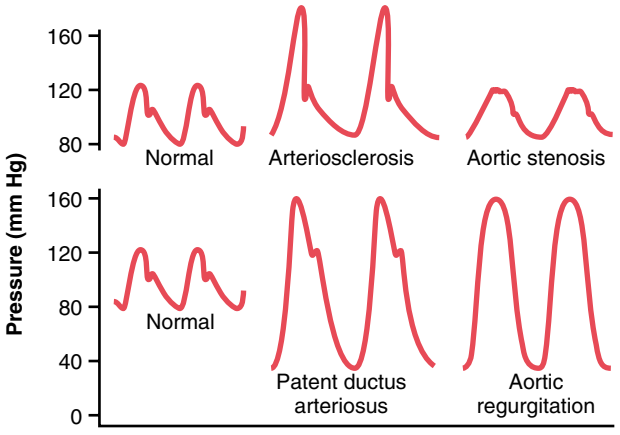


Figure 15-4 Aortic pressure pulse contours in arteriosclerosis, aortic stenosis, patent ductus arteriosus, and aortic regurgitation.

In *patent ductus arteriosus,* one half or more of the blood pumped into the aorta by the left ventricle flows immediately backward through the wide-open ductus into the pulmonary artery and lung blood vessels, thus allowing the diastolic pressure to fall very low before the next heartbeat.

In *aortic regurgitation,* the aortic valve is absent or will not close completely. Therefore, after each heartbeat, the blood that has just been pumped into the aorta flows immediately backward into the left ventricle. As a result, the aortic pressure can fall all the way to zero between heartbeats. Also, there is no incisura in the aortic pulse contour because there is no aortic valve to close.

Transmission of Pressure Pulses to the Peripheral Arteries

When the heart ejects blood into the aorta during systole, at first only the proximal portion of the aorta becomes distended because the inertia of the blood prevents sudden blood movement all the way to the periphery. However, the rising pressure in the proximal aorta rapidly overcomes this inertia, and the wave front of distention spreads farther and farther along the aorta, as shown in Figure 15-5. This is called *transmission of the pressure pulse* in the arteries.

The velocity of pressure pulse transmission in the normal aorta is 3 to 5 m/sec; in the large arterial branches, 7 to 10 m/sec; and in the small arteries, 15 to 35 m/sec. In general, the greater the compliance of each vascular segment, the slower the velocity, which explains the slow transmission in the aorta and the much faster transmission in the much less compliant small distal arteries. In the aorta, the velocity of transmission of the pressure pulse is 15 or more times the velocity of blood flow because the

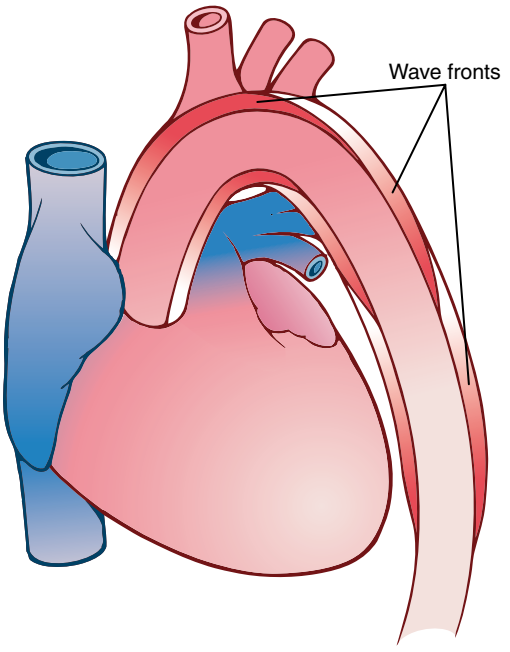


Figure 15-5 Progressive stages in transmission of the pressure pulse along the aorta.

pressure pulse is simply a moving wave of *pressure* that involves little forward total movement of blood volume.

Damping of the Pressure Pulses in the Smaller Arteries, Arterioles, and Capillaries. Figure 15-6 shows typical changes in the contours of the pressure pulse as the pulse travels into the peripheral vessels. Note especially in the three lower curves that the intensity of pulsation becomes progressively less in the smaller arteries, the arterioles, and, especially, the capillaries. In fact, only when the aortic pulsations are extremely large or the arterioles are greatly dilated can pulsations be observed in the capillaries.

This progressive diminution of the pulsations in the periphery is called *damping* of the pressure pulses. The cause of this is twofold: (1) resistance to blood movement in the vessels and (2) compliance of the vessels. The resistance damps the pulsations because a small amount of blood must flow forward at the pulse wave front to distend the next segment of the vessel; the greater the resistance, the more difficult it is for this to occur. The compliance damps the pulsations because the more compliant a vessel, the greater the quantity of blood required at the pulse wave front to cause an increase in pressure. Therefore, *the degree of damping is almost directly proportional to the product of resistance times compliance.*

Clinical Methods for Measuring Systolic and Diastolic Pressures

It is not reasonable to use pressure recorders that require needle insertion into an artery for making routine arterial pressure measurements in human patients, although these are used on occasion when special studies are necessary. Instead, the clinician determines systolic and diastolic pressures by indirect means, usually by the *auscultatory method*.

Auscultatory Method. Figure 15-7 shows the auscultatory method for determining systolic and diastolic arterial pressures. A stethoscope is placed over the antecubital artery and a blood pressure cuff is inflated around the upper arm. As long as the cuff continues to compress the arm with too little pressure to close the brachial artery, no sounds are heard from the antecubital artery with the stethoscope. However, when the cuff pressure is great enough to close the artery during part of the arterial pressure cycle, a sound then is heard with each pulsation. These sounds are called *Korotkoff sounds,*

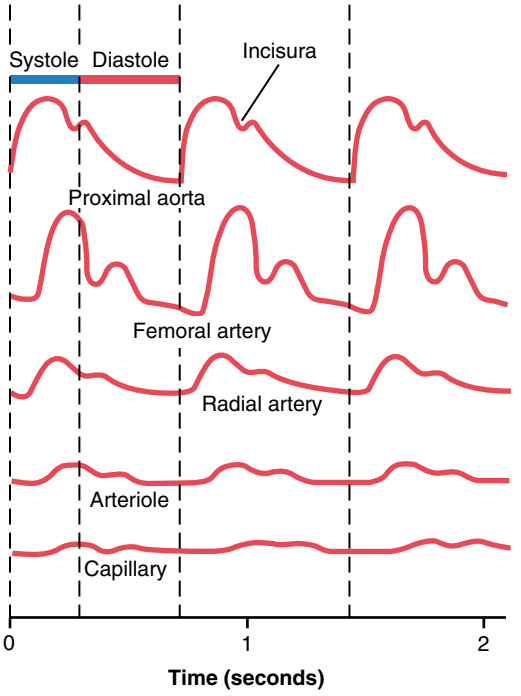


Figure 15-6 Changes in the pulse pressure contour as the pulse wave travels toward the smaller vessels.

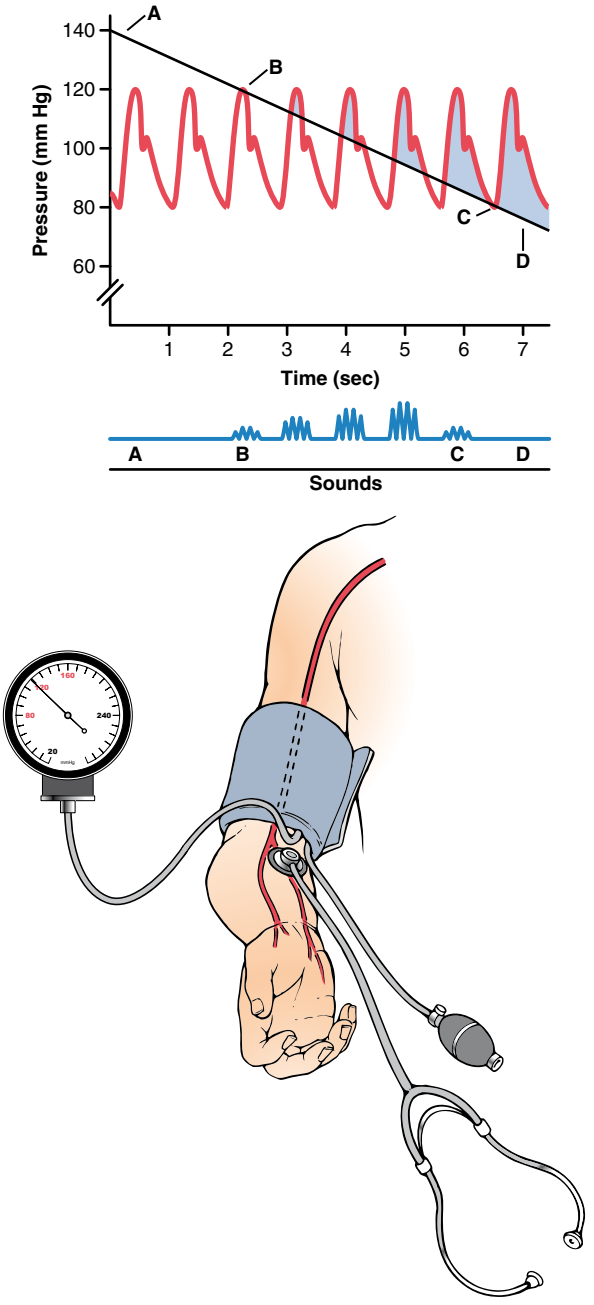


Figure 15-7 Auscultatory method for measuring systolic and diastolic arterial pressures.

named after *Nikolai Korotkoff,* a Russian physician who described them in 1905.

The Korotkoff sounds are believed to be caused mainly by blood jetting through the partly occluded vessel and by vibrations of the vessel wall. The jet causes turbulence in the vessel beyond the cuff, and this sets up the vibrations heard through the stethoscope.

In determining blood pressure by the auscultatory method, the pressure in the cuff is first elevated well above arterial systolic pressure. As long as this cuff pressure is higher than systolic pressure, the brachial artery remains collapsed so that no blood jets into the lower artery during any part of the pressure cycle. Therefore, no Korotkoff sounds are heard in the lower artery. But then the cuff pressure gradually is reduced. Just as soon as the pressure in the cuff falls below systolic pressure (point B, Figure 15-7), blood begins to slip through the artery beneath the cuff during the peak of systolic pressure, and one begins to hear *tapping* sounds from the antecubital artery in synchrony with the heartbeat. As soon as these sounds begin to be heard, the pressure level indicated by the manometer connected to the cuff is about equal to the systolic pressure.

As the pressure in the cuff is lowered still more, the Korotkoff sounds change in quality, having less of the tapping quality and more of a rhythmical and harsher quality. Then, finally, when the pressure in the cuff falls near diastolic pressure, the sounds suddenly change to a muffled quality (point C, Figure 15-7). One notes the manometer pressure when the Korotkoff sounds change to the muffled quality and this pressure is about equal to the diastolic pressure, although it slightly overestimates the diastolic pressure determined by direct intra-arterial catheter. As the cuff pressure falls a few mm Hg further, the artery no longer closes during diastole, which means that the basic factor causing the sounds (the jetting of blood through a squeezed artery) is no longer present. Therefore, the sounds disappear entirely. Many clinicians believe that the pressure at which the Korotkoff sounds completely disappear should be used as the diastolic pressure, except in situations in which the disappearance of sounds cannot reliably be determined because sounds are audible even after complete deflation of the cuff. For example, in patients with arteriovenous fistulas for hemodialysis or with aortic insufficiency, Korotkoff sounds may be heard after complete deflation of the cuff.

The auscultatory method for determining systolic and diastolic pressures is not entirely accurate, but it usually gives values within 10 percent of those determined by direct catheter measurement from inside the arteries.

Normal Arterial Pressures as Measured by the Auscultatory Method. Figure 15-8 shows the approximate normal systolic and diastolic arterial pressures at different ages. The progressive increase in pressure with age results from the effects of aging on the blood pressure control mechanisms. We shall see in Chapter 19 that the kidneys are primarily responsible for this long-term regulation of arterial pressure; and it is well known that the kidneys exhibit definitive changes with age, especially after the age of 50 years.

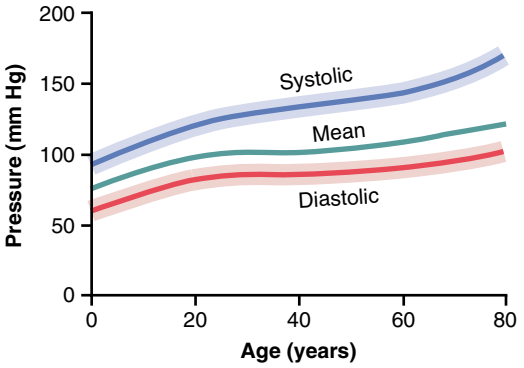


Figure 15-8 Changes in systolic, diastolic, and mean arterial pressures with age. The shaded areas show the approximate normal ranges.

A slight extra increase in *systolic* pressure usually occurs beyond the age of 60 years. This results from decreasing distensibility, or "hardening," of the arteries, which is often a result of *atherosclerosis.* The final effect is a higher systolic pressure with considerable increase in pulse pressure, as previously explained.

Mean Arterial Pressure. The mean arterial pressure is the average of the arterial pressures measured millisecond by millisecond over a period of time. It is not equal to the average of systolic and diastolic pressure because at normal heart rates, a greater fraction of the cardiac cycle is spent in diastole than is systole; thus, the arterial pressure remains nearer to diastolic pressure than to systolic pressure during the greater part of the cardiac cycle. The mean arterial pressure is therefore determined about 60 percent by the diastolic pressure and 40 percent by the systolic pressure. Note in Figure 15-8 that the mean pressure (solid green line) at all ages is nearer to the diastolic pressure than to the systolic pressure. However, at very high heart rates diastole comprises a smaller fraction of the cardiac cycle and the mean arterial pressure is more closely approximated as the average of systolic and diastolic pressures.

Veins and Their Functions

For years, the veins were considered to be nothing more than passageways for flow of blood to the heart, but it is now apparent that they perform other special functions that are necessary for operation of the circulation. Especially important, they are capable of constricting and enlarging and thereby storing either small or large quantities of blood and making this blood available when it is required by the remainder of the circulation. The peripheral veins can also propel blood forward by means of a so-called *venous pump,* and they even help to regulate cardiac output, an exceedingly important function that is described in detail in Chapter 20.

Venous Pressures—Right Atrial Pressure (Central Venous Pressure) and Peripheral Venous Pressures

To understand the various functions of the veins, it is first necessary to know something about pressure in the veins and what determines the pressure.

Blood from all the systemic veins flows into the right atrium of the heart; therefore, the pressure in the right atrium is called the *central venous pressure.*

Right atrial pressure is regulated by a balance between (1) the ability of the heart to pump blood out of the right atrium and ventricle into the lungs and *(2) the tendency for blood to flow from the peripheral veins into the right atrium.* If the right heart is pumping strongly, the right atrial pressure decreases. Conversely, weakness of the heart elevates the right atrial pressure. Also, any effect that causes rapid inflow of blood into the right atrium from the peripheral veins elevates the right atrial pressure. Some of the factors that can increase this venous return (and thereby increase the right atrial pressure) are (1) increased blood volume, (2) increased large vessel tone throughout the body with resultant increased peripheral venous pressures, and (3) dilatation of the arterioles, which decreases the peripheral resistance and allows rapid flow of blood from the arteries into the veins.

The same factors that regulate right atrial pressure also contribute to regulation of cardiac output because the amount of blood pumped by the heart depends on both the ability of the heart to pump and the tendency for blood to flow into the heart from the peripheral vessels. Therefore, we will discuss regulation of right atrial pressure in much more depth in Chapter 20 in connection with regulation of cardiac output.

The *normal right atrial pressure* is about 0 mm Hg, which is equal to the atmospheric pressure around the body. It can increase to 20 to 30 mm Hg under very abnormal conditions, such as (1) serious heart failure or (2) after massive transfusion of blood, which greatly increases the total blood volume and causes excessive quantities of blood to attempt to flow into the heart from the peripheral vessels.

The lower limit to the right atrial pressure is usually about −3 to −5 mm Hg below atmospheric pressure. This is also the pressure in the chest cavity that surrounds the heart. The right atrial pressure approaches these low values when the heart pumps with exceptional vigor or when blood flow into the heart from the peripheral vessels is greatly depressed, such as after severe hemorrhage.

Venous Resistance and Peripheral Venous Pressure

Large veins have so little resistance to blood flow *when they are distended* that the resistance then is almost zero and is of almost no importance. However, as shown in Figure 15-9, most of the large veins that enter the thorax are compressed at many points by the surrounding tissues so that blood flow is impeded at these points. For instance, the veins from the arms are compressed by their sharp angulations over the first rib. Also, the pressure in the neck veins often falls so low that the atmospheric pressure on the outside of the neck causes these veins to collapse. Finally, veins coursing through the abdomen are often compressed by different organs and by the intra-abdominal pressure, so they usually are at least partially collapsed to an ovoid or slitlike state. For these reasons, the *large veins do usually offer some resistance to blood flow,* and because of this, the pressure in the more peripheral small veins in a person lying down is usually +4 to +6 mm Hg greater than the right atrial pressure.

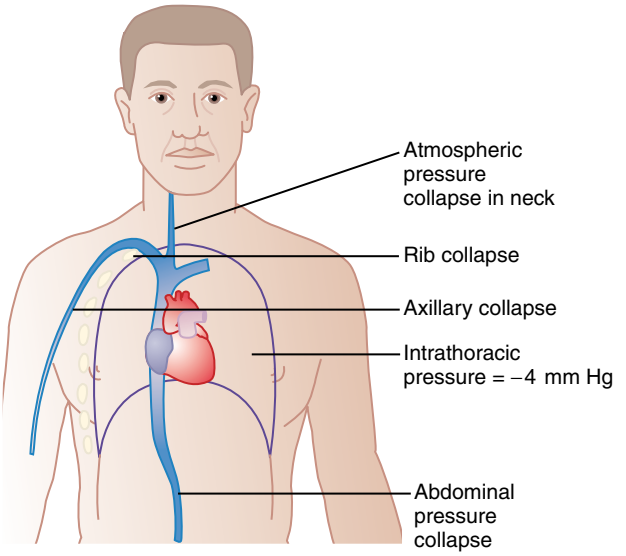


Figure 15-9 Compression points that tend to collapse the veins entering the thorax.

Effect of High Right Atrial Pressure on Peripheral Venous Pressure. When the right atrial pressure rises above its normal value of 0 mm Hg, blood begins to back up in the large veins. This enlarges the veins, and even the collapse points in the veins open up when the right atrial pressure rises above +4 to +6 mm Hg. Then, as the right atrial pressure rises still further, the additional increase causes a corresponding rise in peripheral venous pressure in the limbs and elsewhere. Because the heart must be weakened to cause a rise in right atrial pressure as high as +4 to +6 mm Hg, one often finds that the peripheral venous pressure is not noticeably elevated even in the early stages of heart failure.

Effect of Intra-abdominal Pressure on Venous Pressures of the Leg. The pressure in the abdominal cavity of a recumbent person normally averages about +6 mm Hg, but it can rise to +15 to +30 mm Hg as a result of pregnancy, large tumors, abdominal obesity, or excessive fluid (called "ascites") in the abdominal cavity. When the intra-abdominal pressure does rise, the pressure in the veins of the legs must rise *above* the abdominal pressure before the abdominal veins will open and allow the blood to flow from the legs to the heart. Thus, if the intra-abdominal pressure is +20 mm Hg, the lowest possible pressure in the femoral veins is also about +20 mm Hg.

Effect of Gravitational Pressure on Venous Pressure

In any body of water that is exposed to air, the pressure at the surface of the water is equal to atmospheric pressure, but the pressure rises 1 mm Hg for each 13.6 millimeters

of distance below the surface. This pressure results from the weight of the water and therefore is called *gravitational pressure* or *hydrostatic pressure.*

Gravitational pressure also occurs in the vascular system of the human being because of weight of the blood in the vessels, as shown in Figure 15-10. When a person is standing, the pressure in the right atrium remains about 0 mm Hg because the heart pumps into the arteries any excess blood that attempts to accumulate at this point. However, in an adult *who is standing absolutely still,* the pressure in the veins of the feet is about +90 mm Hg simply because of the gravitational weight of the blood in the veins between the heart and the feet. The venous pressures at other levels of the body are proportionately between 0 and 90 mm Hg.

In the arm veins, the pressure at the level of the top rib is usually about +6 mm Hg because of compression of the subclavian vein as it passes over this rib. The gravitational pressure down the length of the arm then is determined by the distance below the level of this rib. Thus, if the gravitational difference between the level of the rib and the hand is +29 mm Hg, this gravitational pressure is added to the +6 mm Hg pressure caused by compression of the vein as it crosses the rib, making a total of +35 mm Hg pressure in the veins of the hand.

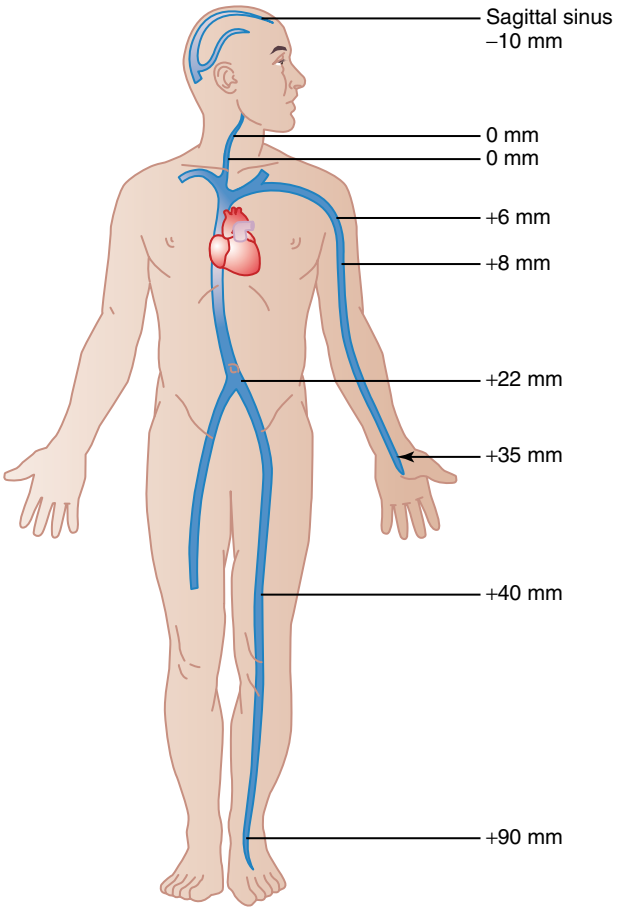


Figure 15-10 Effect of gravitational pressure on the venous pressures throughout the body in the standing person.

The neck veins of a person standing upright collapse almost completely all the way to the skull because of atmospheric pressure on the outside of the neck. This collapse causes the pressure in these veins to remain at zero along their entire extent. The reason for this is that any tendency for the pressure to rise above this level opens the veins and allows the pressure to fall back to zero because of flow of the blood. Conversely, any tendency for the neck vein pressure to fall below zero collapses the veins still more, which further increases their resistance and again returns the pressure back to zero.

The veins inside the skull, on the other hand, are in a noncollapsible chamber (the skull cavity) so that they cannot collapse. Consequently, *negative pressure can exist in the dural sinuses of the head;* in the standing position, the venous pressure in the sagittal sinus at the top of the brain is about –10 mm Hg because of the hydrostatic "suction" between the top of the skull and the base of the skull. Therefore, if the sagittal sinus is opened during surgery, air can be sucked immediately into the venous system; the air may even pass downward to cause air embolism in the heart, and death can ensue.

Effect of the Gravitational Factor on Arterial and Other Pressures. The gravitational factor also affects pressures in the peripheral arteries and capillaries, in addition to its effects in the veins. For instance, a standing person who has a mean arterial pressure of 100 mm Hg at the level of the heart has an arterial pressure in the feet of about 190 mm Hg. Therefore, when one states that the arterial pressure is 100 mm Hg, this generally means that this is the pressure at the gravitational level of the heart but not necessarily elsewhere in the arterial vessels.

Venous Valves and the "Venous Pump": Their Effects on Venous Pressure

Were it not for valves in the veins, the gravitational pressure effect would cause the venous pressure in the feet always to be about +90 mm Hg in a standing adult. However, every time one moves the legs, one tightens the muscles and compresses the veins in or adjacent to the muscles, and this squeezes the blood out of the veins. But the valves in the veins, shown in Figure 15-11, are arranged so that the direction of venous blood flow can be only toward the heart. Consequently, every time a person moves the legs or even tenses the leg muscles, a certain amount of venous blood is propelled toward the heart. This pumping system is known as the "venous pump" or "muscle pump," and it is efficient enough that under ordinary circumstances, the venous pressure in the feet of a walking adult remains less than +20 mm Hg.

If a person stands perfectly still, the venous pump does not work, and the venous pressures in the lower legs increase to the full gravitational value of 90 mm Hg in about 30 seconds. The pressures in the capillaries also increase greatly, causing fluid to leak from the circulatory system into the tissue spaces. As a result, the legs swell and the blood volume diminishes. Indeed, 10 to 20 percent of the blood volume can be lost from the circulatory

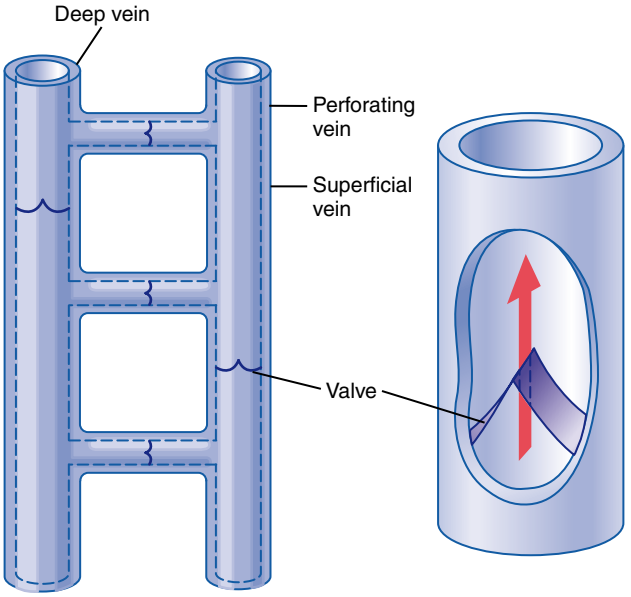


Figure 15-11 Venous valves of the leg.

system within the 15 to 30 minutes of standing absolutely still, as often occurs when a soldier is made to stand at rigid attention.

Venous Valve Incompetence Causes "Varicose" Veins. The valves of the venous system frequently become "incompetent" or sometimes even are destroyed. This is especially true when the veins have been overstretched by excess venous pressure lasting weeks or months, as occurs in pregnancy or when one stands most of the time. Stretching the veins increases their cross-sectional areas, but the leaflets of the valves do not increase in size. Therefore, the leaflets of the valves no longer close completely. When this develops, the pressure in the veins of the legs increases greatly because of failure of the venous pump; this further increases the sizes of the veins and finally destroys the function of the valves entirely. Thus, the person develops "varicose veins," which are characterized by large, bulbous protrusions of the veins beneath the skin of the entire leg, particularly the lower leg.

Whenever people with varicose veins stand for more than a few minutes, the venous and capillary pressures become very high and leakage of fluid from the capillaries causes constant edema in the legs. The edema in turn prevents adequate diffusion of nutritional materials from the capillaries to the muscle and skin cells, so the muscles become painful and weak and the skin frequently becomes gangrenous and ulcerates. The best treatment for such a condition is continual elevation of the legs to a level at least as high as the heart. Tight binders on the legs also can be of considerable assistance in preventing the edema and its sequelae.

Clinical Estimation of Venous Pressure. The venous pressure often can be estimated by simply observing the degree of distention of the peripheral veins—especially of the neck veins. For instance, in the sitting position, the neck veins are never distended in the normal quietly resting person. However, when the right atrial pressure becomes increased to as much as +10 mm Hg, the lower veins of the neck begin to protrude; and at +15 mm Hg atrial pressure essentially all the veins in the neck become distended.

Direct Measurement of Venous Pressure and Right Atrial Pressure

Venous pressure can also be measured with ease by inserting a needle directly into a vein and connecting it to a pressure recorder. The only means by which *right atrial pressure* can be measured accurately is by inserting a catheter through the peripheral veins and into the right atrium. Pressures measured through such *central venous catheters* are used almost routinely in some types of hospitalized cardiac patients to provide constant assessment of heart pumping ability.

Pressure Reference Level for Measuring Venous and Other Circulatory Pressures

In discussions up to this point, we often have spoken of right atrial pressure as being 0 mm Hg and arterial pressure as being 100 mm Hg, but we have not stated the gravitational level in the circulatory system to which this pressure is referred. There is one point in the circulatory system at which gravitational pressure factors caused by changes in body position of a healthy person usually do not affect the pressure measurement by more than 1 to 2 mm Hg. This is at or near the level of the tricuspid valve, as shown by the crossed axes in Figure 15-12. Therefore, all circulatory pressure measurements discussed in this text are referred to this level, which is called the *reference level for pressure measurement.*

The reason for lack of gravitational effects at the tricuspid valve is that the heart automatically prevents significant gravitational changes in pressure at this point in the following way:

If the pressure at the tricuspid valve rises slightly above normal, the right ventricle fills to a greater extent than usual, causing the heart to pump blood more rapidly and therefore to decrease the pressure at the tricuspid valve back toward the normal mean value. Conversely, if the pressure falls, the right ventricle fails to fill adequately, its pumping decreases, and blood dams up in the venous system until

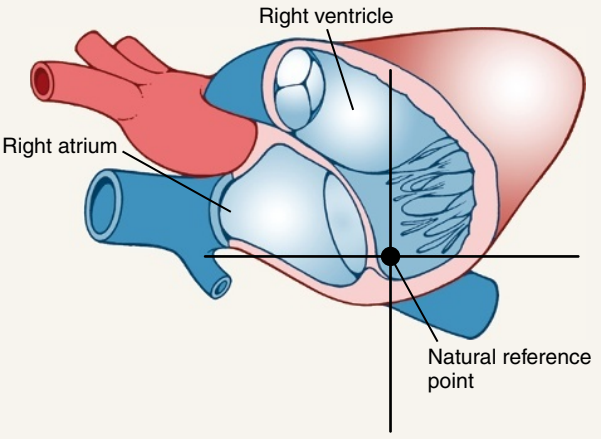


Figure 15-12 Reference point for circulatory pressure measurement (located near the tricuspid valve).

the pressure at the tricuspid level again rises to the normal value. In other words, *the heart acts as a feedback regulator of pressure* at the tricuspid valve.

When a person is lying on his or her back, the tricuspid valve is located at almost exactly 60 percent of the chest thickness in front of the back. This is the *zero pressure reference level* for a person lying down.

Blood Reservoir Function of the Veins

As pointed out in Chapter 14, more than 60 percent of all the blood in the circulatory system is usually in the veins. For this reason and also because the veins are so compliant, it is said that the venous system serves as a *blood reservoir* for the circulation.

When blood is lost from the body and the arterial pressure begins to fall, nervous signals are elicited from the carotid sinuses and other pressure-sensitive areas of the circulation, as discussed in Chapter 18. These in turn elicit nerve signals from the brain and spinal cord mainly through sympathetic nerves to the veins, causing them to constrict. This takes up much of the slack in the circulatory system caused by the lost blood. Indeed, even after as much as 20 percent of the total blood volume has been lost, the circulatory system often functions almost normally because of this variable reservoir function of the veins.

Specific Blood Reservoirs. Certain portions of the circulatory system are so extensive and/or so compliant that they are called "specific blood reservoirs." These include (1) the *spleen,* which sometimes can decrease in size sufficiently to release as much as 100 milliliters of blood into other areas of the circulation; (2) the *liver,* the sinuses of which can release several hundred milliliters of blood into the remainder of the circulation; (3) the *large abdominal veins,* which can contribute as much as 300 milliliters; and (4) the *venous plexus beneath the skin,* which also can contribute several hundred milliliters. The *heart* and the *lungs,* although not parts of the systemic venous reservoir system, must also be considered blood reservoirs. The heart, for instance, shrinks during sympathetic stimulation and in this way can contribute some 50 to 100 milliliters of blood; the lungs can contribute another 100 to 200 milliliters when the pulmonary pressures decrease to low values.

The Spleen as a Reservoir for Storing Red Blood Cells. Figure 15-13 shows that the spleen has two separate areas for storing blood: the *venous sinuses* and the *pulp.* The sinuses can swell the same as any other part of the venous system and store whole blood.

In the splenic pulp, the capillaries are so permeable that whole blood, including the red blood cells, oozes through the capillary walls into a trabecular mesh, forming the *red pulp.* The red cells are trapped by the trabeculae, while the plasma flows on into the venous sinuses and then into the general circulation. As a consequence, the red pulp of the spleen is a *special reservoir that contains large quantities of concentrated red blood cells.* These can then be expelled into the general circulation whenever the sympathetic nervous system becomes excited and causes the spleen and its vessels to contract. As much as 50 milliliters of concentrated red blood cells can be released into the circulation, raising the hematocrit 1 to 2 percent.

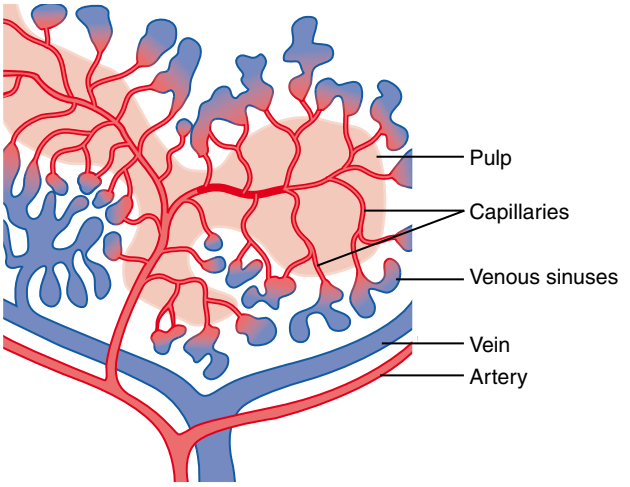


Figure 15-13 Functional structures of the spleen. (Courtesy Dr. Don W. Fawcett, Montana.)

In other areas of the splenic pulp are islands of white blood cells, which collectively are called the *white pulp.* Here lymphoid cells are manufactured similar to those manufactured in the lymph nodes. They are part of the body's immune system, described in Chapter 34.

Blood-Cleansing Function of the Spleen—Removal of Old Cells

Blood cells passing through the splenic pulp before entering the sinuses undergo thorough squeezing. Therefore, it is to be expected that fragile red blood cells would not withstand the trauma. For this reason, many of the red blood cells destroyed in the body have their final demise in the spleen. After the cells rupture, the released hemoglobin and the cell stroma are digested by the reticuloendothelial cells of the spleen, and the products of digestion are mainly reused by the body as nutrients, often for making new blood cells.

Reticuloendothelial Cells of the Spleen

The pulp of the spleen contains many large phagocytic reticuloendothelial cells, and the venous sinuses are lined with similar cells. These cells function as part of a cleansing system for the blood, acting in concert with a similar system of reticuloendothelial cells in the venous sinuses of the liver. When the blood is invaded by infectious agents, the reticuloendothelial cells of the spleen rapidly remove debris, bacteria, parasites, and so forth. Also, in many chronic infectious processes, the spleen enlarges in the same manner that lymph nodes enlarge and then performs its cleansing function even more avidly.

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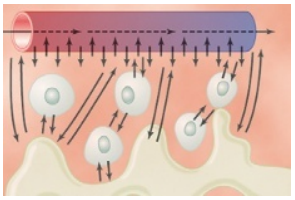
CHAPTER 16

The Microcirculation and Lymphatic System: Capillary Fluid Exchange, Interstitial Fluid, and Lymph Flow



The most purposeful function of the circulation occurs in the microcirculation: This is *transport of nutrients to the tissues and removal of cell excreta*. The small arterioles control blood flow to each tissue, and local conditions in the tissues in turn control the diameters of the arterioles. Thus, each tissue, in most instances, controls its own blood flow in relation to its individual needs, a subject that is discussed in Chapter 17.

The walls of the capillaries are extremely thin, constructed of single-layer, highly permeable endothelial cells. Therefore, water, cell nutrients, and cell excreta can all interchange quickly and easily between the tissues and the circulating blood.

The peripheral circulation of the whole body has about 10 billion capillaries with a total surface area estimated to be 500 to 700 square meters (about one-eighth the surface area of a football field). Indeed, it is rare that any single functional cell of the body is more than 20 to 30 micrometers away from a capillary.

Structure of the Microcirculation and Capillary System

The microcirculation of each organ is organized specifically to serve that organ's needs. In general, each nutrient artery entering an organ branches six to eight times before the arteries become small enough to be called *arterioles*, which generally have internal diameters of only 10 to 15 micrometers. Then the arterioles themselves branch two to five times, reaching diameters of 5 to 9 micrometers at their ends where they supply blood to the capillaries.

The arterioles are highly muscular, and their diameters can change manyfold. The metarterioles (the terminal arterioles) do not have a continuous muscular coat, but smooth muscle fibers encircle the vessel at intermittent points, as shown in Figure 16-1 by the black dots on the sides of the metarteriole.

At the point where each true capillary originates from a metarteriole, a smooth muscle fiber usually encircles the capillary. This is called the *precapillary sphincter*. This sphincter can open and close the entrance to the capillary.

The venules are larger than the arterioles and have a much weaker muscular coat. Yet the pressure in the venules is much less than that in the arterioles, so the venules can still contract considerably despite the weak muscle.

This typical arrangement of the capillary bed is not found in all parts of the body, although a similar arrangement may serve the same purposes. Most important, the metarterioles and the precapillary sphincters are in close contact with the tissues they serve. Therefore, the local conditions of the tissues—the concentrations of nutrients, end products of metabolism, hydrogen ions, and so forth—can cause direct effects on the vessels to control local blood flow in each small tissue area.

Structure of the Capillary Wall. Figure 16-2 shows the ultramicroscopic structure of typical endothelial cells in the capillary wall as found in most organs of the body, especially in muscles and connective tissue. Note that the wall is composed of a unicellular layer of endothelial cells and is surrounded by a thin basement membrane on the outside of the capillary. The total thickness of the capillary wall is only about 0.5 micrometer. The internal diameter of the capillary is 4 to 9 micrometers, barely large enough for red blood cells and other blood cells to squeeze through.

"Pores" in the Capillary Membrane. Figure 16-2 shows two small passageways connecting the interior of the capillary with the exterior. One of these is an *intercellular cleft*, which is the thin-slit, curving channel that lies at the bottom of the figure between adjacent endothelial cells. Each cleft is interrupted periodically by short ridges of protein attachments that hold the endothelial cells together, but between these ridges fluid can percolate freely through the cleft. The cleft normally has a uniform spacing with a width of about 6 to 7 nanometers (60 to 70 angstroms), slightly smaller than the diameter of an albumin protein molecule.

Because the intercellular clefts are located only at the edges of the endothelial cells, they usually represent no more than 1/1000 of the total surface area of the capillary wall. Nevertheless, the rate of thermal motion of water

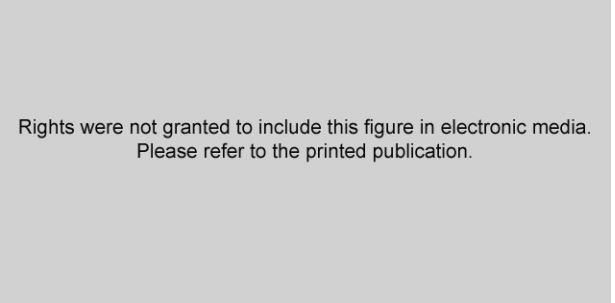


Figure 16-1 Structure of the mesenteric capillary bed. (Redrawn from Zweifach BW: Factors Regulating Blood Pressure. New York: Josiah Macy, Jr., Foundation, 1950.)

molecules, as well as most water-soluble ions and small solutes, is so rapid that all of these diffuse with ease between the interior and exterior of the capillaries through these "slit-pores," the intercellular clefts.

Present in the endothelial cells are many minute *plasmalemmal vesicles,* also called *caveolae (small caves).* These form from oligomers of proteins called *caveolins* that are associated with molecules of *cholesterol* and *sphingolipids*. Although the precise functions of caveolae are still unclear, they are believed to play a role in *endocytosis* (the process by which the cell engulfs material from outside the cell) and *transcytosis* of macromolecules across endothelial cells. The caveolae at the surface of the cell appear to imbibe small packets of plasma or extracellular fluid that contain plasma proteins. These vesicles can then move slowly through the endothelial cell. Some of these vesicles may coalesce to form *vesicular channels* all the way through the endothelial cell, which is demonstrated in Figure 16-2.

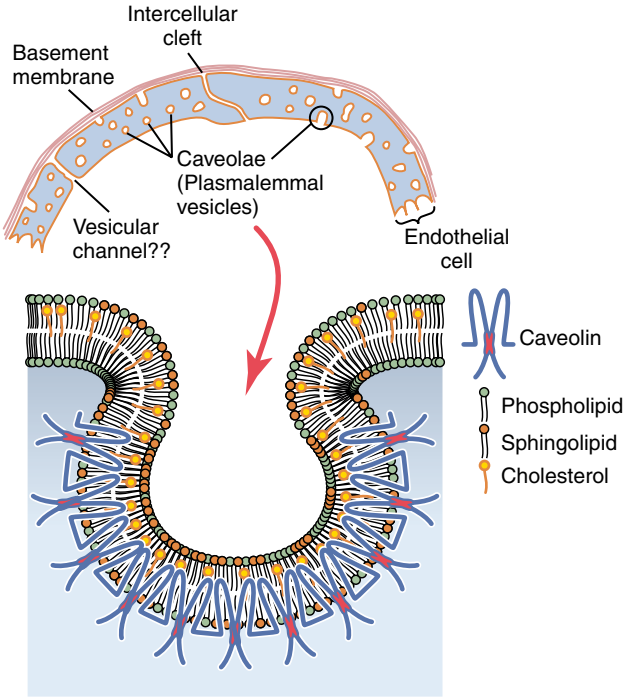


Figure 16-2 Structure of the capillary wall. Note especially the ***intercellular cleft*** at the junction between adjacent endothelial cells; it is believed that most water-soluble substances diffuse through the capillary membrane along the clefts. Small membrane invaginations, called ***caveolae,*** are believed to play a role in transporting macromolecules across the cell membrane. Caveolae contain caveolins, proteins which interact with cholesterol and polymerize to form the caveolae.

Special Types of "Pores" Occur in the Capillaries of Certain Organs. The "pores" in the capillaries of some organs have special characteristics to meet the peculiar needs of the organs. Some of these characteristics are as follows:

1. In the *brain,* the junctions between the capillary endothelial cells are mainly "tight" junctions that allow only extremely small molecules such as water, oxygen, and carbon dioxide to pass into or out of the brain tissues.
2. In the *liver,* the opposite is true. The clefts between the capillary endothelial cells are wide open so that almost all dissolved substances of the plasma, including the plasma proteins, can pass from the blood into the liver tissues.
3. The pores of the *gastrointestinal capillary membranes* are midway between those of the muscles and those of the liver.
4. In the *glomerular capillaries of the kidney,* numerous small oval windows called *fenestrae* penetrate all the way through the middle of the endothelial cells so that tremendous amounts of very small molecular and ionic substances (but not the large molecules of the plasma proteins) can filter through the glomeruli without having to pass through the clefts between the endothelial cells.

Flow of Blood in the Capillaries—Vasomotion

Blood usually does not flow continuously through the capillaries. Instead, it flows intermittently, turning on and off every few seconds or minutes. The cause of this intermittency is the phenomenon called *vasomotion,* which means intermittent contraction of the metarterioles and precapillary sphincters (and sometimes even the very small arterioles as well).

Regulation of Vasomotion. The most important factor found thus far to affect the degree of opening and closing of the metarterioles and precapillary sphincters is the concentration of *oxygen* in the tissues. When the rate of oxygen usage by the tissue is great so that tissue oxygen concentration decreases below normal, the intermittent periods of capillary blood flow occur more often, and the duration of each period of flow lasts longer, thereby allowing the capillary blood to carry increased quantities of oxygen (as well as other nutrients) to the tissues.

This effect, along with multiple other factors that control local tissue blood flow, is discussed in Chapter 17.

Average Function of the Capillary System

Despite the fact that blood flow through each capillary is intermittent, so many capillaries are present in the tissues that their overall function becomes averaged. That is, there is an *average rate of blood flow* through each tissue capillary bed, an *average capillary pressure* within the capillaries, and an *average rate of transfer of substances* between the blood of the capillaries and the surrounding interstitial fluid. In the remainder of this chapter, we are concerned with these averages, although one must remember that the average functions are, in reality, the functions of literally billions of individual capillaries, each operating intermittently in response to local conditions in the tissues.

Exchange of Water, Nutrients, and Other Substances Between the Blood and Interstitial Fluid

Diffusion Through the Capillary Membrane

By far the most important means by which substances are transferred between the plasma and the interstitial fluid is *diffusion*. Figure 16-3 demonstrates this process, showing that as the blood flows along the lumen of the capillary, tremendous numbers of water molecules and dissolved particles diffuse back and forth through the capillary wall, providing continual mixing between the interstitial fluid and the plasma. *Diffusion results from thermal motion of the water molecules and dissolved substances in the fluid,* the different molecules and ions moving first in one direction and then another, bouncing randomly in every direction.

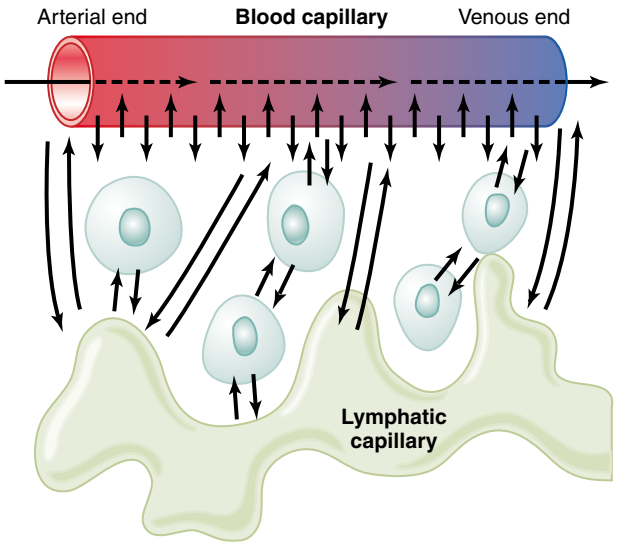


Figure 16-3 Diffusion of fluid molecules and dissolved substances between the capillary and interstitial fluid spaces.

Lipid-Soluble Substances Can Diffuse Directly Through the Cell Membranes of the Capillary Endothelium. If a substance is lipid soluble, it can diffuse directly through the cell membranes of the capillary without having to go through the pores. Such substances include *oxygen* and *carbon dioxide.* Because these substances can permeate all areas of the capillary membrane, their rates of transport through the capillary membrane are many times faster than the rates for lipid-insoluble substances, such as sodium ions and glucose that can go only through the pores.

Water-Soluble, Non-Lipid-Soluble Substances Diffuse Through Intercellular "Pores" in the Capillary Membrane. Many substances needed by the tissues are soluble in water but cannot pass through the lipid membranes of the endothelial cells; such substances include *water molecules* themselves, *sodium ions, chloride ions,* and *glucose.* Despite the fact that not more than 1/1000 of the surface area of the capillaries is represented by the intercellular clefts between the endothelial cells, the velocity of thermal molecular motion in the clefts is so great that even this small area is sufficient to allow tremendous diffusion of water and water-soluble substances through these cleft-pores. To give one an idea of the rapidity with which these substances diffuse, *the rate at which water molecules diffuse through the capillary membrane is about 80 times as great as the rate at which plasma itself flows linearly along the capillary*. That is, the water of the plasma is exchanged with the water of the interstitial fluid 80 times before the plasma can flow the entire distance through the capillary.

Effect of Molecular Size on Passage Through the Pores. The width of the capillary intercellular cleft-pores, 6 to 7 nanometers, is about 20 times the diameter of the water molecule, which is the smallest molecule that normally passes through the capillary pores. Conversely, the diameters of plasma protein molecules are slightly greater than the width of the pores. Other substances, such as sodium ions, chloride ions, glucose, and urea, have intermediate diameters. Therefore, the permeability of the capillary pores for different substances varies according to their molecular diameters.

Table 16-1 gives the relative permeabilities of the capillary pores in skeletal muscle for substances commonly encountered, demonstrating, for instance, that the permeability for glucose molecules is 0.6 times that for water molecules, whereas the permeability for albumin molecules is very, very slight, only 1/1000 that for water molecules.

A word of caution must be issued at this point. The capillaries in various tissues have extreme differences in their permeabilities. For instance, the membranes of the liver capillary sinusoids are so permeable that even plasma proteins pass freely through these walls, almost as easily as water and other substances. Also, the permeability of the renal glomerular membrane for water

Table 16-1 Relative Permeability of Skeletal Muscle Capillary Pores to Different-Sized Molecules

Substance	Molecular Weight	Permeability
Water	18	1.00
NaCl	58.5	0.96
Urea	60	0.8
Glucose	180	0.6
Sucrose	342	0.4
Inulin	5,000	0.2
Myoglobin	17,600	0.03
Hemoglobin	68,000	0.01
Albumin	69,000	0.001

Data from Pappenheimer JR: Passage of molecules through capillary walls. Physiol Rev 33:387, 1953.

and electrolytes is about 500 times the permeability of the muscle capillaries, but this is not true for the plasma proteins; for these, the capillary permeabilities are very slight, as in other tissues and organs. When we study these different organs later in this text, it should become clear why some tissues—the liver, for instance—require greater degrees of capillary permeability than others to transfer tremendous amounts of nutrients between the blood and liver parenchymal cells, and the kidneys to allow filtration of large quantities of fluid for formation of urine.

Effect of Concentration Difference on Net Rate of Diffusion Through the Capillary Membrane. The "net" rate of diffusion of a substance through any membrane is proportional to the *concentration difference of the substance* between the two sides of the membrane. That is, the greater the difference between the concentrations of any given substance on the two sides of the capillary membrane, the greater the net movement of the substance in one direction through the membrane. For instance, the concentration of oxygen in capillary blood is normally greater than in the interstitial fluid. Therefore, large quantities of oxygen normally move from the blood toward the tissues. Conversely, the concentration of carbon dioxide is greater in the tissues than in the blood, which causes excess carbon dioxide to move into the blood and to be carried away from the tissues.

The rates of diffusion through the capillary membranes of most nutritionally important substances are so great that only slight concentration differences suffice to cause more than adequate transport between the plasma and interstitial fluid. For instance, the concentration of oxygen in the interstitial fluid immediately outside the capillary is no more than a few percent less than its concentration in the plasma of the blood, yet this slight difference causes enough oxygen to move from the blood into the interstitial spaces to provide all the oxygen required for tissue metabolism, often as much as several liters of oxygen per minute during very active states of the body.

Interstitium and Interstitial Fluid

About one sixth of the total volume of the body consists of spaces between cells, which collectively are called the *interstitium.* The fluid in these spaces is the *interstitial fluid.*

The structure of the interstitium is shown in Figure 16-4. It contains two major types of solid structures: (1) *collagen fiber bundles* and (2) *proteoglycan filaments.* The collagen fiber bundles extend long distances in the interstitium. They are extremely strong and therefore provide most of the tensional strength of the tissues. The proteoglycan filaments, however, are extremely thin coiled or twisted molecules composed of about 98 percent *hyaluronic acid* and 2 percent protein. These molecules are so thin that they cannot be seen with a light microscope and are difficult to demonstrate even with the electron microscope. Nevertheless, they form a mat of very fine reticular filaments aptly described as a "brush pile."

"Gel" in the Interstitium. The fluid in the interstitium is derived by filtration and diffusion from the capillaries. It contains almost the same constituents as plasma except for much lower concentrations of proteins because proteins do not easily pass outward through the pores of the capillaries. The interstitial fluid is entrapped mainly in the minute spaces among the proteoglycan filaments. This combination of proteoglycan filaments and fluid entrapped within them has the characteristics of a *gel* and therefore is called *tissue gel.*

Because of the large number of proteoglycan filaments, it is *difficult for fluid to flow* easily through the tissue gel.

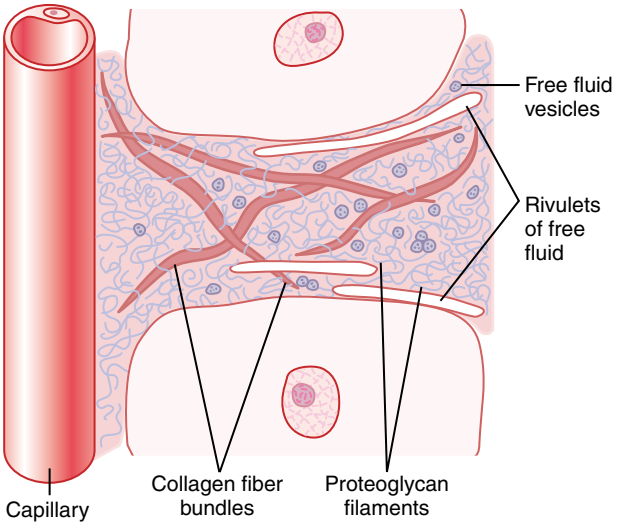


Figure 16-4 Structure of the interstitium. Proteoglycan filaments are everywhere in the spaces between the collagen fiber bundles. Free fluid vesicles and small amounts of free fluid in the form of rivulets occasionally also occur.

Instead, *fluid mainly diffuses* through the gel; that is, it moves molecule by molecule from one place to another by kinetic, thermal motion rather than by large numbers of molecules moving together.

Diffusion through the gel occurs about 95 to 99 percent as rapidly as it does through free fluid. For the short distances between the capillaries and the tissue cells, this diffusion allows rapid transport through the interstitium not only of water molecules but also of electrolytes, small molecular weight nutrients, cellular excreta, oxygen, carbon dioxide, and so forth.

"Free" Fluid in the Interstitium. Although almost all the fluid in the interstitium normally is entrapped within the tissue gel, occasionally small *rivulets of "free" fluid* and *small free fluid vesicles* are also present, which means fluid that is free of the proteoglycan molecules and therefore can flow freely. When a dye is injected into the circulating blood, it often can be seen to flow through the interstitium in the small rivulets, usually coursing along the surfaces of collagen fibers or surfaces of cells.

The amount of "free" fluid present in *normal* tissues is slight, usually less than 1 percent. Conversely, when the tissues develop *edema, these small pockets and rivulets of free fluid expand tremendously* until one half or more of the edema fluid becomes freely flowing fluid independent of the proteoglycan filaments.

Fluid Filtration Across Capillaries Is Determined by Hydrostatic and Colloid Osmotic Pressures, as Well as Capillary Filtration Coefficient

The hydrostatic pressure in the capillaries tends to force fluid and its dissolved substances through the capillary pores into the interstitial spaces. Conversely, osmotic pressure caused by the plasma proteins (called *colloid osmotic pressure*) tends to cause fluid movement by osmosis from the interstitial spaces into the blood. This osmotic pressure exerted by the plasma proteins normally prevents significant loss of fluid volume from the blood into the interstitial spaces.

Also important is the *lymphatic system,* which returns to the circulation the small amounts of excess protein and fluid that leak from the blood into the interstitial spaces. In the remainder of this chapter, we discuss the mechanisms that control capillary filtration and lymph flow function together to regulate the respective volumes of the plasma and the interstitial fluid.

Hydrostatic and Colloid Osmotic Forces Determine Fluid Movement Through the Capillary Membrane. Figure 16-5 shows the four primary forces that determine whether fluid will move out of the blood into the interstitial fluid or in the opposite direction. These forces, called "Starling forces" in honor of the physiologist who first demonstrated their importance, are:

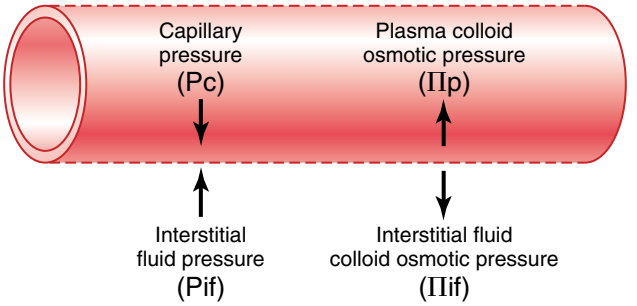


Figure 16-5 Fluid pressure and colloid osmotic pressure forces operate at the capillary membrane, tending to move fluid either outward or inward through the membrane pores.

1. The *capillary pressure* (Pc), which tends to force fluid *outward* through the capillary membrane.
2. The *interstitial fluid pressure* (Pif), which tends to force fluid *inward* through the capillary membrane when Pif is positive but outward when Pif is negative.
3. The capillary *plasma colloid osmotic pressure* (Πp), which tends to cause osmosis of fluid *inward* through the capillary membrane.
4. The *interstitial fluid colloid osmotic pressure* (Πif), which tends to cause osmosis of fluid *outward* through the capillary membrane.

If the sum of these forces—the *net filtration pressure*—is positive, there will be a net *fluid filtration* across the capillaries. If the sum of the Starling forces is negative, there will be a net *fluid absorption* from the interstitial spaces into the capillaries. The net filtration pressure (NFP) is calculated as:

$$NFP = Pc - Pif - \Pi p + \Pi if$$

As discussed later, the NFP is slightly positive under normal conditions, resulting in a net filtration of fluid across the capillaries into the interstitial space in most organs. The rate of fluid filtration in a tissue is also determined by the number and size of the pores in each capillary, as well as the number of capillaries in which blood is flowing. These factors are usually expressed together as the *capillary filtration coefficient* (K_f). The K_f is therefore a measure of the capacity of the capillary membranes to filter water for a given NFP and is usually expressed as ml/min per mm Hg net filtration pressure.

The rate of capillary fluid filtration is therefore determined as:

$$\text{Filtration} = K_f \times NFP$$

In the following sections we discuss each of the forces that determine the rate of capillary fluid filtration.

Capillary Hydrostatic Pressure

Various methods have been used to estimate the capillary hydrostatic pressure: (1) *direct micropipette cannulation of the capillaries,* which has given an average mean capillary pressure of about 25 mm Hg in some tissues such as

the skeletal muscle and the gut, and (2) *indirect functional measurement of the capillary pressure,* which has given a capillary pressure averaging about 17 mm Hg in these tissues.

Micropipette Method for Measuring Capillary Pressure. To measure pressure in a capillary by cannulation, a microscopic glass pipette is thrust directly into the capillary, and the pressure is measured by an appropriate micromanometer system. Using this method, capillary pressures have been measured in capillaries of exposed tissues of animals and in large capillary loops of the eponychium at the base of the fingernail in humans. These measurements have given pressures of 30 to 40 mm Hg in the arterial ends of the capillaries, 10 to 15 mm Hg in the venous ends, and about 25 mm Hg in the middle.

In some capillaries, such as the *glomerular capillaries* of the kidneys, the pressures measured by the micropipette method are much higher, averaging about 60 mm Hg. The *peritubular capillaries* of the kidneys, in contrast, have hydrostatic pressure that average only about 13 mm Hg. Thus, the capillary hydrostatic pressures in different tissues are highly variable, depending on the particular tissue and the physiological condition.

Isogravimetric Method for Indirectly Measuring "Functional" Capillary Pressure. Figure 16-6 demonstrates an *isogravimetric* method for indirectly estimating capillary pressure. This figure shows a section of gut held up by one arm of a gravimetric balance. Blood is perfused through the blood vessels of the gut wall. When the arterial pressure is decreased, the resulting decrease in capillary pressure allows the osmotic pressure of the plasma proteins to cause absorption of fluid out of the gut wall and makes the weight of the gut decrease. This immediately causes displacement of the balance arm. To prevent this weight decrease, the venous pressure is increased an amount sufficient to overcome the effect of decreasing the arterial pressure. In other words, the capillary pressure is kept constant while simultaneously (1) decreasing the arterial pressure and (2) increasing the venous pressure.

In the graph in the lower part of the figure, the changes in arterial and venous pressures that exactly nullify all weight changes are shown. The arterial and venous lines meet each other at a value of 17 mm Hg. Therefore, the capillary pressure must have remained at this same level of 17 mm Hg throughout these maneuvers; otherwise, either filtration or absorption of fluid through the capillary walls would have occurred. Thus, in a roundabout way, the "functional" capillary pressure in this tissue is measured to be about 17 mm Hg.

It is clear that the isogravimetric method, which determines the capillary pressure that exactly balances all the forces tending to move fluid into or out of the capillaries, gives a lower value compared with the capillary pressure measured directly with a micropipette. A major reason for this is that capillary fluid filtration is not exactly balanced

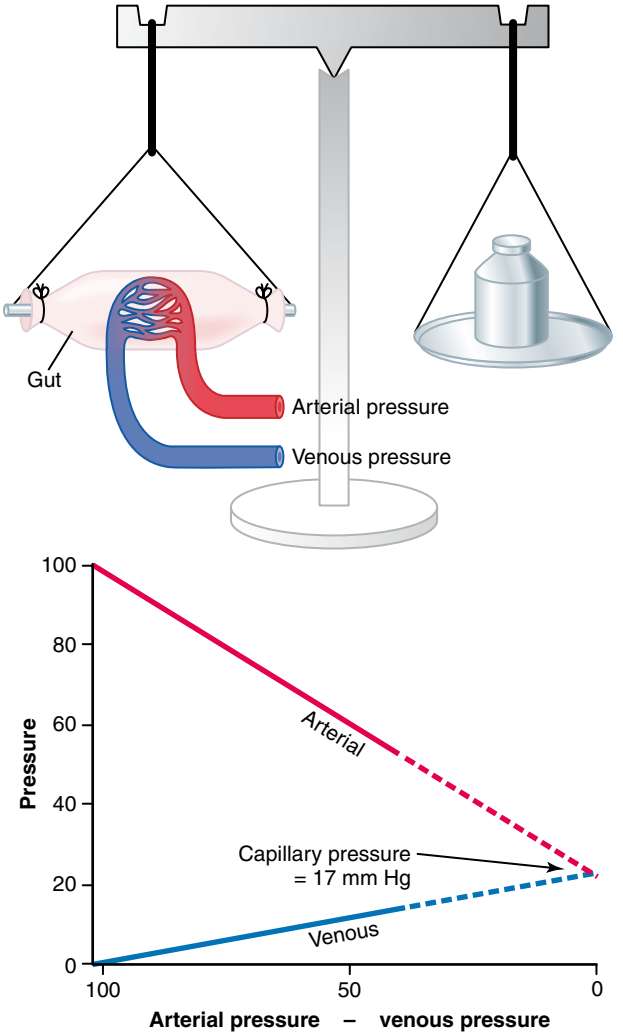


Figure 16-6 Isogravimetric method for measuring capillary pressure.

with fluid reabsorption in most tissues. The fluid that is filtered in excess of what is reabsorbed is carried away by lymph vessels in most tissues. In the glomerular capillaries of the kidneys, a very large amount of fluid, approximately 125 ml/min, is continuously filtered.

Interstitial Fluid Hydrostatic Pressure

There are several methods for measuring interstitial fluid hydrostatic pressure and each of these gives slightly different values, depending on the method used and the tissue in which the pressure is measured. In loose subcutaneous tissue, interstitial fluid pressure measured by the different methods is usually a few millimeters of mercury less than atmospheric pressure; that is, the values are called *negative interstitial fluid pressure.* In other tissues that are surrounded by capsules, such as the kidneys, the interstitial pressure is generally *positive* (greater than atmospheric pressure). The methods most widely used have been (1) direct cannulation of the tissues with a micropipette, (2) measurement of the pressure from implanted perforated capsules, and (3) measurement of the pressure from a cotton wick inserted into the tissue.

Measurement of Interstitial Fluid Pressure Using the Micropipette. The same type of micropipette used for measuring capillary pressure can also be used in some tissues for measuring interstitial fluid pressure. The tip of the micropipette is about 1 micrometer in diameter, but even this is 20 or more times larger than the sizes of the spaces between the proteoglycan filaments of the interstitium. Therefore, the pressure that is measured is probably the pressure in a free fluid pocket.

The first pressures measured using the micropipette method ranged from −1 to +2 mm Hg but were usually slightly positive. With experience and improved equipment for making such measurements, more recent pressures have averaged about −2 mm Hg, giving average pressure values in *loose* tissues, such as skin, that are slightly less than atmospheric pressure.

Measurement of Interstitial Free Fluid Pressure in Implanted Perforated Hollow Capsules. Interstitial free fluid pressure measured by this method when using 2-centimeter diameter capsules in normal *loose* subcutaneous tissue averages about −6 mm Hg, but with smaller capsules, the values are not greatly different from the −2 mm Hg measured by the micropipette.

Interstitial Fluid Pressures in Tightly Encased Tissues

Some tissues of the body are surrounded by tight encasements, such as the cranial vault around the brain, the strong fibrous capsule around the kidney, the fibrous sheaths around the muscles, and the sclera around the eye. In most of these, regardless of the method used for measurement, the interstitial fluid pressures are positive. However, these interstitial fluid pressures almost invariably are still less than the pressures exerted on the outsides of the tissues by their encasements. For instance, the cerebrospinal fluid pressure surrounding the brain of an animal lying on its side averages about +10 mm Hg, whereas the *brain interstitial fluid pressure* averages about +4 to +6 mm Hg. In the kidneys, the capsular pressure surrounding the kidney averages about +13 mm Hg, whereas the reported *renal interstitial fluid pressures* have averaged about +6 mm Hg. Thus, if one remembers that the pressure exerted on the skin is atmospheric pressure, which is considered to be zero pressure, one might formulate a general rule that the normal interstitial fluid pressure is usually several millimeters of mercury negative with respect to the pressure that surrounds each tissue.

Is the True Interstitial Fluid Pressure in Loose Subcutaneous Tissue Subatmospheric?

The concept that the interstitial fluid pressure is subatmospheric in some tissues of the body began with clinical observations that could not be explained by the previously held concept that interstitial fluid pressure was always positive. Some of the pertinent observations are the following:

1. When a skin graft is placed on a concave surface of the body, such as in an eye socket after removal of the eye, before the skin becomes attached to the sublying socket, fluid tends to collect underneath the graft. Also, the skin attempts to shorten, with the result that it tends to pull it away from the concavity. Nevertheless, some negative force underneath the skin causes absorption of the fluid and usually literally pulls the skin back into the concavity.
2. Less than 1 mm Hg of positive pressure is required to inject large volumes of fluid into loose subcutaneous tissues, such as beneath the lower eyelid, in the axillary space, and in the scrotum. Amounts of fluid calculated to be more than 100 times the amount of fluid normally in the interstitial space, when injected into these areas, cause no more than about 2 mm Hg of positive pressure. The importance of these observations is that they show that such tissues do not have strong fibers that can prevent the accumulation of fluid. Therefore, some other mechanism, such as a low compliance system, must be available to prevent such fluid accumulation.
3. In most natural cavities of the body where there is free fluid in dynamic equilibrium with the surrounding interstitial fluids, the pressures that have been measured have been negative. Some of these are the following:
   Intrapleural space: −8 mm Hg
   Joint synovial spaces: −4 to −6 mm Hg
   Epidural space: −4 to −6 mm Hg
4. The implanted capsule for measuring the interstitial fluid pressure can be used to record dynamic changes in this pressure. The changes are approximately those that one would calculate to occur (1) when the arterial pressure is increased or decreased, (2) when fluid is injected into the surrounding tissue space, or (3) when a highly concentrated colloid osmotic agent is injected into the blood to absorb fluid from the tissue spaces. It is not likely that these dynamic changes could be recorded this accurately unless the capsule pressure closely approximated the true interstitial pressure.

Summary—An Average Value for Negative Interstitial Fluid Pressure in Loose Subcutaneous Tissue. Although the aforementioned different methods give slightly different values for interstitial fluid pressure, there currently is a general belief among most physiologists that the true interstitial fluid pressure in *loose* subcutaneous tissue is slightly less subatmospheric, averaging about −3 mm Hg.

Pumping by the Lymphatic System Is the Basic Cause of the Negative Interstitial Fluid Pressure

The lymphatic system is discussed later in the chapter, but we need to understand here the basic role that this system plays in determining interstitial fluid pressure. The lymphatic system is a "scavenger" system that removes excess fluid, excess protein molecules, debris, and other matter from the tissue spaces. Normally, when fluid enters the

terminal lymphatic capillaries, the lymph vessel walls automatically contract for a few seconds and pump the fluid into the blood circulation. This overall process creates the slight negative pressure that has been measured for fluid in the interstitial spaces.

Plasma Colloid Osmotic Pressure

Proteins in the Plasma Cause Colloid Osmotic Pressure. In the basic discussion of osmotic pressure in Chapter 4, it was pointed out that only those molecules or ions that fail to pass through the pores of a semipermeable membrane exert osmotic pressure. Because the proteins are the only dissolved constituents in the plasma and interstitial fluids that do not readily pass through the capillary pores, it is the proteins of the plasma and interstitial fluids that are responsible for the osmotic pressures on the two sides of the capillary membrane. To distinguish this osmotic pressure from that which occurs at the cell membrane, it is called either *colloid osmotic pressure* or *oncotic pressure.* The term "colloid" osmotic pressure is derived from the fact that a protein solution resembles a colloidal solution despite the fact that it is actually a true molecular solution.

Normal Values for Plasma Colloid Osmotic Pressure. The colloid osmotic pressure of normal human plasma averages about 28 mm Hg; 19 mm of this is caused by molecular effects of the dissolved protein and 9 mm by the *Donnan effect*—that is, extra osmotic pressure caused by sodium, potassium, and the other cations held in the plasma by the proteins.

Effect of the Different Plasma Proteins on Colloid Osmotic Pressure. The plasma proteins are a mixture that contains albumin, with an average molecular weight of 69,000; globulins, 140,000; and fibrinogen, 400,000. Thus, 1 gram of globulin contains only half as many molecules as 1 gram of albumin, and 1 gram of fibrinogen contains only one sixth as many molecules as 1 gram of albumin. It should be recalled from the discussion of osmotic pressure in Chapter 4 that osmotic pressure is determined by the *number of molecules* dissolved in a fluid rather than by the mass of these molecules. Therefore, when corrected for number of molecules rather than mass, the following chart gives both the relative mass concentrations (g/dl) of the different types of proteins in normal plasma and their respective contributions to the total plasma colloid osmotic pressure (Πp).

	g/dl	Πp (mm Hg)
Albumin	4.5	21.8
Globulins	2.5	6.0
Fibrinogen	0.3	0.2
Total	7.3	28.0

Thus, about 80 percent of the total colloid osmotic pressure of the plasma results from the albumin fraction, 20 percent from the globulins, and almost none from the fibrinogen. Therefore, from the point of view of capillary and tissue fluid dynamics, it is mainly albumin that is important.

Interstitial Fluid Colloid Osmotic Pressure

Although the size of the usual capillary pore is smaller than the molecular sizes of the plasma proteins, this is not true of all the pores. Therefore, small amounts of plasma proteins do leak through the pores into the interstitial spaces through pores and by transcytosis in small vesicles.

The total quantity of protein in the entire 12 liters of interstitial fluid of the body is slightly greater than the total quantity of protein in the plasma itself, but because this volume is four times the volume of plasma, the average protein *concentration* of the interstitial fluid is usually only 40 percent of that in plasma, or about 3 g/dl. Quantitatively, one finds that the average interstitial fluid colloid osmotic pressure for this concentration of proteins is about 8 mm Hg.

Exchange of Fluid Volume Through the Capillary Membrane

Now that the different factors affecting fluid movement through the capillary membrane have been discussed, it is possible to put all these together to see how the capillary system maintains normal fluid volume distribution between the plasma and the interstitial fluid.

The average capillary pressure at the arterial ends of the capillaries is 15 to 25 mmHg greater than at the venous ends. Because of this difference, fluid "filters" out of the capillaries at their arterial ends, but at their venous ends fluid is reabsorbed back into the capillaries. Thus, a small amount of fluid actually "flows" through the tissues from the arterial ends of the capillaries to the venous ends. The dynamics of this flow are as follows.

Analysis of the Forces Causing Filtration at the Arterial End of the Capillary. The approximate average forces operative at the *arterial end* of the capillary that cause movement through the capillary membrane are shown as follows:

	mm Hg
Forces tending to move fluid outward:	
Capillary pressure (arterial end of capillary)	30
Negative interstitial free fluid pressure	3
Interstitial fluid colloid osmotic pressure	8
TOTAL OUTWARD FORCE	41
Forces tending to move fluid inward:	
Plasma colloid osmotic pressure	28
TOTAL INWARD FORCE	28
Summation of forces:	
Outward	41
Inward	28
NET OUTWARD FORCE (AT ARTERIAL END)	13

Thus, the summation of forces at the arterial end of the capillary shows a net *filtration pressure* of 13 mm Hg, tending to move fluid outward through the capillary pores.

This 13 mm Hg filtration pressure causes, on average, about 1/200 of the plasma in the flowing blood to filter out of the arterial ends of the capillaries into the interstitial spaces each time the blood passes through the capillaries.

Analysis of Reabsorption at the Venous End of the Capillary. The low blood pressure at the venous end of the capillary changes the balance of forces in favor of absorption as follows:

	mm Hg
Forces tending to move fluid inward:	
Plasma colloid osmotic pressure	28
TOTAL INWARD FORCE	28
Forces tending to move fluid outward:	
Capillary pressure (venous end of capillary)	10
Negative interstitial free fluid pressure	3
Interstitial fluid colloid osmotic pressure	8
TOTAL OUTWARD FORCE	21
Summation of forces:	
Inward	28
Outward	21
NET INWARD FORCE	7

Thus, the force that causes fluid to move into the capillary, 28 mm Hg, is greater than that opposing reabsorption, 21 mm Hg. The difference, 7 mm Hg, is the *net reabsorption pressure* at the venous ends of the capillaries. This reabsorption pressure is considerably less than the filtration pressure at the capillary arterial ends, but remember that the venous capillaries are more numerous and more permeable than the arterial capillaries, so that less reabsorption pressure is required to cause inward movement of fluid.

The reabsorption pressure causes about nine tenths of the fluid that has filtered out of the arterial ends of the capillaries to be reabsorbed at the venous ends. The remaining one tenth flows into the lymph vessels and returns to the circulating blood.

Starling Equilibrium for Capillary Exchange

Ernest H. Starling pointed out more than a century ago that under normal conditions, a state of near-equilibrium exists in most capillaries. That is, the amount of fluid filtering outward from the arterial ends of capillaries equals almost exactly the fluid returned to the circulation by absorption. The slight disequilibrium that does occur accounts for the fluid that is eventually returned to the circulation by way of the lymphatics.

The following chart shows the principles of the Starling equilibrium. For this chart, the pressures in the arterial and venous capillaries are averaged to calculate mean *functional* capillary pressure for the entire length of the capillary. This calculates to be 17.3 mm Hg.

	mm Hg
Mean forces tending to move fluid outward:	
Mean capillary pressure	17.3
Negative interstitial free fluid pressure	3.0
Interstitial fluid colloid osmotic pressure	8.0
TOTAL OUTWARD FORCE	28.3
Mean force tending to move fluid inward:	
Plasma colloid osmotic pressure	28.0
TOTAL INWARD FORCE	28.0
Summation of mean forces:	
Outward	28.3
Inward	28.0
NET OUTWARD FORCE	0.3

Thus, for the total capillary circulation, we find a near-equilibrium between the total outward forces, 28.3 mm Hg, and the total inward force, 28.0 mm Hg. This slight imbalance of forces, 0.3 mm Hg, causes slightly more filtration of fluid into the interstitial spaces than reabsorption. This slight excess of filtration is called *net filtration,* and it is the fluid that must be returned to the circulation through the lymphatics. The normal rate of net filtration *in the entire body,* not including the kidneys, is only about 2 ml/min.

Filtration Coefficient. In the previous example, an average net imbalance of forces at the capillary membranes of 0.3 mm Hg causes net fluid filtration in the entire body of 2 ml/min. Expressing this for each millimeter of mercury imbalance, one finds a net filtration rate of 6.67 ml/min of fluid per mm Hg for the entire body. This is called the whole body capillary *filtration coefficient.*

The filtration coefficient can also be expressed for separate parts of the body in terms of rate of filtration per minute per mm Hg per 100 grams of tissue. On this basis, the filtration coefficient of the average tissue is about 0.01 ml/min/mm Hg/100 g of tissue. But, because of extreme differences in permeabilities of the capillary systems in different tissues, this coefficient varies more than 100-fold among the different tissues. It is very small in brain and muscle, moderately large in subcutaneous tissue, large in the intestine, and extreme in the liver and glomerulus of the kidney where the pores are either numerous or wide open. By the same token, the permeation of proteins through the capillary membranes varies greatly as well. The concentration of protein in the interstitial fluid of muscles is about 1.5 g/dl; in subcutaneous tissue, 2 g/dl; in intestine, 4 g/dl; and in liver, 6 g/dl.

Effect of Abnormal Imbalance of Forces at the Capillary Membrane

If the mean capillary pressure rises above 17 mm Hg, the net force tending to cause filtration of fluid into the tissue spaces rises. Thus, a 20 mm Hg rise in mean capillary pressure causes an increase in net filtration pressure from 0.3 mm Hg to 20.3 mm Hg, which results in 68 times as

much net filtration of fluid into the interstitial spaces as normally occurs. To prevent accumulation of excess fluid in these spaces would require 68 times the normal flow of fluid into the lymphatic system, an amount that is 2 to 5 times too much for the lymphatics to carry away. As a result, fluid will begin to accumulate in the interstitial spaces and edema will result.

Conversely, if the capillary pressure falls very low, net reabsorption of fluid into the capillaries will occur instead of net filtration and the blood volume will increase at the expense of the interstitial fluid volume. These effects of imbalance at the capillary membrane in relation to the development of different kinds of edema are discussed in Chapter 25.

Lymphatic System

The lymphatic system represents an accessory route through which fluid can flow from the interstitial spaces into the blood. Most important, the lymphatics can carry proteins and large particulate matter away from the tissue spaces, neither of which can be removed by absorption directly into the blood capillaries. This return of proteins to the blood from the interstitial spaces is an essential function without which we would die within about 24 hours.

Lymph Channels of the Body

Almost all tissues of the body have special lymph channels that drain excess fluid directly from the interstitial spaces. The exceptions include the superficial portions of the skin, the central nervous system, the endomysium of muscles, and the bones. But, even these tissues have minute interstitial channels called *prelymphatics* through which interstitial fluid can flow; this fluid eventually empties either into lymphatic vessels or, in the case of the brain, into the cerebrospinal fluid and then directly back into the blood.

Essentially all the lymph vessels from the lower part of the body eventually empty into the *thoracic duct,* which in turn empties into the blood venous system at the juncture of the *left* internal jugular vein and left subclavian vein, as shown in Figure 16-7.

Lymph from the left side of the head, the left arm, and parts of the chest region also enters the thoracic duct before it empties into the veins.

Lymph from the right side of the neck and head, the right arm, and parts of the right thorax enters the *right lymph duct* (much smaller than the thoracic duct), which empties into the blood venous system at the juncture of the *right* subclavian vein and internal jugular vein.

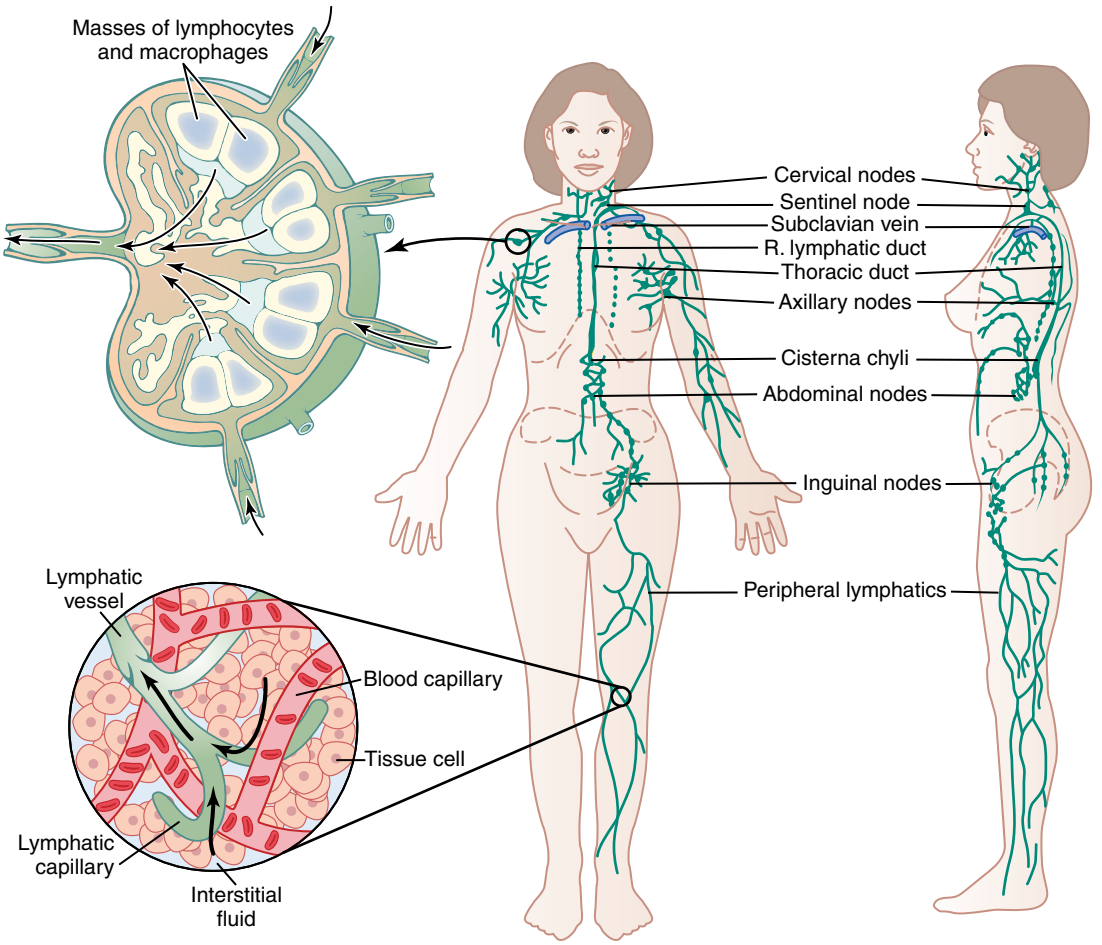


Figure 16-7 Lymphatic system.

Terminal Lymphatic Capillaries and Their Permeability. Most of the fluid filtering from the *arterial ends* of *blood capillaries* flows among the cells and finally is reabsorbed back into the *venous ends* of the *blood capillaries;* but on the average, about one tenth of the fluid instead enters the *lymphatic capillaries* and returns to the blood through the lymphatic system rather than through the venous capillaries. The total quantity of all this lymph is normally only 2 to 3 liters each day.

The fluid that returns to the circulation by way of the lymphatics is extremely important because substances of high molecular weight, such as proteins, cannot be absorbed from the tissues in any other way, although they can enter the lymphatic capillaries almost unimpeded. The reason for this is a special structure of the lymphatic capillaries, demonstrated in Figure 16-8. This figure shows the endothelial cells of the lymphatic capillary attached by *anchoring filaments* to the surrounding connective tissue. At the junctions of adjacent endothelial cells, the edge of one endothelial cell overlaps the edge of the adjacent cell in such a way that the overlapping edge is free to flap inward, thus forming a minute valve that opens to the interior of the lymphatic capillary. Interstitial fluid, along with its suspended particles, can push the valve open and flow directly into the lymphatic capillary. But this fluid has difficulty leaving the capillary once it has entered because any backflow closes the flap valve. Thus, the lymphatics have valves at the very tips of the terminal lymphatic capillaries, as well as valves along their larger vessels up to the point where they empty into the blood circulation.

Formation of Lymph

Lymph is derived from interstitial fluid that flows into the lymphatics. Therefore, lymph as it first enters the terminal lymphatics has almost the same composition as the interstitial fluid.

The protein concentration in the interstitial fluid of most tissues averages about 2 g/dl, and the protein concentration of lymph flowing from these tissues is near this value. In the liver, lymph formed has a protein concentration as high as 6 g/dl, and lymph formed in the intestines has a protein concentration as high as 3 to 4 g/dl. Because about two thirds of all lymph normally is derived from the liver and intestines, the thoracic duct lymph, which is a mixture of lymph from all areas of the body, usually has a protein concentration of 3 to 5 g/dl.

The lymphatic system is also one of the major routes for absorption of nutrients from the gastrointestinal tract, especially for absorption of virtually all fats in food, as discussed in Chapter 65. Indeed, after a fatty meal, thoracic duct lymph sometimes contains as much as 1 to 2 percent fat.

Finally, even large particles, such as bacteria, can push their way between the endothelial cells of the lymphatic capillaries and in this way enter the lymph. As the lymph passes through the lymph nodes, these particles are almost entirely removed and destroyed, as discussed in Chapter 33.

Rate of Lymph Flow

About 100 milliliters per hour of lymph flows through the *thoracic duct* of a resting human, and approximately another 20 milliliters flows into the circulation each hour through other channels, making a total estimated lymph flow of about 120 ml/hr or 2 to 3 liters per day.

Effect of Interstitial Fluid Pressure on Lymph Flow. Figure 16-9 shows the effect of different levels of interstitial fluid pressure on lymph flow as measured in dog legs. Note that normal lymph flow is very little at interstitial fluid pressures more negative than the normal value of −6 mm Hg. Then, as the pressure rises to 0 mm Hg (atmospheric pressure), flow increases more than 20-fold. Therefore, any factor that increases interstitial fluid

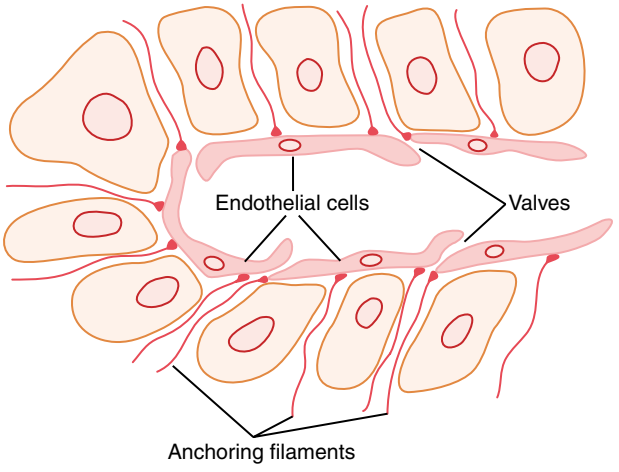


Figure 16-8 Special structure of the lymphatic capillaries that permits passage of substances of high molecular weight into the lymph.

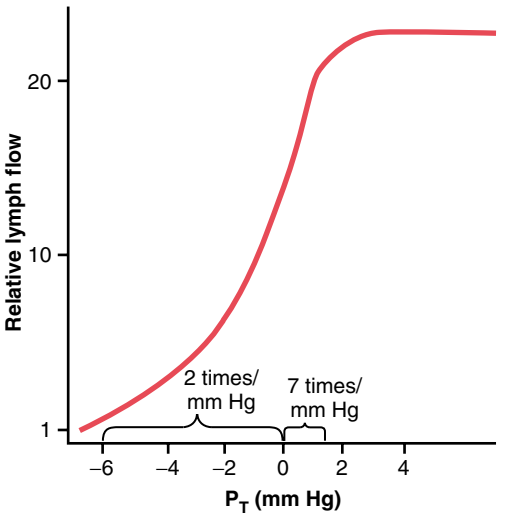


Figure 16-9 Relation between interstitial fluid pressure and lymph flow in the leg of a dog. Note that lymph flow reaches a maximum when the interstitial pressure, P_T, rises slightly above atmospheric pressure (0 mm Hg). (Courtesy Drs. Harry Gibson and Aubrey Taylor.)

pressure also increases lymph flow if the lymph vessels are functioning normally. Such factors include the following:

- Elevated capillary hydrostatic pressure
- Decreased plasma colloid osmotic pressure
- Increased interstitial fluid colloid osmotic pressure
- Increased permeability of the capillaries

All of these cause a balance of fluid exchange at the blood capillary membrane to favor fluid movement into the interstitium, thus increasing interstitial fluid volume, interstitial fluid pressure, and lymph flow all at the same time.

However, note in Figure 16-9 that when the interstitial fluid pressure becomes 1 or 2 mm Hg greater than atmospheric pressure (>0 mm Hg), lymph flow fails to rise any further at still higher pressures. This results from the fact that the increasing tissue pressure not only increases entry of fluid into the lymphatic capillaries but also compresses the outside surfaces of the larger lymphatics, thus impeding lymph flow. At the higher pressures, these two factors balance each other almost exactly, so lymph flow reaches what is called the "maximum lymph flow rate." This is illustrated by the upper level plateau in Figure 16-9.

Lymphatic Pump Increases Lymph Flow. Valves exist in all lymph channels; typical valves are shown in Figure 16-10 in collecting lymphatics into which the lymphatic capillaries empty.

Motion pictures of exposed lymph vessels in animals and in human beings show that when a collecting lymphatic or larger lymph vessel becomes stretched with fluid, the smooth muscle in the wall of the vessel automatically contracts. Furthermore, each segment of the lymph vessel between successive valves functions as a separate automatic pump. That is, even slight filling of a segment causes it to contract and the fluid is pumped through the next valve into the next lymphatic segment. This fills the subsequent segment, and a few seconds later it, too, contracts, the process continuing all along the lymph vessel until the fluid is finally emptied into the blood circulation. In a very large lymph vessel such as the thoracic duct, this lymphatic pump can generate pressures as great as 50 to 100 mm Hg.

Pumping Caused by External Intermittent Compression of the Lymphatics. In addition to the pumping caused by intrinsic intermittent contraction of the lymph vessel walls, any external factor that intermittently compresses the lymph vessel also can cause pumping. In order of their importance, such factors are as follows:

- Contraction of surrounding skeletal muscles
- Movement of the parts of the body
- Pulsations of arteries adjacent to the lymphatics
- Compression of the tissues by objects outside the body

The lymphatic pump becomes very active during exercise, often increasing lymph flow 10- to 30-fold. Conversely, during periods of rest, lymph flow is sluggish, almost zero.

Lymphatic Capillary Pump. The terminal lymphatic capillary is also capable of pumping lymph, in addition to the pumping by the larger lymph vessels. As explained earlier in the chapter, the walls of the lymphatic capillaries are tightly adherent to the surrounding tissue cells by means of their anchoring filaments. Therefore, each time excess fluid enters the tissue and causes the tissue to swell, the anchoring filaments pull on the wall of the lymphatic capillary and fluid flows into the terminal lymphatic capillary through the junctions between the endothelial cells. Then, when the tissue is compressed, the pressure inside the capillary increases and causes the overlapping edges of the endothelial cells to close like valves. Therefore, the pressure pushes the lymph forward into the collecting lymphatic instead of backward through the cell junctions.

The lymphatic capillary endothelial cells also contain a few contractile actomyosin filaments. In some animal tissues (e.g., the bat's wing) these filaments have been observed to cause rhythmical contraction of the lymphatic capillaries in the same way that many of the small blood and larger lymphatic vessels also contract rhythmically. Therefore, it is probable that at least part of lymph

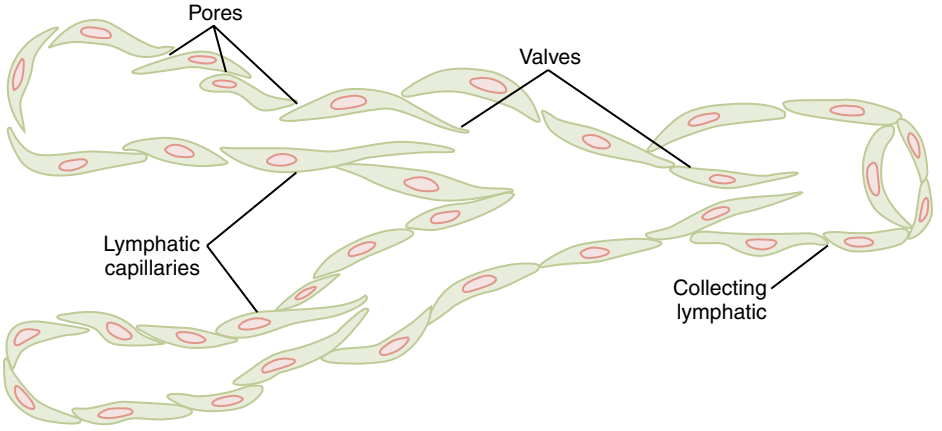


Figure 16-10 Structure of lymphatic capillaries and a collecting lymphatic, showing also the lymphatic valves.

pumping results from lymph capillary endothelial cell contraction in addition to contraction of the larger muscular lymphatics.

Summary of Factors That Determine Lymph Flow. From the previous discussion, one can see that the two primary factors that determine lymph flow are (1) the interstitial fluid pressure and (2) the activity of the lymphatic pump. Therefore, one can state that, roughly, *the rate of lymph flow is determined by the product of interstitial fluid pressure times the activity of the lymphatic pump*.

Role of the Lymphatic System in Controlling Interstitial Fluid Protein Concentration, Interstitial Fluid Volume, and Interstitial Fluid Pressure

It is already clear that the lymphatic system functions as an "overflow mechanism" to return to the circulation excess proteins and excess fluid volume from the tissue spaces. Therefore, the lymphatic system also plays a central role in controlling (1) the concentration of proteins in the interstitial fluids, (2) the volume of interstitial fluid, and (3) the interstitial fluid pressure. Let us explain how these factors interact.

First, remember that small amounts of proteins leak continuously out of the blood capillaries into the interstitium. Only minute amounts, if any, of the leaked proteins return to the circulation by way of the venous ends of the blood capillaries. Therefore, these proteins tend to accumulate in the interstitial fluid, and this in turn increases the colloid osmotic pressure of the interstitial fluids.

Second, the increasing colloid osmotic pressure in the interstitial fluid shifts the balance of forces at the blood capillary membranes in favor of fluid filtration into the interstitium. Therefore, in effect, fluid is translocated osmotically outward through the capillary wall by the proteins and into the interstitium, thus increasing both interstitial fluid volume and interstitial fluid pressure.

Third, the increasing interstitial fluid pressure greatly increases the rate of lymph flow, as explained previously. This in turn carries away the excess interstitial fluid volume and excess protein that has accumulated in the spaces.

Thus, once the interstitial fluid protein concentration reaches a certain level and causes a comparable increase in interstitial fluid volume and interstitial fluid pressure, the return of protein and fluid by way of the lymphatic system becomes great enough to balance exactly the rate of leakage of these into the interstitium from the blood capillaries. Therefore, the quantitative values of all these factors reach a steady state; they will remain balanced at these steady state levels until something changes the rate of leakage of proteins and fluid from the blood capillaries.

Significance of Negative Interstitial Fluid Pressure as a Means for Holding the Body Tissues Together

Traditionally, it has been assumed that the different tissues of the body are held together entirely by connective tissue fibers. However, at many places in the body, connective tissue fibers are very weak or even absent. This occurs particularly at points where tissues slide over one another, such as the skin sliding over the back of the hand or over the face. Yet even at these places, the tissues are held together by the negative interstitial fluid pressure, which is actually a partial vacuum. When the tissues lose their negative pressure, fluid accumulates in the spaces and the condition known as *edema* occurs. This is discussed in Chapter 25.

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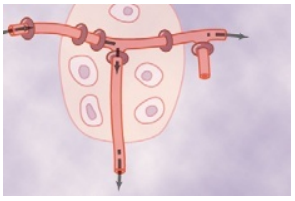
CHAPTER 17

Local and Humoral Control of Tissue Blood Flow



Local Control of Blood Flow in Response to Tissue Needs

One of the most fundamental principles of circulatory function is the ability of each tissue to control its own local blood flow in proportion to its metabolic needs.

What are some of the specific needs of the tissues for blood flow? The answer to this is manyfold, including the following:

1. Delivery of oxygen to the tissues.
2. Delivery of other nutrients, such as glucose, amino acids, and fatty acids.
3. Removal of carbon dioxide from the tissues.
4. Removal of hydrogen ions from the tissues.
5. Maintenance of proper concentrations of other ions in the tissues.
6. Transport of various hormones and other substances to the different tissues.

Certain organs have special requirements. For instance, blood flow to the skin determines heat loss from the body and in this way helps to control body temperature. Also, delivery of adequate quantities of blood plasma to the kidneys allows the kidneys to excrete the waste products of the body and to regulate body fluid volumes and electrolytes.

We shall see that these factors exert extreme degrees of local blood flow control and that different tissues place different levels of importance on these factors in controlling blood flow.

Variations in Blood Flow in Different Tissues and Organs. Note in Table 17-1 the very large blood flows in some organs—for example, several hundred ml/min per 100 g of thyroid or adrenal gland tissue and a total blood flow of 1350 ml/min in the liver, which is 95 ml/min/100 g of liver tissue.

Also note the extremely large blood flow through the kidneys—1100 ml/min. This extreme amount of flow is required for the kidneys to perform their function of cleansing the blood of waste products.

Conversely, most surprising is the low blood flow to all the *inactive* muscles of the body, only a total of 750 ml/min, even though the muscles constitute between 30 and 40 percent of the total body mass. In the resting state, the metabolic activity of the muscles is very low, and so also is the blood flow, only 4 ml/min/100 g. Yet, during heavy exercise, muscle metabolic activity can increase more than 60-fold and the blood flow as much as 20-fold, increasing to as high as 16,000 ml/min in the body's total muscle vascular bed (or 80 ml/min/100 g of muscle).

Importance of Blood Flow Control by the Local Tissues. One might ask the simple question: Why not simply allow a very large blood flow all the time through every tissue of the body, always enough to supply the tissue's needs whether the activity of the tissue is little or great? The answer is equally simple: To do this would require many times more blood flow than the heart can pump.

Experiments have shown that the blood flow to each tissue usually is regulated at the minimal level that will supply the tissue's requirements—no more, no less. For instance, in tissues for which the most important requirement is delivery of oxygen, the blood flow is always controlled at a level only slightly more than required to maintain full tissue oxygenation but no more than this. By controlling local blood flow in such an exact way, the tissues almost never suffer from oxygen nutritional deficiency and the workload on the heart is kept at a minimum.

Mechanisms of Blood Flow Control

Local blood flow control can be divided into two phases: (1) acute control and (2) long-term control.

Acute control is achieved by rapid changes in local vasodilation or vasoconstriction of the arterioles, metarterioles, and precapillary sphincters, occurring within seconds to minutes to provide very rapid maintenance of appropriate local tissue blood flow.

Long-term control, however, means slow, controlled changes in flow over a period of days, weeks, or even

Table 17-1 Blood Flow to Different Organs and Tissues Under Basal Conditions

	Percent of Cardiac Output	ml/min	ml/min/100 g of Tissue Weight
Brain	14	700	50
Heart	4	200	70
Bronchi	2	100	25
Kidneys	22	1100	360
Liver	27	1350	95
Portal	(21)	1050	
Arterial	(6)	300	
Muscle (inactive state)	15	750	4
Bone	5	250	3
Skin (cool weather)	6	300	3
Thyroid gland	1	50	160
Adrenal glands	0.5	25	300
Other tissues	3.5	175	1.3
Total	100.0	5000	

months. In general, these long-term changes provide even better control of the flow in proportion to the needs of the tissues. These changes come about as a result of an increase or decrease in the physical sizes and numbers of actual blood vessels supplying the tissues.

Acute Control of Local Blood Flow

Effect of Tissue Metabolism on Local Blood Flow. Figure 17-1 shows the approximate acute effect on blood flow of increasing the rate of metabolism in a local tissue, such as in a skeletal muscle. Note that an increase in metabolism up to eight times normal increases the blood flow acutely about fourfold.

Acute Local Blood Flow Regulation When Oxygen Availability Changes. One of the most necessary of the metabolic nutrients is oxygen. Whenever the availability of oxygen to the tissues decreases, such as (1) at high altitude at the top of a high mountain, (2) in pneumonia, (3) in carbon monoxide poisoning (which poisons the ability of hemoglobin to transport oxygen), or (4) in cyanide poisoning (which poisons the ability of the tissues to use oxygen), the blood flow through the tissues increases markedly. Figure 17-2 shows that as the arterial oxygen saturation decreases to about 25 percent of normal, the blood flow through an isolated leg increases about threefold; that is, the blood flow increases almost enough, but not quite enough, to make up for the decreased amount of oxygen in the blood, thus almost maintaining a relatively constant supply of oxygen to the tissues.

Total cyanide poisoning of oxygen usage by a local tissue area can cause local blood flow to increase as much as sevenfold, thus demonstrating the extreme effect of oxygen deficiency to increase blood flow.

There are two basic theories for the regulation of local blood flow when either the rate of tissue metabolism changes or the availability of oxygen changes. They are (1) the *vasodilator theory* and (2) the *oxygen lack theory.*

Vasodilator Theory for Acute Local Blood Flow Regulation—Possible Special Role of Adenosine. According to this theory, the greater the rate of metabolism or the less the availability of oxygen or some other nutrients to a tissue, the greater the rate of formation of *vasodilator substances* in the tissue cells. The vasodilator substances then are believed to diffuse through the tissues to the precapillary sphincters, metarterioles, and arterioles to cause dilation. Some of the different vasodilator substances that have been suggested are *adenosine,*

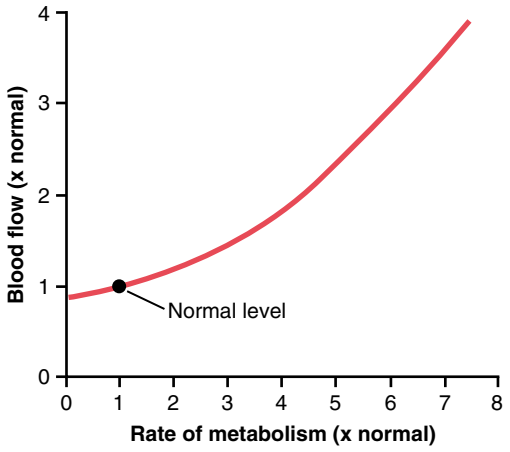


Figure 17-1 Effect of increasing rate of metabolism on tissue blood flow.

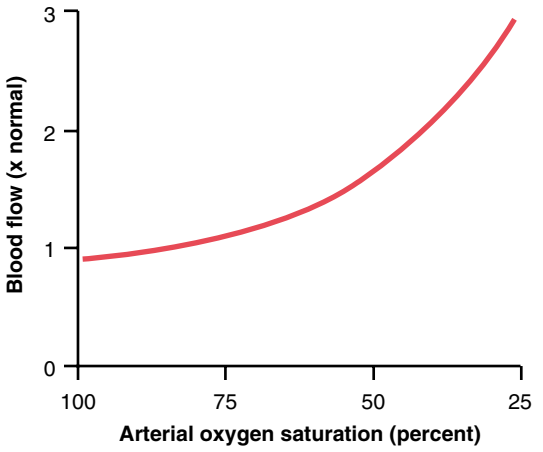


Figure 17-2 Effect of decreasing arterial oxygen saturation on blood flow through an isolated dog leg.

carbon dioxide, adenosine phosphate compounds, histamine, potassium ions, and *hydrogen ions.*

Vasodilator substances may be released from the tissue in response to oxygen deficiency. For instance, experiments have shown that decreased availability of oxygen can cause both adenosine and lactic acid (containing hydrogen ions) to be released into the spaces between the tissue cells; these substances then cause intense acute vasodilation and therefore are responsible, or partially responsible, for the local blood flow regulation. Vasodilator substances, such as carbon dioxide, lactic acid, and potassium ions, tend to increase in the tissues when blood flow is reduced and cell metabolism continues at the same rate, or when cell metabolism is suddenly increased. As the concentration of vasodilator metabolites increases, this causes vasodilation of the arterioles, increasing the tissue blood flow and returning the tissue concentration of the metabolites toward normal.

Many physiologists believe that *adenosine* is an important local vasodilator for controlling local blood flow. For example, minute quantities of adenosine are released from heart muscle cells when coronary blood flow becomes too little, and this causes enough local vasodilation in the heart to return coronary blood flow back to normal. Also, whenever the heart becomes more active than normal and the heart's metabolism increases an extra amount, this, too, causes increased utilization of oxygen, followed by (1) decreased oxygen concentration in the heart muscle cells with (2) consequent degradation of adenosine triphosphate (ATP), which (3) increases the release of adenosine. It is believed that much of this adenosine leaks out of the heart muscle cells to cause coronary vasodilation, providing increased coronary blood flow to supply the increased nutrient demands of the active heart.

Although research evidence is less clear, many physiologists also have suggested that the same adenosine mechanism is an important controller of blood flow in skeletal muscle and many other tissues, as well as in the heart. It has been difficult, however, to prove that sufficient quantities of any single vasodilator substance, including adenosine, are indeed formed in the tissues to cause all the measured increase in blood flow. It is likely that a combination of several different vasodilators released by the tissues contributes to blood flow regulation.

Oxygen Lack Theory for Local Blood Flow Control. Although the vasodilator theory is widely accepted, several critical facts have made other physiologists favor still another theory, which can be called either the *oxygen lack theory* or, more accurately, the *nutrient lack theory* (because other nutrients besides oxygen are involved). Oxygen (and other nutrients as well) is required as one of the metabolic nutrients to cause vascular muscle contraction. Therefore, in the absence of adequate oxygen, it is reasonable to believe that the blood vessels simply would relax and therefore naturally dilate. Also, increased utilization of oxygen in the tissues as a result of increased metabolism theoretically could decrease the availability of oxygen to the smooth muscle fibers in the local blood vessels, and this, too, would cause local vasodilation.

A mechanism by which the oxygen lack theory could operate is shown in Figure 17-3. This figure shows a tissue unit, consisting of a metarteriole with a single sidearm capillary and its surrounding tissue. At the origin of the capillary is a *precapillary sphincter,* and around the metarteriole are several other smooth muscle fibers. Observing such a tissue under a microscope—for example, in a bat's wing—one sees that the precapillary sphincters are normally either completely open or completely closed. The number of precapillary sphincters that are open at any given time is roughly proportional to the requirements of the tissue for nutrition. The precapillary sphincters and metarterioles open and close cyclically several times per minute, with the duration of the open phases being proportional to the metabolic needs of the tissues for oxygen. The cyclical opening and closing is called *vasomotion.*

Let us explain how oxygen concentration in the local tissue could regulate blood flow through the area. Because smooth muscle requires oxygen to remain contracted, one might assume that the strength of contraction of the sphincters would increase with an increase in oxygen concentration. Consequently, when the oxygen concentration in the tissue rises above a certain level, the precapillary and metarteriole sphincters presumably would close until the tissue cells consume the excess oxygen. But when the excess oxygen is gone and the oxygen concentration falls low enough, the sphincters would open once more to begin the cycle again.

Thus, on the basis of available data, either a *vasodilator substance theory* or an *oxygen lack theory* could explain acute local blood flow regulation in response to the metabolic needs of the tissues. Probably the truth lies in a combination of the two mechanisms.

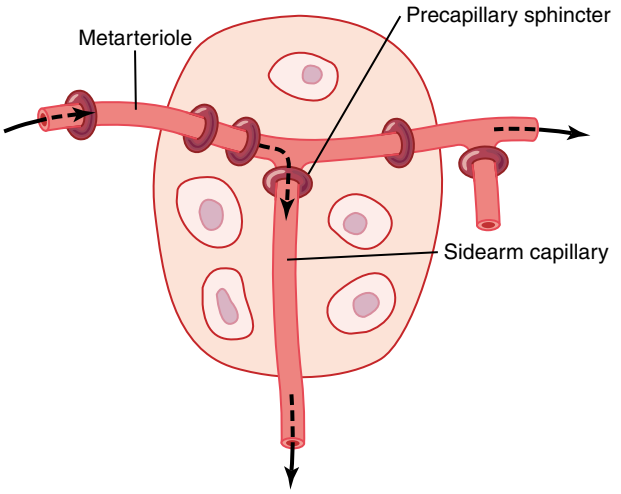


Figure 17-3 Diagram of a tissue unit area for explanation of acute local feedback control of blood flow, showing a ***metarteriole*** passing through the tissue and a ***sidearm capillary*** with its ***precapillary sphincter*** for controlling capillary blood flow.

Possible Role of Other Nutrients Besides Oxygen in Control of Local Blood Flow. Under special conditions, it has been shown that lack of glucose in the perfusing blood can cause local tissue vasodilation. Also, it is possible that this same effect occurs when other nutrients, such as amino acids or fatty acids, are deficient, although this has not been studied adequately. In addition, vasodilation occurs in the vitamin deficiency disease *beriberi,* in which the patient has deficiencies of the vitamin B substances *thiamine, niacin,* and *riboflavin.* In this disease, the peripheral vascular blood flow almost everywhere in the body often increases twofold to threefold. Because all these vitamins are necessary for oxygen-induced phosphorylation, which is required to produce ATP in the tissue cells, one can well understand how deficiency of these vitamins might lead to diminished smooth muscle contractile ability and therefore also local vasodilation.

Special Examples of Acute "Metabolic" Control of Local Blood Flow

The mechanisms that we have described thus far for local blood flow control are called "metabolic mechanisms" because all of them function in response to the metabolic needs of the tissues. Two additional special examples of metabolic control of local blood flow are *reactive hyperemia* and *active hyperemia.*

Reactive Hyperemia. When the blood supply to a tissue is blocked for a few seconds to as long as an hour or more and then is unblocked, blood flow through the tissue usually increases immediately to four to seven times normal; this increased flow will continue for a few seconds if the block has lasted only a few seconds but sometimes continues for as long as many hours if the blood flow has been stopped for an hour or more. This phenomenon is called *reactive hyperemia.*

Reactive hyperemia is another manifestation of the local "metabolic" blood flow regulation mechanism; that is, lack of flow sets into motion all of those factors that cause vasodilation. After short periods of vascular occlusion, the extra blood flow during the reactive hyperemia phase lasts long enough to repay almost exactly the tissue oxygen deficit that has accrued during the period of occlusion. This mechanism emphasizes the close connection between local blood flow regulation and delivery of oxygen and other nutrients to the tissues.

Active Hyperemia. When any tissue becomes highly active, such as an exercising muscle, a gastrointestinal gland during a hypersecretory period, or even the brain during rapid mental activity, the rate of blood flow through the tissue increases. Here again, by simply applying the basic principles of local blood flow control, one can easily understand this *active hyperemia.* The increase in local metabolism causes the cells to devour tissue fluid nutrients rapidly and also to release large quantities of vasodilator substances. The result is to dilate the local blood vessels and, therefore, to increase local blood flow. In this way, the active tissue receives the additional nutrients required to sustain its new level of function. As pointed out earlier, active hyperemia in skeletal muscle can increase local muscle blood flow as much as 20-fold during intense exercise.

"Autoregulation" of Blood Flow When the Arterial Pressure Changes from Normal—"Metabolic" and "Myogenic" Mechanisms

In any tissue of the body, a rapid increase in arterial pressure causes an immediate rise in blood flow. But, within less than a minute, the blood flow in most tissues returns almost to the normal level, even though the arterial pressure is kept elevated. This return of flow toward normal is called "*autoregulation*" of blood flow. After autoregulation has occurred, the local blood flow in most body tissues will be related to arterial pressure approximately in accord with the solid "acute" curve in Figure 17-4. Note that between arterial pressures of about 70 mm Hg and 175 mm Hg the blood flow increases only 20 to 30 percent even though the arterial pressure increases 150 percent.

For almost a century, two views have been proposed to explain this acute autoregulation mechanism. They have been called (1) the metabolic theory and (2) the myogenic theory.

The *metabolic theory* can be understood easily by applying the basic principles of local blood flow regulation discussed in previous sections. Thus, when the arterial pressure becomes too great, the excess flow provides too much oxygen and too many other nutrients to the tissues and "washes out" the vasodilators released by the tissues. These nutrients (especially oxygen) and decreased tissue levels of vasodilators then cause the blood vessels to constrict and the flow to return nearly to normal despite the increased pressure.

The *myogenic theory,* however, suggests that still another mechanism not related to tissue metabolism explains the phenomenon of autoregulation. This theory is based on the observation that sudden stretch of small blood vessels causes the smooth muscle of the vessel wall

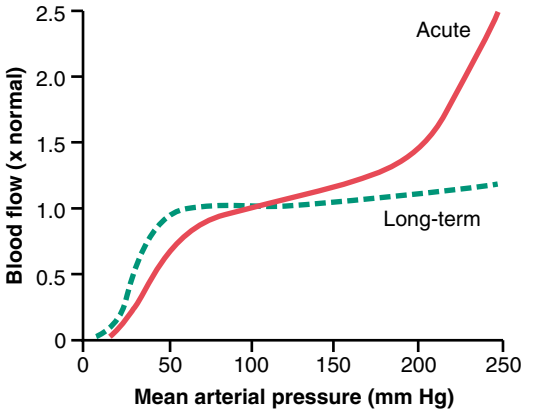


Figure 17-4 Effect of different levels of arterial pressure on blood flow through a muscle. The *solid red curve* shows the effect if the arterial pressure is raised over a period of a few minutes. The *dashed green curve* shows the effect if the arterial pressure is raised slowly over a period of many weeks.

to contract. Therefore, it has been proposed that when high arterial pressure stretches the vessel, this in turn causes reactive vascular constriction that reduces blood flow nearly back to normal. Conversely, at low pressures, the degree of stretch of the vessel is less, so that the smooth muscle relaxes, reducing vascular resistance and helping to return flow toward normal.

The myogenic response is inherent to vascular smooth muscle and can occur in the absence of neural or hormonal influences. It is most pronounced in arterioles but can also be observed in arteries, venules, veins, and even lymphatic vessels. Myogenic contraction is initiated by stretch-induced vascular depolarization, which then rapidly increases calcium ion entry from the extracellular fluid into the cells, causing them to contract. Changes in vascular pressure may also open or close other ion channels that influence vascular contraction. The precise mechanisms by which changes in pressure cause opening or closing of vascular ion channels are still uncertain but likely involve mechanical effects of pressure on extracellular proteins that are tethered to cytoskeleton elements of the vascular wall or to the ion channels themselves.

The myogenic mechanism appears to be important in preventing excessive stretch of blood vessel when blood pressure is increased. However, the role of the myogenic mechanism in blood flow regulation is unclear because this pressure-sensing mechanism cannot directly detect changes in blood flow in the tissue. Indeed, metabolic factors appear to override the myogenic mechanism in circumstances where the metabolic demands of the tissues are significantly increased, such as during vigorous muscle exercise, which can cause dramatic increases in skeletal muscle blood flow.

Special Mechanisms for Acute Blood Flow Control in Specific Tissues

Although the general mechanisms for local blood flow control discussed thus far are present in almost all tissues of the body, distinctly different mechanisms operate in a few special areas. All mechanisms are discussed throughout this text in relation to specific organs, but two notable ones are as follows:

1. In the *kidneys,* blood flow control is vested to a great extent in a mechanism called *tubuloglomerular feedback,* in which the composition of the fluid in the early distal tubule is detected by an epithelial structure of the distal tubule itself called the *macula densa.* This is located where the distal tubule lies adjacent to the afferent and efferent arterioles at the nephron *juxtaglomerular apparatus.* When too much fluid filters from the blood through the glomerulus into the tubular system, feedback signals from the macula densa cause constriction of the afferent arterioles, in this way reducing both renal blood flow and glomerular filtration rate back to or near to normal. The details of this mechanism are discussed in Chapter 26.
2. In the *brain,* in addition to control of blood flow by tissue oxygen concentration, the concentrations of carbon dioxide and hydrogen ions play prominent roles. An increase of either or both of these dilates the cerebral vessels and allows rapid washout of the excess carbon dioxide or hydrogen ions from the brain tissues. This is important because the *level of excitability of the brain itself is highly dependent on exact control of both carbon dioxide concentration and hydrogen ion concentration*. This special mechanism for cerebral blood flow control is presented in Chapter 61.
3. In the *skin,* blood flow control is closely linked to regulation of body temperature. Cutaneous and subcutaneous flow regulates heat loss from the body by metering the flow of heat from the core to the surface of the body, where heat is lost to the environment. Skin blood flow is controlled largely by the central nervous system through the sympathetic nerves, as discussed in Chapter 73. Although skin blood flow is only about 3 ml/min/100 g of tissue in cool weather, large changes from that value can occur as needed. When humans are exposed to body heating, skin blood flow may increase manyfold, to as high as *7 to 8 L/min* for the entire body. When body temperature is reduced, skin blood flow decreases, falling to barely above zero at very low temperatures. Even with severe vasoconstriction, skin blood flow is usually great enough to meet the basic metabolic demands of the skin.

Control of Tissue Blood Flow by Endothelial-Derived Relaxing or Constricting Factors

The endothelial cells lining the blood vessels synthesize several substances that, when released, can affect the degree of relaxation or contraction of the arterial wall. For many of these endothelial-derived relaxing or constrictor factors, the physiological roles are just beginning to be understood and clinical applications have, in most cases, not yet been developed.

Nitric Oxide—A Vasodilator Released from Healthy Endothelial Cells. The most important of the endothelial-derived relaxing factors is *nitric oxide (NO),* a lipophilic gas that is released from endothelial cells in response to a variety of chemical and physical stimuli. *Nitric oxide synthase (NOS) enzymes* in endothelial cells synthesize NO from *arginine* and oxygen and by reduction of inorganic nitrate. After diffusing out of the endothelial cell, NO has a half-life in the blood of only about 6 seconds and acts mainly in the local tissues where it is released. NO activates *soluble guanylate cyclases* in vascular smooth muscle cells (Figure 17-5), resulting in conversion of cyclic guanosine triphosphate (cGTP) to cyclic guanosine monophosphate (cGMP) and activation of *cGMP-dependent protein kinase (PKG),* which has several actions that cause the blood vessels to relax.

When blood flows through the arteries and arterioles, this causes *shear stress* on the endothelial cells because of viscous drag of the blood against the vascular walls.

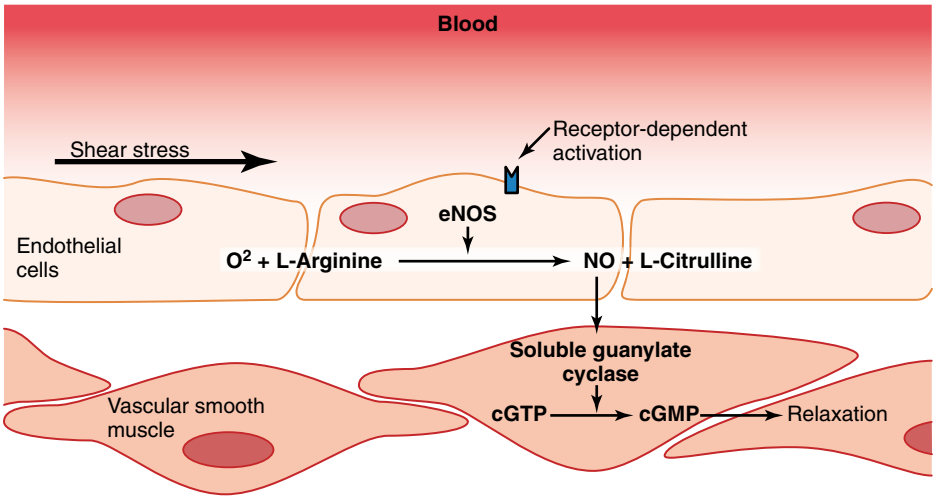


Figure 17-5 Nitric oxide synthase (eNOS) enzyme in endothelial cells synthesizes nitric oxide (NO) from arginine and oxygen. NO activates soluble guanylate cyclases in vascular smooth muscle cells, resulting in conversion of cyclic guanosine triphosphate (cGTP) to cyclic guanosine monophosphate (cGMP) which ultimately causes the blood vessels to relax.

This stress contorts the endothelial cells in the direction of flow and causes significant increase in the release of NO. The NO then relaxes the blood vessels. This is fortunate because the local metabolic mechanisms for controlling tissue blood flow dilate mainly the very small arteries and arterioles in each tissue. Yet, when blood flow through a microvascular portion of the circulation increases, this secondarily stimulates the release of NO from larger vessels due to increased flow and shear stress in these vessels. The released NO increases the diameters of the larger upstream blood vessels whenever microvascular blood flow increases downstream. Without such a response, the effectiveness of local blood flow control would be decreased because a significant part of the resistance to blood flow is in the upstream small arteries.

NO synthesis and release from endothelial cells are also stimulated by some vasoconstrictors, such as *angiotensin II,* which bind to specific receptors on endothelial cells. The increased NO release protects against excessive vasoconstriction.

When endothelial cells are damaged by chronic hypertension or atherosclerosis, impaired NO synthesis may contribute to excessive vasoconstriction and worsening of the hypertension and endothelial damage, which, if untreated, may eventually cause vascular injury and damage to vulnerable tissues such as the heart, kidneys, and brain.

Even before NO was discovered, clinicians used nitroglycerin, amyl nitrates, and other nitrate derivatives to treat patients suffering from *angina pectoris,* severe chest pain caused by ischemia of the heart muscle. These drugs, when broken down chemically, release NO and evoke dilation of blood vessels throughout the body, including the coronary blood vessels.

Other important applications of NO physiology and pharmacology are the development and clinical use of drugs (e.g., sildenafil) that inhibit *cGMP specific phosphodiesterase-5 (PDE-5),* an enzyme that degrades cGMP. By preventing the degradation of cGMP the PDE-5 inhibitors effectively prolong the actions of NO to cause vasodilation. The primary clinical use of the PDE-5 inhibitors is to treat erectile dysfunction. Penile erection is caused by parasympathetic nerve impulses through the pelvic nerves to the penis, where the neurotransmitters acetylcholine and NO are released. By preventing the degradation of NO, the PDE-5 inhibitors enhance the dilation of the blood vessels in the penis and aid in erection, as discussed in Chapter 80.

Endothelin—A Powerful Vasoconstrictor Released from Damaged Endothelium. Endothelial cells also release vasoconstrictor substances. The most important of these is *endothelin,* a large 21 amino acid peptide that requires only nanogram quantities to cause powerful vasoconstriction. This substance is present in the endothelial cells of all or most blood vessels but greatly increases when the vessels are injured. The usual stimulus for release is damage to the endothelium, such as that caused by crushing the tissues or injecting a traumatizing chemical into the blood vessel. After severe blood vessel damage, release of local endothelin and subsequent vasoconstriction helps to prevent extensive bleeding from arteries as large as 5 millimeters in diameter that might have been torn open by crushing injury.

Increased endothelin release is also believed to contribute to vasoconstriction when the endothelium is damaged by hypertension. Drugs that block endothelin receptors have been used to treat *pulmonary hypertension* but have not generally been used for lowering blood pressure in patients with systemic arterial hypertension.

Long-Term Blood Flow Regulation

Thus far, most of the mechanisms for local blood flow regulation that we have discussed act within a few seconds to a few minutes after the local tissue conditions have changed. Yet, even after full activation of these acute mechanisms, the blood flow usually is adjusted only about three quarters of the way to the exact additional

requirements of the tissues. For instance, when the arterial pressure suddenly increases from 100 to 150 mm Hg, the blood flow increases almost instantaneously about 100 percent. Then, within 30 seconds to 2 minutes, the flow decreases back to about 10 to 15 percent above the original control value. This illustrates the rapidity of the acute mechanisms for local blood flow regulation, but at the same time, it demonstrates that the regulation is still incomplete because there remains a 10 to 15 percent excess blood flow.

However, over a period of hours, days, and weeks, a long-term type of local blood flow regulation develops in addition to the acute control. This long-term regulation gives far more complete control of blood flow. For instance, in the aforementioned example, if the arterial pressure remains at 150 mm Hg indefinitely, within a few weeks the blood flow through the tissues gradually approaches almost exactly the normal flow level. Figure 17-4 shows by the dashed green curve the extreme effectiveness of this long-term local blood flow regulation. Note that once the long-term regulation has had time to occur, long-term changes in arterial pressure between 50 and 250 mm Hg have little effect on the rate of local blood flow.

Long-term regulation of blood flow is especially important when the metabolic demands of a tissue change. Thus, if a tissue becomes chronically overactive and therefore requires increased quantities of oxygen and other nutrients, the arterioles and capillary vessels usually increase both in number and size within a few weeks to match the needs of the tissue—unless the circulatory system has become pathological or too old to respond.

Mechanism of Long-Term Regulation—Change in "Tissue Vascularity"

The mechanism of long-term local blood flow regulation is principally to change the amount of vascularity of the tissues. For instance, if the metabolism in a tissue is increased for a prolonged period, vascularity increases, a process generally called *angiogenesis;* if the metabolism is decreased, vascularity decreases. Figure 17-6 shows the large increase in the number of capillaries in a rat anterior tibialis muscle that was stimulated electrically to contract for short periods of time each day for 30 days, compared with the unstimulated muscle in the other leg of the animal.

Thus, there is actual physical reconstruction of the tissue vasculature to meet the needs of the tissues. This reconstruction occurs rapidly (within days) in young animals. It also occurs rapidly in new growth tissue, such as in scar tissue and cancerous tissue; however, it occurs much slower in old, well-established tissues. Therefore, the time required for long-term regulation to take place may be only a few days in the neonate or as long as months in the elderly person. Furthermore, the final degree of response is much better in younger tissues than in older, so that in the neonate, the vascularity will adjust to match almost exactly the needs of the tissue for blood flow, whereas in older tissues, vascularity frequently lags far behind the needs of the tissues.

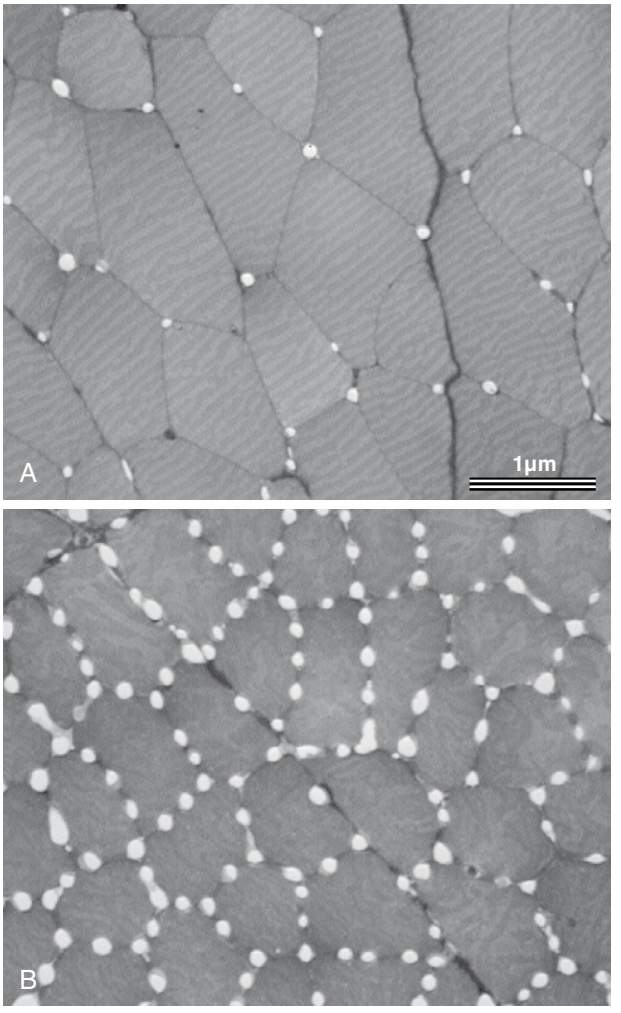


Figure 17-6 Large increase in the number of capillaries (*white dots*) in a rat anterior tibialis muscle that was stimulated electrically to contract for short periods of time each day for 30 days (*B*), compared with the unstimulated muscle (*A*).The 30 days of intermittent electrical stimulation converted the predominantly fast twitch, glycolytic anterior tibialis muscle to a predominantly slow twitch, oxidative muscle with increased numbers of capillaries and decreased fiber diameter as shown. (Photo courtesy Dr. Thomas Adair.)

Role of Oxygen in Long-Term Regulation. Oxygen is important not only for acute control of local blood flow but also for long-term control. One example of this is increased vascularity in tissues of animals that live at high altitudes, where the atmospheric oxygen is low. A second example is that fetal chicks hatched in low oxygen have up to twice as much tissue blood vessel conductivity as is normally true. This same effect is also dramatically demonstrated in premature human babies put into oxygen tents for therapeutic purposes. The excess oxygen causes almost immediate cessation of new vascular growth in the retina of the premature baby's eyes and even causes degeneration of some of the small vessels that already have formed. Then when the infant is taken out of the oxygen tent, there is explosive overgrowth of new vessels

to make up for the sudden decrease in available oxygen; indeed, there is often so much overgrowth that the retinal vessels grow out from the retina into the eye's vitreous humor and eventually cause blindness. (This condition is called *retrolental fibroplasia.*)

Importance of Vascular Endothelial Growth Factor in Formation of New Blood Vessels

A dozen or more factors that increase growth of new blood vessels have been found, almost all of which are small peptides. Three of those that have been best characterized are *vascular endothelial growth factor (VEGF), fibroblast growth factor,* and *angiogenin,* each of which has been isolated from tissues that have inadequate blood supply. Presumably, it is deficiency of tissue oxygen or other nutrients, or both, that leads to formation of the vascular growth factors (also called "angiogenic factors").

Essentially all the angiogenic factors promote new vessel growth in the same way. They cause new vessels to sprout from other small vessels. The first step is dissolution of the basement membrane of the endothelial cells at the point of sprouting. This is followed by rapid reproduction of new endothelial cells that stream outward through the vessel wall in extended cords directed toward the source of the angiogenic factor. The cells in each cord continue to divide and rapidly fold over into a tube. Next, the tube connects with another tube budding from another donor vessel (another arteriole or venule) and forms a capillary loop through which blood begins to flow. If the flow is great enough, smooth muscle cells eventually invade the wall, so some of the new vessels eventually grow to be new arterioles or venules or perhaps even larger vessels. Thus, angiogenesis explains the manner in which metabolic factors in local tissues can cause growth of new vessels.

Certain other substances, such as some steroid hormones, have exactly the opposite effect on small blood vessels, occasionally even causing dissolution of vascular cells and disappearance of vessels. Therefore, blood vessels can also be made to disappear when not needed. Peptides produced in the tissues can also block the growth of new blood vessels. For example, *angiostatin*, a fragment of the protein plasminogen, is a naturally occurring inhibitor of angiogenesis. *Endostatin* is another antiangiogenic peptide that is derived from the breakdown of collagen type XVII. Although the precise physiological functions of these antiangiogenic substances are still unknown, there is great interest in their potential use in arresting blood vessel growth in cancerous tumors and therefore preventing the large increases in blood flow needed to sustain the nutrient supply of rapidly growing tumors.

Vascularity Is Determined by Maximum Blood Flow Need, Not by Average Need. An especially valuable characteristic of long-term vascular control is that vascularity is determined mainly by the *maximum* level of blood flow need rather than by average need. For instance, during heavy exercise the need for whole body blood flow often increases to six to eight times the resting blood flow. This great excess of flow may not be required for more than a few minutes each day. Nevertheless, even this short need can cause enough VEGF to be formed by the muscles to increase their vascularity as required. Were it not for this capability, every time that a person attempted heavy exercise, the muscles would fail to receive the required nutrients, especially the required oxygen, so that the muscles simply would fail to contract.

However, after extra vascularity does develop, the extra blood vessels normally remain mainly vasoconstricted, opening to allow extra flow only when appropriate local stimuli such as oxygen lack, nerve vasodilatory stimuli, or other stimuli call forth the required extra flow.

Development of Collateral Circulation—a Phenomenon of Long-Term Local Blood Flow Regulation

When an artery or a vein is blocked in virtually any tissue of the body, a new vascular channel usually develops around the blockage and allows at least partial resupply of blood to the affected tissue. The first stage in this process is dilation of small vascular loops that already connect the vessel above the blockage to the vessel below. This dilation occurs within the first minute or two, indicating that the dilation is likely mediated by metabolic factors that relax the muscle fibers of the small vessels involved. After this initial opening of collateral vessels, the blood flow often is still less than one quarter that is needed to supply all the tissue needs. However, further opening occurs within the ensuing hours, so within 1 day as much as half the tissue needs may be met, and within a few days the blood flow is usually sufficient to meet the tissue needs.

The collateral vessels continue to grow for many months thereafter, almost always forming multiple small collateral channels rather than one single large vessel. Under resting conditions, the blood flow usually returns very near to normal, but the new channels seldom become large enough to supply the blood flow needed during strenuous tissue activity. Thus, the development of collateral vessels follows the usual principles of both acute and long-term local blood flow control, the acute control being rapid metabolic dilation, followed chronically by growth and enlargement of new vessels over a period of weeks and months.

The most important example of the development of collateral blood vessels occurs after thrombosis of one of the coronary arteries. Almost all people by the age of 60 years have had at least one of the smaller branch coronary vessels closed, or at least partially occluded. Yet most people do not know that this has happened because collaterals have developed rapidly enough to prevent myocardial damage. It is in those other instances in which coronary insufficiency occurs too rapidly or too severely for collaterals to develop that serious heart attacks occur.

Humoral Control of the Circulation

Humoral control of the circulation means control by substances secreted or absorbed into the body fluids—such as hormones and locally produced factors. Some of these substances are formed by special glands and transported in the blood throughout the entire body. Others are formed in local tissue areas and cause only local circulatory effects. Among the most important of the humoral factors that affect circulatory function are the following.

Vasoconstrictor Agents

Norepinephrine and Epinephrine. *Norepinephrine* is an especially powerful vasoconstrictor hormone; *epinephrine* is less so and in some tissues even causes mild vasodilation. (A special example of vasodilation caused by epinephrine occurs to dilate the coronary arteries during increased heart activity.)

When the sympathetic nervous system is stimulated in most or all parts of the body during stress or exercise, the sympathetic nerve endings in the individual tissues release norepinephrine, which excites the heart and contracts the veins and arterioles. In addition, the sympathetic nerves to the adrenal medullae cause these glands to secrete both norepinephrine and epinephrine into the blood. These hormones then circulate to all areas of the body and cause almost the same effects on the circulation as direct sympathetic stimulation, thus providing a dual system of control: (1) direct nerve stimulation and (2) indirect effects of norepinephrine and/or epinephrine in the circulating blood.

Angiotensin II. Angiotensin II is another powerful vasoconstrictor substance. As little as *one millionth* of a gram can increase the arterial pressure of a human being 50 mm Hg or more.

The effect of angiotensin II is to constrict powerfully the small arterioles. If this occurs in an isolated tissue area, the blood flow to that area can be severely depressed. However, the real importance of angiotensin II is that it normally acts on many of the arterioles of the body at the same time to increase the *total peripheral resistance,* thereby increasing the arterial pressure. Thus, this hormone plays an integral role in the regulation of arterial pressure, as is discussed in detail in Chapter 19.

Vasopressin. *Vasopressin,* also called *antidiuretic hormone,* is even more powerful than angiotensin II as a vasoconstrictor, thus making it one of the body's most potent vascular constrictor substances. It is formed in nerve cells in the hypothalamus of the brain (see Chapters 28 and 75) but is then transported downward by nerve axons to the posterior pituitary gland, where it is finally secreted into the blood.

It is clear that vasopressin could have enormous effects on circulatory function. Yet normally, only minute amounts of vasopressin are secreted, so most physiologists have thought that vasopressin plays little role in vascular control. However, experiments have shown that the concentration of circulating blood vasopressin after severe hemorrhage can increase enough to raise the arterial pressure as much as 60 mm Hg. In many instances, this can, by itself, bring the arterial pressure almost back up to normal.

Vasopressin has a major function to increase greatly water reabsorption from the renal tubules back into the blood (discussed in Chapter 28), and therefore to help control body fluid volume. That is why this hormone is also called *antidiuretic hormone.*

Vasodilator Agents

Bradykinin. Several substances called *kinins* cause powerful vasodilation when formed in the blood and tissue fluids of some organs.

The kinins are small polypeptides that are split away by proteolytic enzymes from alpha2-globulins in the plasma or tissue fluids. A proteolytic enzyme of particular importance for this purpose is *kallikrein,* which is present in the blood and tissue fluids in an inactive form. This inactive kallikrein is activated by maceration of the blood, by tissue inflammation, or by other similar chemical or physical effects on the blood or tissues. As kallikrein becomes activated, it acts immediately on alpha2-globulin to release a kinin called *kallidin* that is then converted by tissue enzymes into *bradykinin.* Once formed, bradykinin persists for only a few minutes because it is inactivated by the enzyme *carboxypeptidase* or by *converting enzyme,* the same enzyme that also plays an essential role in activating angiotensin, as discussed in Chapter 19. The activated kallikrein enzyme is destroyed by a *kallikrein inhibitor* also present in the body fluids.

Bradykinin causes both powerful *arteriolar dilation* and *increased capillary permeability.* For instance, injection of *1 microgram* of bradykinin into the brachial artery of a person increases blood flow through the arm as much as sixfold, and even smaller amounts injected locally into tissues can cause marked local edema resulting from increase in capillary pore size.

There is reason to believe that kinins play special roles in regulating blood flow and capillary leakage of fluids in inflamed tissues. It also is believed that bradykinin plays a normal role to help regulate blood flow in the skin, as well as in the salivary and gastrointestinal glands.

Histamine. Histamine is released in essentially every tissue of the body if the tissue becomes damaged or inflamed or is the subject of an allergic reaction. Most of the histamine is derived from *mast cells* in the damaged tissues and from *basophils* in the blood.

Histamine has a powerful vasodilator effect on the arterioles and, like bradykinin, has the ability to increase greatly capillary porosity, allowing leakage of both fluid and plasma protein into the tissues. In many pathological conditions, the intense arteriolar dilation and increased capillary porosity produced by histamine cause tremendous quantities of fluid to leak out of the circulation into the tissues,

inducing edema. The local vasodilatory and edema-producing effects of histamine are especially prominent during allergic reactions and are discussed in Chapter 34.

Vascular Control by Ions and Other Chemical Factors

Many different ions and other chemical factors can either dilate or constrict local blood vessels. Most of them have little function in *overall regulation* of the circulation, but some specific effects are:

1. An increase in *calcium ion* concentration causes *vasoconstriction.* This results from the general effect of calcium to stimulate smooth muscle contraction, as discussed in Chapter 8.
2. An increase in *potassium ion* concentration, within the physiological range, causes *vasodilation.* This results from the ability of potassium ions to inhibit smooth muscle contraction.
3. An increase in *magnesium* ion concentration causes *powerful vasodilation* because magnesium ions inhibit smooth muscle contraction.
4. An *increase in hydrogen ion* concentration (decrease in pH) causes dilation of the arterioles. Conversely, *slight decrease in hydrogen ion* concentration causes arteriolar constriction.
5. *Anions* that have significant effects on blood vessels are *acetate* and *citrate,* both of which cause mild degrees of vasodilation.
6. An *increase in carbon dioxide concentration* causes moderate vasodilation in most tissues but marked vasodilation in the brain. Also, carbon dioxide in the blood, acting on the brain vasomotor center, has an extremely powerful indirect effect, transmitted through the sympathetic nervous vasoconstrictor system, to cause widespread vasoconstriction throughout the body.

Most Vasodilators or Vasoconstrictors Have Little Effect on Long-Term Blood Flow Unless They Alter Metabolic Rate of the Tissues. In most cases, tissue blood flow and cardiac output (the sum of flow to all of the body's tissues) are not substantially altered, except for a day or two, in experimental studies when one chronically infuses large amounts of powerful vasoconstrictors such as angiotensin II or vasodilators such as bradykinin. Why is blood flow not significantly altered in most tissues even in the presence of very large amounts of these vasoactive agents?

To answer this question we must return to one of the fundamental principles of circulatory function that we previously discussed—the ability of each tissue to *autoregulate* its own blood flow according to the metabolic needs and other functions of the tissue. Administration of a powerful vasoconstrictor, such as angiotensin II, may cause transient decreases in tissue blood flow and cardiac output but usually has little long-term effect if it does not alter metabolic rate of the tissues. Likewise, most vasodilators cause only short-term changes in tissue blood flow and cardiac output if they do not alter tissue metabolism. Therefore, blood flow is generally regulated according to the specific needs of the tissues as long as the arterial pressure is adequate to perfuse the tissues.

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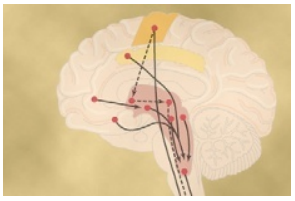
Nervous Regulation of the Circulation, and Rapid Control of Arterial Pressure



Nervous Regulation of the Circulation

As discussed in Chapter 17, adjustment of blood flow in the tissues and organs of the body is mainly the function of local tissue control mechanisms. In this chapter we discuss how nervous control of the circulation has more global functions, such as redistributing blood flow to different areas of the body, increasing or decreasing pumping activity by the heart, and providing very rapid control of systemic arterial pressure.

The nervous system controls the circulation almost entirely through the *autonomic nervous system*. The total function of this system is presented in Chapter 60, and this subject was also introduced in Chapter 17. For our present discussion, we will consider additional specific anatomical and functional characteristics, as follows.

Autonomic Nervous System

By far the most important part of the autonomic nervous system for regulating the circulation is the *sympathetic nervous system*. The *parasympathetic nervous system,* however, contributes importantly to regulation of heart function, as described later in the chapter.

Sympathetic Nervous System. Figure 18-1 shows the anatomy of sympathetic nervous control of the circulation. Sympathetic vasomotor nerve fibers leave the spinal cord through all the thoracic spinal nerves and through the first one or two lumbar spinal nerves. They then pass immediately into a *sympathetic chain,* one of which lies on each side of the vertebral column. Next, they pass by two routes to the circulation: (1) through specific *sympathetic nerves* that innervate mainly the vasculature of the internal viscera and the heart, as shown on the right side of Figure 18-1, and (2) almost immediately into peripheral portions of the *spinal nerves* distributed to the vasculature of the peripheral areas. The precise pathways of these fibers in the spinal cord and in the sympathetic chains are discussed in Chapter 60.

Sympathetic Innervation of the Blood Vessels. Figure 18-2 shows distribution of sympathetic nerve fibers to the blood vessels, demonstrating that in most tissues all the vessels *except* the capillaries are innervated. Precapillary sphincters and metarterioles are innervated in some tissues, such as the mesenteric blood vessels, although their sympathetic innervation is usually not as dense as in the small arteries, arterioles, and veins.

The innervation of the *small arteries* and *arterioles* allows sympathetic stimulation to increase *resistance* to blood flow and thereby to *decrease* rate of blood flow through the tissues.

The innervation of the large vessels, particularly of the *veins,* makes it possible for sympathetic stimulation to *decrease* the volume of these vessels. This can push blood into the heart and thereby play a major role in regulation of heart pumping, as we explain later in this and subsequent chapters.

Sympathetic Nerve Fibers to the Heart. Sympathetic fibers also go directly to the heart, as shown in Figure 18-1 and as discussed in Chapter 9. It should be recalled that sympathetic stimulation markedly increases the activity of the heart, both increasing the heart rate and enhancing its strength and volume of pumping.

Parasympathetic Control of Heart Function, Especially Heart Rate. Although the parasympathetic nervous system is exceedingly important for many other autonomic functions of the body, such as control of multiple gastrointestinal actions, it plays only a minor role in regulation of vascular function in most tissues. Its most important circulatory effect is to control heart rate by way of *parasympathetic nerve fibers* to the heart in the *vagus nerves,* shown in Figure 18-1 by the dashed red line from the brain medulla directly to the heart.

The effects of parasympathetic stimulation on heart function were discussed in detail in Chapter 9. Principally, parasympathetic stimulation causes a marked *decrease* in heart rate and a slight decrease in heart muscle contractility.

Sympathetic Vasoconstrictor System and Its Control by the Central Nervous System

The sympathetic nerves carry tremendous numbers of *vasoconstrictor nerve fibers* and only a few vasodilator fibers. The vasoconstrictor fibers are distributed to essentially all

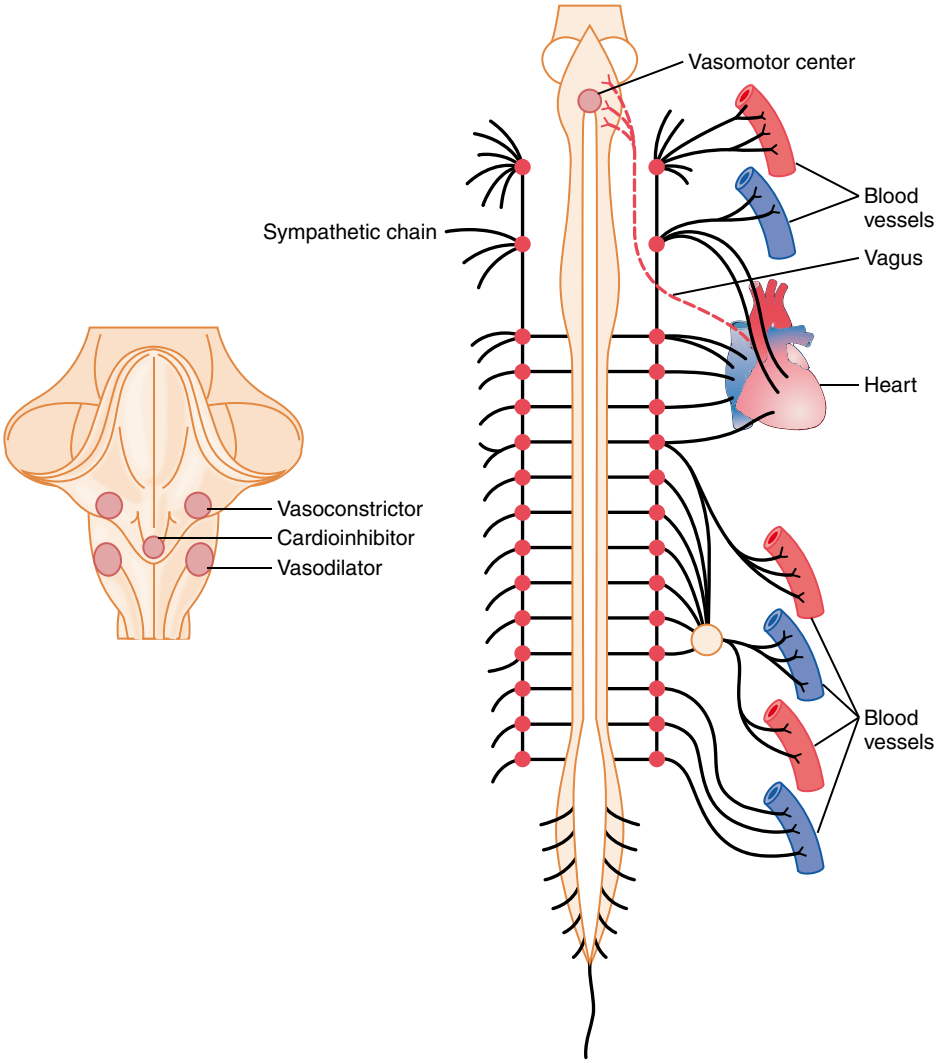


Figure 18-1 Anatomy of *sympathetic nervous control* of the circulation. Also shown by the dashed red line, a vagus nerve that carries *parasympathetic signals* to the heart.

segments of the circulation, but more to some tissues than others. This sympathetic vasoconstrictor effect is especially powerful in the kidneys, intestines, spleen, and skin but much less potent in skeletal muscle and the brain.

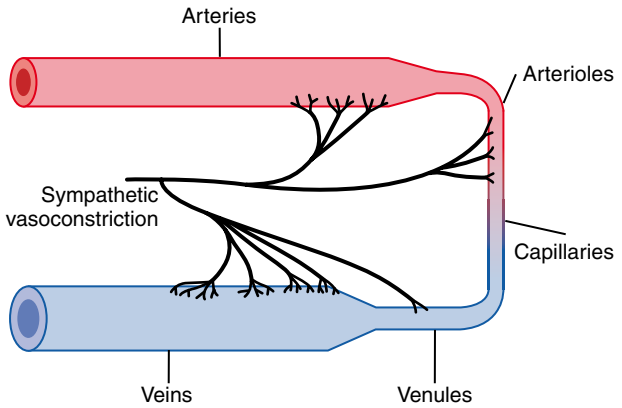


Figure 18-2 Sympathetic innervation of the systemic circulation.

Vasomotor Center in the Brain and Its Control of the Vasoconstrictor System. Located bilaterally mainly in the reticular substance of the medulla and of the lower third of the pons is an area called the *vasomotor center,* shown in Figures 18-1 and 18-3. This center transmits parasympathetic impulses through the vagus nerves to the heart and transmits sympathetic impulses through the spinal cord and peripheral sympathetic nerves to virtually all arteries, arterioles, and veins of the body.

Although the total organization of the vasomotor center is still unclear, experiments have made it possible to identify certain important areas in this center, as follows:

1. A *vasoconstrictor area* located bilaterally in the anterolateral portions of the upper medulla. The neurons originating in this area distribute their fibers to all levels of the spinal cord, where they excite preganglionic vasoconstrictor neurons of the sympathetic nervous system.

2. A *vasodilator area* located bilaterally in the anterolateral portions of the lower half of the medulla. The fibers from these neurons project upward to the vasoconstrictor area just described; they inhibit the vasoconstrictor activity of this area, thus causing vasodilation.
3. A *sensory area* located bilaterally in the *tractus solitarius* in the posterolateral portions of the medulla and lower pons. The neurons of this area receive sensory nerve signals from the circulatory system mainly through the *vagus* and *glossopharyngeal nerves,* and output signals from this sensory area then help to control activities of both the vasoconstrictor and vasodilator areas of the vasomotor center, thus providing "reflex" control of many circulatory functions. An example is the baroreceptor reflex for controlling arterial pressure, which we describe later in this chapter.

Continuous Partial Constriction of the Blood Vessels Is Normally Caused by Sympathetic Vasoconstrictor Tone. Under normal conditions, the vasoconstrictor area of the vasomotor center transmits signals continuously to the sympathetic vasoconstrictor nerve fibers over the entire body, causing slow firing of these fibers at a rate of about one half to two impulses per second. This continual firing is called *sympathetic vasoconstrictor tone.* These impulses normally maintain a partial state of contraction in the blood vessels, called *vasomotor tone.*

Figure 18-4 demonstrates the significance of vasoconstrictor tone. In the experiment of this figure, total spinal anesthesia was administered to an animal. This blocked all transmission of sympathetic nerve impulses from the spinal cord to the periphery. As a result, the arterial pressure fell from 100 to 50 mm Hg, demonstrating the effect of losing vasoconstrictor tone throughout the body. A few minutes later, a small amount of the hormone norepinephrine was injected into the blood (norepinephrine is the principal vasoconstrictor hormonal substance secreted at the endings of the sympathetic vasoconstrictor nerve fibers throughout the body). As this injected hormone was transported in the blood to blood vessels, the vessels once again became constricted and the arterial pressure rose to a level even greater than normal for 1 to 3 minutes, until the norepinephrine was destroyed.

Control of Heart Activity by the Vasomotor Center. At the same time that the vasomotor center regulates the amount of vascular constriction, it also controls heart activity. The *lateral* portions of the vasomotor center transmit excitatory impulses through the sympathetic nerve fibers to the heart when there is need to increase heart rate and contractility. Conversely, when there is need to decrease heart pumping, the *medial* portion of the vasomotor center sends signals to the adjacent *dorsal motor nuclei of the vagus nerves,* which then transmit parasympathetic impulses through the vagus nerves to the heart to decrease heart rate and heart contractility. Therefore, the vasomotor center can either increase or decrease heart activity. Heart rate and strength of heart contraction ordinarily increase when vasoconstriction occurs and ordinarily decrease when vasoconstriction is inhibited.

Control of the Vasomotor Center by Higher Nervous Centers. Large numbers of small neurons located throughout the *reticular substance* of the *pons, mesencephalon,* and *diencephalon* can either excite or inhibit the vasomotor center. This reticular substance is shown in Figure 18-3 by the rose-colored area. In general, the neurons in the more lateral and superior portions of the reticular substance cause excitation, whereas the more medial and inferior portions cause inhibition.

The *hypothalamus* plays a special role in controlling the vasoconstrictor system because it can exert either powerful excitatory or inhibitory effects on the vasomotor center. The *posterolateral portions* of the hypothalamus cause mainly excitation, whereas the *anterior portion* can cause either mild excitation or inhibition, depending on the precise part of the anterior hypothalamus stimulated.

Many parts of the *cerebral cortex* can also excite or inhibit the vasomotor center. Stimulation of the *motor cortex,* for instance, excites the vasomotor center because of impulses transmitted downward into the hypothalamus and then to the vasomotor center. Also, stimulation of the *anterior temporal lobe,* the *orbital areas of the frontal cortex,* the *anterior part of the cingulate gyrus,* the *amygdala,* the *septum,* and the *hippocampus* can all either excite or inhibit the vasomotor center, depending on the precise portions of these areas that are stimulated and on the intensity of stimulus. Thus, widespread basal areas of the brain can have profound effects on cardiovascular function.

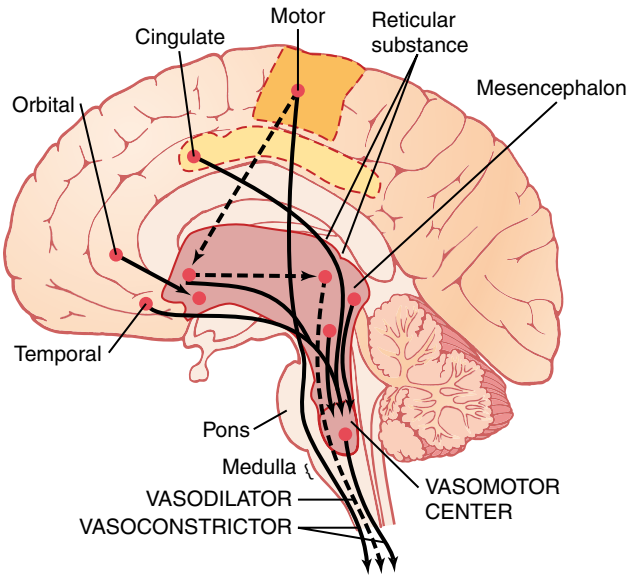


Figure 18-3 Areas of the brain that play important roles in the nervous regulation of the circulation. The *dashed lines* represent inhibitory pathways.

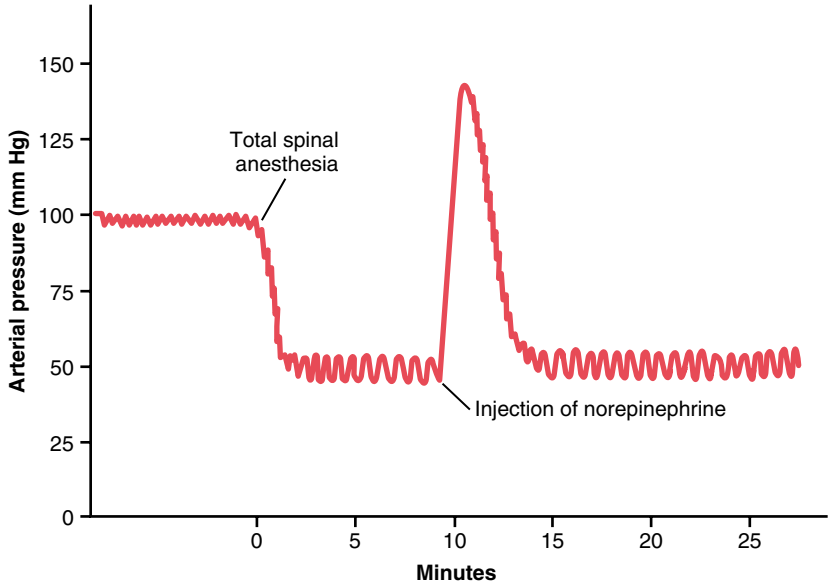


Figure 18-4 Effect of total spinal anesthesia on the arterial pressure, showing marked decrease in pressure resulting from loss of "vasomotor tone."

Norepinephrine—The Sympathetic Vasoconstrictor Transmitter Substance. The substance secreted at the endings of the vasoconstrictor nerves is almost entirely norepinephrine, which acts directly on the *alpha adrenergic receptors* of the vascular smooth muscle to cause vasoconstriction, as discussed in Chapter 60.

Adrenal Medullae and Their Relation to the Sympathetic Vasoconstrictor System. Sympathetic impulses are transmitted to the adrenal medullae at the same time that they are transmitted to the blood vessels. They cause the medullae to *secrete both epinephrine and norepinephrine into the circulating blood.* These two hormones are carried in the blood stream to all parts of the body, where they act directly on all blood vessels, usually to cause vasoconstriction. In a few tissues epinephrine causes vasodilation because it also has a "beta" adrenergic receptor stimulatory effect, which dilates rather than constricts certain vessels, as discussed in Chapter 60.

Sympathetic *Vasodilator* System and Its Control by the Central Nervous System. The sympathetic nerves to skeletal muscles carry sympathetic *vasodilator* fibers, as well as constrictor fibers. In some animals such as the cat, these dilator fibers release *acetylcholine,* not norepinephrine, at their endings, although in primates, the vasodilator effect is believed to be caused by epinephrine exciting specific beta-adrenergic receptors in the muscle vasculature.

The pathway for central nervous system control of the vasodilator system is shown by the dashed lines in Figure 18-3. The principal area of the brain controlling this system is the *anterior hypothalamus.*

Possible Unimportance of the Sympathetic Vasodilator System. It is doubtful that the sympathetic vasodilator system plays a major role in the control of the circulation in the human being because complete block of the sympathetic nerves to the muscles hardly affects the ability of these muscles to control their own blood flow in response to their needs. Yet some experiments suggest that at the onset of exercise, the sympathetic vasodilator system might cause initial vasodilation in skeletal muscles to allow *anticipatory increase in blood flow* even before the muscles require increased nutrients.

Emotional Fainting—Vasovagal Syncope. A particularly interesting vasodilatory reaction occurs in people who experience intense emotional disturbances that cause fainting. In this case, the muscle vasodilator system becomes activated, and at the same time, the vagal cardioinhibitory center transmits strong signals to the heart to slow the heart rate markedly. The arterial pressure falls rapidly, which reduces blood flow to the brain and causes the person to lose consciousness. This overall effect is called *vasovagal syncope.* Emotional fainting begins with disturbing thoughts in the cerebral cortex. The pathway probably then goes to the vasodilatory center of the anterior hypothalamus next to the vagal centers of the medulla, to the heart through the vagus nerves, and also through the spinal cord to the *sympathetic vasodilator* nerves of the muscles.

Role of the Nervous System in Rapid Control of Arterial Pressure

One of the most important functions of nervous control of the circulation is its capability to cause rapid increases in arterial pressure. For this purpose, the entire vasoconstrictor and cardioaccelerator functions of the sympathetic nervous system are stimulated together. At the same time, there is reciprocal inhibition of parasympathetic vagal inhibitory signals to the heart. Thus, three major changes occur simultaneously, each of which helps to increase arterial pressure. They are as follows:

1. *Most arterioles of the systemic circulation are constricted.* This greatly increases the total peripheral resistance, thereby increasing the arterial pressure.
2. *The veins especially (but the other large vessels of the circulation as well) are strongly constricted.* This displaces blood out of the large peripheral blood vessels toward the heart, thus increasing the volume of blood in the heart chambers. The stretch of the heart then causes the heart to beat with far greater force and therefore to pump increased quantities of blood. This, too, increases the arterial pressure.
3. Finally, *the heart itself is directly stimulated by the autonomic nervous system, further enhancing cardiac pumping.* Much of this is caused by an increase in the heart rate, the rate sometimes increasing to as great as three times normal. In addition, sympathetic nervous signals have a significant direct effect to increase contractile force of the heart muscle, this, too, increasing the capability of the heart to pump larger volumes of blood. During strong sympathetic stimulation, the heart can pump about two times as much blood as under normal conditions. This contributes still more to the acute rise in arterial pressure.

Rapidity of Nervous Control of Arterial Pressure. An especially important characteristic of nervous control of arterial pressure is its rapidity of response, beginning within seconds and often increasing the pressure to two times normal within 5 to 10 seconds. Conversely, sudden inhibition of nervous cardiovascular stimulation can decrease the arterial pressure to as little as one-half normal within 10 to 40 seconds. Therefore, nervous control of arterial pressure is by far the most rapid of all our mechanisms for pressure control.

Increase in Arterial Pressure During Muscle Exercise and Other Types of Stress

An important example of the ability of the nervous system to increase the arterial pressure is the increase in pressure that occurs during muscle exercise. During heavy exercise, the muscles require greatly increased blood flow. Part of this increase results from local vasodilation of the muscle vasculature caused by increased metabolism of the muscle cells, as explained in Chapter 17. Additional increase results from simultaneous elevation of arterial pressure caused by sympathetic stimulation of the overall circulation during exercise. In most heavy exercise, the arterial pressure rises about 30 to 40 percent, which increases blood flow almost an additional twofold.

The increase in arterial pressure during exercise results mainly from the following effect: At the same time that the motor areas of the brain become activated to cause exercise, most of the reticular activating system of the brain stem is also activated, which includes greatly increased stimulation of the vasoconstrictor and cardioacceleratory areas of the vasomotor center. These increase the arterial pressure instantaneously to keep pace with the increase in muscle activity.

In many other types of stress besides muscle exercise, a similar rise in pressure can also occur. For instance, during extreme fright, the arterial pressure sometimes rises by as much as 75 to 100 mm Hg within a few seconds. This is called the *alarm reaction,* and it provides an excess of arterial pressure that can immediately supply blood to the muscles of the body that might need to respond instantly to cause flight from danger.

Reflex Mechanisms for Maintaining Normal Arterial Pressure

Aside from the exercise and stress functions of the autonomic nervous system to increase arterial pressure, there are multiple subconscious special nervous control mechanisms that operate all the time to maintain the arterial pressure at or near normal. Almost all of these are *negative feedback reflex mechanisms,* which we explain in the following sections.

Baroreceptor Arterial Pressure Control System—Baroreceptor Reflexes

By far the best known of the nervous mechanisms for arterial pressure control is the *baroreceptor reflex.* Basically, this reflex is initiated by stretch receptors, called either *baroreceptors* or *pressoreceptors,* located at specific points in the walls of several large systemic arteries. A rise in arterial pressure stretches the baroreceptors and causes them to transmit signals into the central nervous system. "Feedback" signals are then sent back through the autonomic nervous system to the circulation to reduce arterial pressure downward toward the normal level.

Physiologic Anatomy of the Baroreceptors and Their Innervation. Baroreceptors are spray-type nerve endings that lie in the walls of the arteries; they are stimulated when stretched. A few baroreceptors are located in the wall of almost every large artery of the thoracic and neck regions; but, as shown in Figure 18-5, baroreceptors are extremely abundant in (1) the wall of each internal carotid artery slightly above the carotid bifurcation, an area known as the *carotid sinus,* and (2) the wall of the aortic arch.

Figure 18-5 shows that signals from the "carotid baroreceptors" are transmitted through small *Hering's nerves* to the *glossopharyngeal nerves* in the high neck, and then to the *tractus solitarius* in the medullary area of the brain stem. Signals from the "aortic baroreceptors" in the arch of the aorta are transmitted through the *vagus nerves* also to the same tractus solitarius of the medulla.

Response of the Baroreceptors to Arterial Pressure. Figure 18-6 shows the effect of different arterial pressure levels on the rate of impulse transmission in a Hering's carotid sinus nerve. Note that the carotid sinus baroreceptors are not stimulated at all by pressures between 0 and 50 to 60 mm Hg, but above these levels, they respond progressively more rapidly and reach a

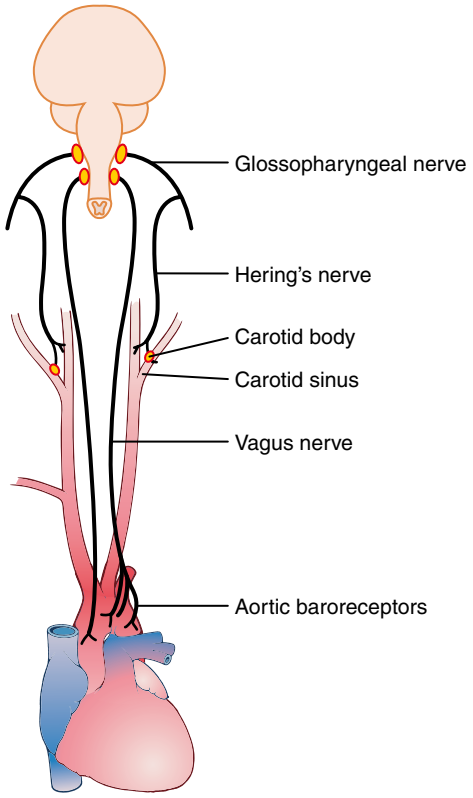


Figure 18-5 The baroreceptor system for controlling arterial pressure.

maximum at about 180 mm Hg. The responses of the aortic baroreceptors are similar to those of the carotid receptors except that they operate, in general, at arterial pressure levels about 30 mm Hg higher.

Note especially that in the normal operating range of arterial pressure, around 100 mm Hg, even a slight change in pressure causes a strong change in the baroreflex signal to readjust arterial pressure back toward normal. Thus, the baroreceptor feedback mechanism functions most effectively in the pressure range where it is most needed.

The baroreceptors respond rapidly to changes in arterial pressure; in fact, the rate of impulse firing increases in the fraction of a second during each systole and decreases again during diastole. Furthermore, the baroreceptors *respond much more to a rapidly changing pressure* than to a stationary pressure. That is, if the mean arterial pressure is 150 mm Hg but at that moment is rising rapidly, the rate of impulse transmission may be as much as twice that when the pressure is stationary at 150 mm Hg.

Circulatory Reflex Initiated by the Baroreceptors. After the baroreceptor signals have entered the tractus solitarius of the medulla, secondary signals *inhibit the vasoconstrictor center* of the medulla and *excite the vagal parasympathetic center.* The net effects are (1) *vasodilation* of the veins and arterioles throughout the peripheral circulatory system and (2) *decreased heart rate* and *strength of heart contraction.* Therefore, excitation of the baroreceptors by high pressure in the arteries reflexly *causes the arterial pressure to decrease* because of both a decrease in peripheral resistance and a decrease in cardiac output. Conversely, low pressure has opposite effects, reflexly causing the pressure to rise back toward normal.

Figure 18-7 shows a typical reflex change in arterial pressure caused by occluding the two common carotid arteries. This reduces the carotid sinus pressure; as a result, signals from the baroreceptors decrease and cause less inhibitory effect on the vasomotor center. The vasomotor center then becomes much more active than usual, causing the aortic arterial pressure to rise and remain elevated during the 10 minutes that the carotids are occluded. Removal of the occlusion allows the pressure in the carotid sinuses to rise, and the carotid sinus reflex now causes the aortic pressure to fall immediately to slightly below normal as a momentary overcompensation and then return to normal in another minute.

Function of the Baroreceptors During Changes in Body Posture. The ability of the baroreceptors to maintain relatively constant arterial pressure in the upper body

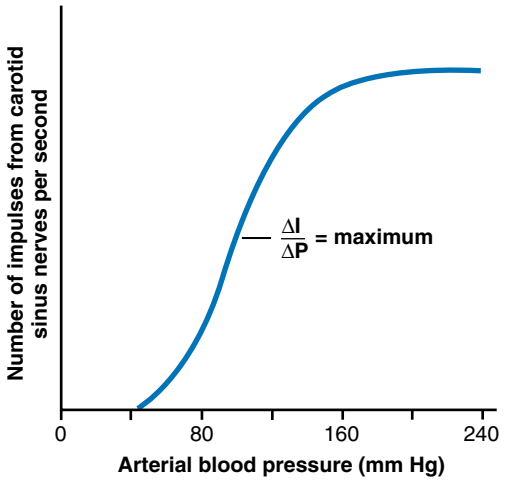


Figure 18-6 Activation of the baroreceptors at different levels of arterial pressure. ΔI, change in carotid sinus nerve impulses per second; ΔP, change in arterial blood pressure in mm Hg.

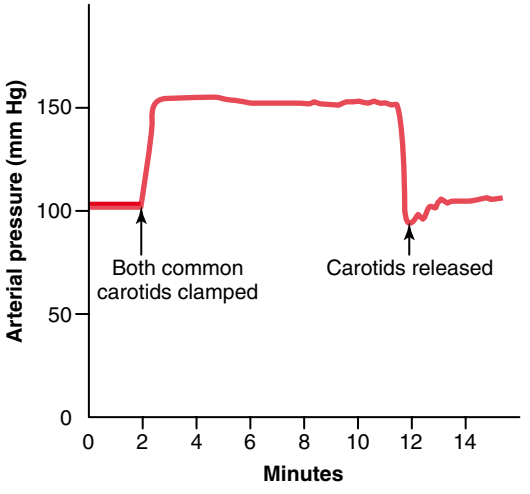


Figure 18-7 Typical carotid sinus reflex effect on aortic arterial pressure caused by clamping both common carotids (after the two vagus nerves have been cut).

is important when a person stands up after having been lying down. Immediately on standing, the arterial pressure in the head and upper part of the body tends to fall, and marked reduction of this pressure could cause loss of consciousness. However, the falling pressure at the baroreceptors elicits an immediate reflex, resulting in strong sympathetic discharge throughout the body. This minimizes the decrease in pressure in the head and upper body.

Pressure "Buffer" Function of the Baroreceptor Control System. Because the baroreceptor system opposes either increases or decreases in arterial pressure, it is called a *pressure buffer system* and the nerves from the baroreceptors are called *buffer nerves.*

Figure 18-8 shows the importance of this buffer function of the baroreceptors. The upper record in this figure shows an arterial pressure recording for 2 hours from a normal dog, and the lower record shows an arterial pressure recording from a dog whose baroreceptor nerves from both the carotid sinuses and the aorta had been removed. Note the extreme variability of pressure in the denervated dog caused by simple events of the day, such as lying down, standing, excitement, eating, defecation, and noises.

Figure 18-9 shows the frequency distributions of the mean arterial pressures recorded for a 24-hour day in both the normal dog and the denervated dog. Note that when the baroreceptors were functioning normally the mean

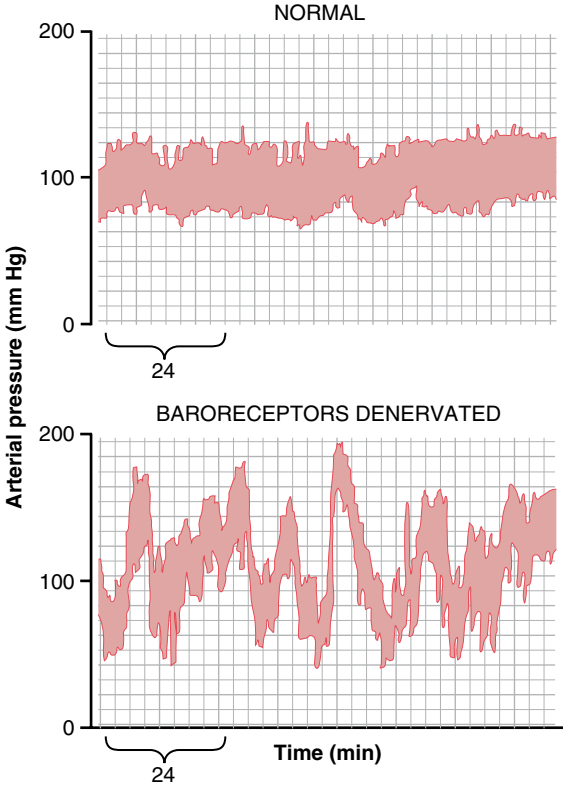


Figure 18-8 Two-hour records of arterial pressure in a normal dog (*above*) and in the same dog (*below*) several weeks after the baroreceptors had been denervated. (Redrawn from Cowley AW Jr, Liard JF, Guyton AC: Role of baroreceptor reflex in daily control of arterial blood pressure and other variables in dogs. Circ Res 32:564, 1973. By permission of the American Heart Association, Inc.)

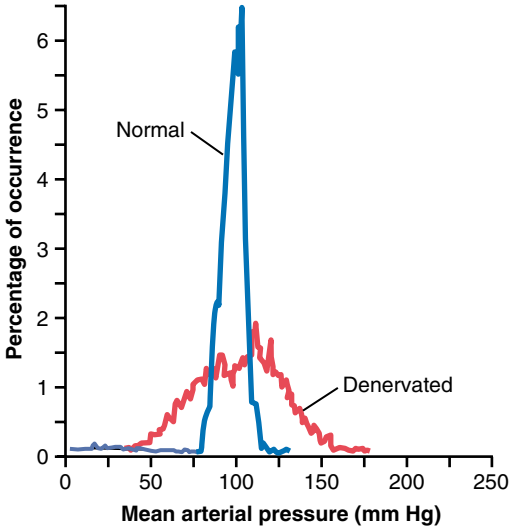


Figure 18-9 Frequency distribution curves of the arterial pressure for a 24-hour period in a normal dog and in the same dog several weeks after the baroreceptors had been denervated. (Redrawn from Cowley AW Jr, Liard JP, Guyton AC: Role of baroreceptor reflex in daily control of arterial blood pressure and other variables in dogs. Circ Res 32:564, 1973. By permission of the American Heart Association, Inc.)

arterial pressure remained throughout the day within a narrow range between 85 and 115 mm Hg—indeed, during most of the day at almost exactly 100 mm Hg. Conversely, after denervation of the baroreceptors, the frequency distribution curve became the broad, low curve of the figure, showing that the pressure range increased 2.5-fold, frequently falling to as low as 50 mm Hg or rising to over 160 mm Hg. Thus, one can see the extreme variability of pressure in the absence of the arterial baroreceptor system.

In summary, a primary purpose of the arterial baroreceptor system is to reduce the minute-by-minute variation in arterial pressure to about one-third that which would occur if the baroreceptor system was not present.

Are the Baroreceptors Important in Long-Term Regulation of Arterial Pressure? Although the arterial baroreceptors provide powerful moment-to-moment control of arterial pressure, their importance in long-term blood pressure regulation has been controversial. One reason that the baroreceptors have been considered by some physiologists to be relatively unimportant in chronic regulation of arterial pressure chronically is that they tend to *reset* in 1 to 2 days to the pressure level to which they are exposed. That is, if the arterial pressure rises from the normal value of 100 mm Hg to 160 mm Hg, a very high rate of baroreceptor impulses are at first transmitted. During the next few minutes, the rate of firing diminishes considerably; then it diminishes much more slowly during the next 1 to 2 days, at the end of which time the rate of firing will have returned to nearly normal despite the fact that the mean arterial pressure still remains at 160 mm Hg. Conversely, when the arterial pressure falls to a very low level, the baroreceptors at first transmit no impulses,

but gradually, over 1 to 2 days, the rate of baroreceptor firing returns toward the control level.

This "resetting" of the baroreceptors may attenuate their potency as a control system for correcting disturbances that tend to change arterial pressure for longer than a few days at a time. Experimental studies, however, have suggested that the baroreceptors do not completely reset and may therefore contribute to long-term blood pressure regulation, especially by influencing sympathetic nerve activity of the kidneys. For example, with prolonged increases in arterial pressure, the baroreceptor reflexes may mediate decreases in renal sympathetic nerve activity that promote increased excretion of sodium and water by the kidneys. This, in turn, causes a gradual decrease in blood volume, which helps to restore arterial pressure toward normal. Thus, long-term regulation of mean arterial pressure by the baroreceptors requires interaction with additional systems, principally the renal–body fluid–pressure control system (along with its associated nervous and hormonal mechanisms), discussed in Chapters 19 and 29.

Control of Arterial Pressure by the Carotid and Aortic Chemoreceptors—Effect of Oxygen Lack on Arterial Pressure. Closely associated with the baroreceptor pressure control system is a *chemoreceptor reflex* that operates in much the same way as the baroreceptor reflex except that *chemoreceptors,* instead of stretch receptors, initiate the response.

The chemoreceptors are chemosensitive cells sensitive to oxygen lack, carbon dioxide excess, and hydrogen ion excess. They are located in several small *chemoreceptor organs* about 2 millimeters in size (two *carotid bodies,* one of which lies in the bifurcation of each common carotid artery, and usually one to three *aortic bodies* adjacent to the aorta). The chemoreceptors excite nerve fibers that, along with the baroreceptor fibers, pass through Hering's nerves and the vagus nerves into the vasomotor center of the brain stem.

Each carotid or aortic body is supplied with an abundant blood flow through a small nutrient artery, so the chemoreceptors are always in close contact with arterial blood. Whenever the arterial pressure falls below a critical level, the chemoreceptors become stimulated because diminished blood flow causes decreased oxygen, as well as excess buildup of carbon dioxide and hydrogen ions that are not removed by the slowly flowing blood.

The signals transmitted from the chemoreceptors *excite* the vasomotor center, and this elevates the arterial pressure back toward normal. However, this chemoreceptor reflex is not a powerful arterial pressure controller until the arterial pressure falls below 80 mm Hg. Therefore, it is at the lower pressures that this reflex becomes important to help prevent further decreases in arterial pressure.

The chemoreceptors are discussed in much more detail in Chapter 41 in relation to *respiratory control,* in which they play a far more important role than in blood pressure control.

Atrial and Pulmonary Artery Reflexes Regulate Arterial Pressure. Both the atria and the pulmonary arteries have in their walls stretch receptors called *low-pressure receptors.* They are similar to the baroreceptor stretch receptors of the large systemic arteries. These low-pressure receptors play an important role, especially in minimizing arterial pressure changes in response to changes in blood volume. For example, if 300 milliliters of blood suddenly are infused into a dog with all receptors intact, the arterial pressure rises only about 15 mm Hg. With the *arterial baroreceptors* denervated, the pressure rises about 40 mm Hg. If the *low-pressure receptors* also are denervated, the arterial pressure rises about 100 mm Hg.

Thus, one can see that even though the low-pressure receptors in the pulmonary artery and in the atria cannot detect the systemic arterial pressure, they do detect simultaneous increases in pressure in the low-pressure areas of the circulation caused by increase in volume, and they elicit reflexes parallel to the baroreceptor reflexes to make the total reflex system more potent for control of arterial pressure.

Atrial Reflexes That Activate the Kidneys—The "Volume Reflex." Stretch of the atria also causes significant reflex dilation of the afferent arterioles in the kidneys. Signals are also transmitted simultaneously from the atria to the hypothalamus to decrease secretion of antidiuretic hormone (ADH). The decreased afferent arteriolar resistance in the kidneys causes the glomerular capillary pressure to rise, with resultant increase in filtration of fluid into the kidney tubules. The diminution of ADH diminishes the reabsorption of water from the tubules. Combination of these two effects—increase in glomerular filtration and decrease in reabsorption of the fluid—increases fluid loss by the kidneys and reduces an increased blood volume back toward normal. (We will also see in Chapter 19 that atrial stretch caused by increased blood volume also elicits a hormonal effect on the kidneys—release of *atrial natriuretic peptide*—that adds still further to the excretion of fluid in the urine and return of blood volume toward normal.)

All these mechanisms that tend to return the blood volume back toward normal after a volume overload act indirectly as pressure controllers, as well as blood volume controllers, because excess volume drives the heart to greater cardiac output and leads, therefore, to greater arterial pressure. This volume reflex mechanism is discussed again in Chapter 29, along with other mechanisms of blood volume control.

Atrial Reflex Control of Heart Rate (the Bainbridge Reflex). An increase in atrial pressure also causes an increase in heart rate, sometimes increasing the heart rate as much as 75 percent. A small part of this increase is caused by a direct effect of the increased atrial volume to stretch the sinus node; it was pointed out in Chapter 10 that such direct stretch can increase the heart rate as much as 15 percent. An additional 40 to 60 percent increase in rate is caused by a nervous reflex called the *Bainbridge reflex.* The stretch receptors of the atria that elicit the Bainbridge reflex transmit their afferent signals through the vagus

nerves to the medulla of the brain. Then efferent signals are transmitted back through vagal and sympathetic nerves to increase heart rate and strength of heart contraction. Thus, this reflex helps prevent damming of blood in the veins, atria, and pulmonary circulation.

Central Nervous System Ischemic Response—Control of Arterial Pressure by the Brain's Vasomotor Center in Response to Diminished Brain Blood Flow

Most nervous control of blood pressure is achieved by reflexes that originate in the baroreceptors, the chemoreceptors, and the low-pressure receptors, all of which are located in the peripheral circulation outside the brain. However, when blood flow to the vasomotor center in the lower brain stem becomes decreased severely enough to cause nutritional deficiency—that is, to cause *cerebral ischemia*—the vasoconstrictor and cardioaccelerator neurons in the vasomotor center respond directly to the ischemia and become strongly excited. When this occurs, the systemic arterial pressure often rises to a level as high as the heart can possibly pump. This effect is believed to be caused by failure of the slowly flowing blood to carry carbon dioxide away from the brain stem vasomotor center: At low levels of blood flow to the vasomotor center, the local concentration of carbon dioxide increases greatly and has an extremely potent effect in stimulating the sympathetic vasomotor nervous control areas in the brain's medulla.

It is possible that other factors, such as buildup of lactic acid and other acidic substances in the vasomotor center, also contribute to the marked stimulation and elevation in arterial pressure. This arterial pressure elevation in response to cerebral ischemia is known as the *central nervous system (CNS) ischemic response.*

The ischemic effect on vasomotor activity can elevate the mean arterial pressure dramatically, sometimes to as high as 250 mm Hg for as long as 10 minutes. *The degree of sympathetic vasoconstriction caused by intense cerebral ischemia is often so great that some of the peripheral vessels become totally or almost totally occluded.* The kidneys, for instance, often entirely cease their production of urine because of renal arteriolar constriction in response to the sympathetic discharge. Therefore, *the CNS ischemic response is one of the most powerful of all the activators of the sympathetic vasoconstrictor system.*

Importance of the CNS Ischemic Response as a Regulator of Arterial Pressure. Despite the powerful nature of the CNS ischemic response, it does not become significant until the arterial pressure falls far below normal, down to 60 mm Hg and below, reaching its greatest degree of stimulation at a pressure of 15 to 20 mm Hg. Therefore, it is not one of the normal mechanisms for regulating arterial pressure. Instead, it operates principally as an *emergency pressure control system that acts rapidly and very powerfully to prevent further decrease in arterial pressure whenever blood flow to the brain decreases dangerously close to the lethal level.* It is sometimes called the "last ditch stand" pressure control mechanism.

Cushing Reaction to Increased Pressure Around the Brain. The so-called *Cushing reaction* is a special type of CNS ischemic response that results from increased pressure of the cerebrospinal fluid around the brain in the cranial vault. For instance, when the cerebrospinal fluid pressure rises to equal the arterial pressure, it compresses the whole brain, as well as the arteries in the brain, and cuts off the blood supply to the brain. This initiates a CNS ischemic response that causes the arterial pressure to rise. When the arterial pressure has risen to a level higher than the cerebrospinal fluid pressure, blood will flow once again into the vessels of the brain to relieve the brain ischemia. Ordinarily, the blood pressure comes to a new equilibrium level slightly higher than the cerebrospinal fluid pressure, thus allowing blood to begin again to flow through the brain. The Cushing reaction helps protect the vital centers of the brain from loss of nutrition if ever the cerebrospinal fluid pressure rises high enough to compress the cerebral arteries.

Special Features of Nervous Control of Arterial Pressure

Role of the Skeletal Nerves and Skeletal Muscles in Increasing Cardiac Output and Arterial Pressure

Although most rapidly acting nervous control of the circulation is effected through the autonomic nervous system, at least two conditions in which the skeletal nerves and muscles also play major roles in circulatory responses are the following.

Abdominal Compression Reflex. When a baroreceptor or chemoreceptor reflex is elicited, nerve signals are transmitted simultaneously through skeletal nerves to skeletal muscles of the body, particularly to the abdominal muscles. This compresses all the venous reservoirs of the abdomen, helping to translocate blood out of the abdominal vascular reservoirs toward the heart. As a result, increased quantities of blood are made available for the heart to pump. This overall response is called the *abdominal compression reflex.* The resulting effect on the circulation is the same as that caused by sympathetic vasoconstrictor impulses when they constrict the veins: an increase in both cardiac output and arterial pressure. The abdominal compression reflex is probably much more important than has been realized in the past because it is well known that people whose skeletal muscles have been paralyzed are considerably more prone to hypotensive episodes than are people with normal skeletal muscles.

Increased Cardiac Output and Arterial Pressure Caused by Skeletal Muscle Contraction During Exercise. When the skeletal muscles contract during exercise, they compress blood vessels throughout the body. Even anticipation of exercise tightens the muscles, thereby compressing the vessels in the muscles and in the abdomen. The resulting effect is to translocate blood from the peripheral vessels into the heart and lungs and, therefore, to increase the cardiac output. This is an essential effect in helping to cause the fivefold to sevenfold increase in cardiac output that sometimes occurs in heavy exercise. The increase in cardiac output in turn is an essential ingredient in increasing the arterial pressure during exercise, an increase usually from a normal mean of 100 mm Hg up to 130 to 160 mm Hg.

Respiratory Waves in the Arterial Pressure

With each cycle of respiration, the arterial pressure usually rises and falls 4 to 6 mm Hg in a wavelike manner, causing *respiratory waves* in the arterial pressure. The waves result from several different effects, some of which are reflex in nature, as follows:

1. Many of the "breathing signals" that arise in the respiratory center of the medulla "spill over" into the vasomotor center with each respiratory cycle.
2. Every time a person inspires, the pressure in the thoracic cavity becomes more negative than usual, causing the blood vessels in the chest to expand. This reduces the quantity of blood returning to the left side of the heart and thereby momentarily decreases the cardiac output and arterial pressure.
3. The pressure changes caused in the thoracic vessels by respiration can excite vascular and atrial stretch receptors.

Although it is difficult to analyze the exact relations of all these factors in causing the respiratory pressure waves, the net result during normal respiration is usually an increase in arterial pressure during the early part of expiration and a decrease in pressure during the remainder of the respiratory cycle. During deep respiration, the blood pressure can rise and fall as much as 20 mm Hg with each respiratory cycle.

Arterial Pressure "Vasomotor" Waves—Oscillation of Pressure Reflex Control Systems

Often while recording arterial pressure from an animal, in addition to the small pressure waves caused by respiration, some much larger waves are also noted—as great as 10 to 40 mm Hg at times—that rise and fall more slowly than the respiratory waves. The duration of each cycle varies from 26 seconds in the anesthetized dog to 7 to 10 seconds in the unanesthetized human. These waves are called *vasomotor waves* or "*Mayer waves*." Such records are demonstrated in Figure 18-10, showing the cyclical rise and fall in arterial pressure.

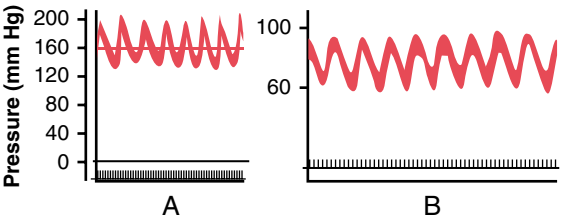


Figure 18-10 *A*, Vasomotor waves caused by oscillation of the CNS ischemic response. *B*, Vasomotor waves caused by baroreceptor reflex oscillation.

The cause of vasomotor waves is "reflex oscillation" of one or more nervous pressure control mechanisms, some of which are the following.

Oscillation of the Baroreceptor and Chemoreceptor Reflexes. The vasomotor waves of Figure 18-10*B* are often seen in experimental pressure recordings, although usually much less intense than shown in the figure. They are caused mainly by oscillation of the *baroreceptor reflex.* That is, a high pressure excites the baroreceptors; this then inhibits the sympathetic nervous system and lowers the pressure a few seconds later. The decreased pressure in turn reduces the baroreceptor stimulation and allows the vasomotor center to become active once again, elevating the pressure to a high value. The response is not instantaneous, and it is delayed until a few seconds later. This high pressure then initiates another cycle, and the oscillation continues on and on.

The *chemoreceptor reflex* can also oscillate to give the same type of waves. This reflex usually oscillates simultaneously with the baroreceptor reflex. It probably plays the major role in causing vasomotor waves when the arterial pressure is in the range of 40 to 80 mm Hg because in this low range, chemoreceptor control of the circulation becomes powerful, whereas baroreceptor control becomes weaker.

Oscillation of the CNS Ischemic Response. The record in Figure 18-10*A* resulted from oscillation of the CNS ischemic pressure control mechanism. In this experiment, the cerebrospinal fluid pressure was raised to 160 mm Hg, which compressed the cerebral vessels and initiated a CNS ischemic pressure response up to 200 mm Hg. When the arterial pressure rose to such a high value, the brain ischemia was relieved and the sympathetic nervous system became inactive. As a result, the arterial pressure fell rapidly back to a much lower value, causing brain ischemia once again. The ischemia then initiated another rise in pressure. Again the ischemia was relieved and again the pressure fell. This repeated itself cyclically as long as the cerebrospinal fluid pressure remained elevated.

Thus, any reflex pressure control mechanism can oscillate if the intensity of "feedback" is strong enough and if there is a delay between excitation of the pressure receptor and the subsequent pressure response. The vasomotor

waves are of considerable theoretical importance because they show that the nervous reflexes that control arterial pressure obey the same principles as those applicable to mechanical and electrical control systems. For instance, if the feedback "gain" is too great in the guiding mechanism of an automatic pilot for an airplane and there is also delay in response time of the guiding mechanism, the plane will oscillate from side to side instead of following a straight course.

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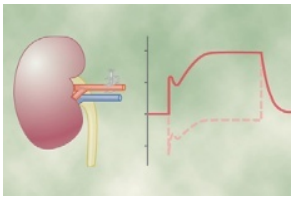
Role of the Kidneys in Long-Term Control of Arterial Pressure and in Hypertension: The Integrated System for Arterial Pressure Regulation



Short-term control of arterial pressure by the sympathetic nervous system, as discussed in Chapter 18, occurs primarily through the effects of the nervous system on total peripheral vascular resistance and capacitance, as well as on cardiac pumping ability.

The body, however, also has powerful mechanisms for regulating arterial pressure week after week and month after month. This long-term control of arterial pressure is closely intertwined with homeostasis of body fluid volume, which is determined by the balance between the fluid intake and output. For long-term survival, fluid intake and output must be precisely balanced, a task that is performed by multiple nervous and hormonal controls, and by local control systems within the kidneys that regulate their excretion of salt and water. In this chapter we discuss these renal–body fluid systems that play a dominant role in long-term blood pressure regulation.

Renal–Body Fluid System for Arterial Pressure Control

The renal–body fluid system for arterial pressure control acts slowly but powerfully as follows: If blood volume increases and vascular capacitance is not altered, arterial pressure will also increase. The rising pressure in turn causes the kidneys to excrete the excess volume, thus returning the pressure back toward normal.

In the phylogenetic history of animal development, this renal–body fluid system for pressure control is a primitive one. It is fully operative in one of the lowest of vertebrates, the hagfish. This animal has a low arterial pressure, only 8 to 14 mm Hg, and this pressure increases almost directly in proportion to its blood volume. The hagfish continually drinks sea water, which is absorbed into its blood, increasing the blood volume and blood pressure. However, when the pressure rises too high, the kidney simply excretes the excess volume into the urine and relieves the pressure. At low pressure, the kidney excretes less fluid than is ingested. Therefore, because the hagfish continues to drink, extracellular fluid volume, blood volume, and pressure all build up again to the higher levels.

Throughout the ages, this primitive mechanism of pressure control has survived almost as it functions in the hagfish; in the humans, kidney output of water and salt is just as sensitive to pressure changes as in the hagfish, if not more so. Indeed, an increase in arterial pressure in the human of only a few mm Hg can double renal output of water, which is called *pressure diuresis,* as well as double the output of salt, which is called *pressure natriuresis.*

In the human being, the renal–body fluid system for arterial pressure control, just as in the hagfish, is a fundamental mechanism for long-term arterial pressure control. However, through the stages of evolution, multiple refinements have been added to make this system much more exact in its control in the human being. An especially important refinement, as discussed later, has been the addition of the renin-angiotensin mechanism.

Quantitation of Pressure Diuresis as a Basis for Arterial Pressure Control

Figure 19-1 shows the approximate average effect of different arterial pressure levels on urinary volume output by an isolated kidney, demonstrating markedly increased urine volume output as the pressure rises. This increased urinary output is the phenomenon of *pressure diuresis.* The curve in this figure is called a *renal urinary output curve* or a *renal function curve.* In the human being, at an arterial pressure of 50 mm Hg, the urine output is essentially zero. At 100 mm Hg it is normal, and at 200 mm Hg it is about six to eight times normal. Furthermore, not only does increasing the arterial pressure increase urine volume output, but it causes approximately equal increase in sodium output, which is the phenomenon of *pressure natriuresis.*

An Experiment Demonstrating the Renal–Body Fluid System for Arterial Pressure Control. Figure 19-2 shows the results of an experiment in dogs in which all the nervous reflex mechanisms for blood pressure control were first blocked. Then the arterial pressure was suddenly elevated by infusing about 400 ml of blood intravenously. Note the rapid increase in cardiac output

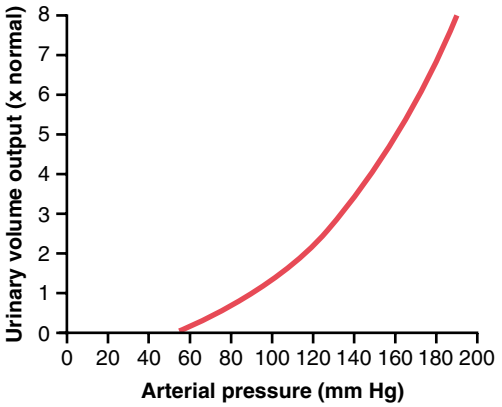


Figure 19-1 Typical renal urinary output curve measured in a perfused isolated kidney, showing pressure diuresis when the arterial pressure rises above normal.

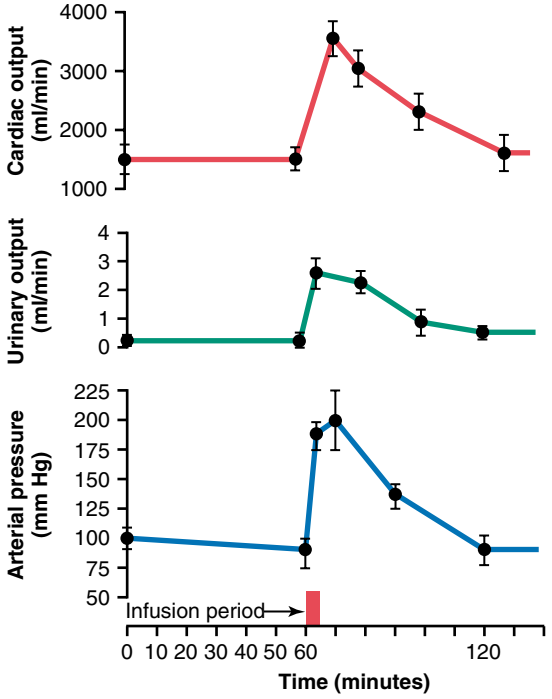


Figure 19-2 Increases in cardiac output, urinary output, and arterial pressure caused by increased blood volume in dogs whose nervous pressure control mechanisms had been blocked. This figure shows return of arterial pressure to normal after about an hour of fluid loss into the urine. (Courtesy Dr. William Dobbs.)

to about double normal and increase in mean arterial pressure to 205 mm Hg, 115 mm Hg above its resting level. Shown by the middle curve is the effect of this increased arterial pressure on urine output, which increased 12-fold. Along with this tremendous loss of fluid in the urine, both the cardiac output and the arterial pressure returned to normal during the subsequent hour. Thus, one sees an extreme capability of the kidneys to eliminate fluid volume from the body in response to high arterial pressure and in so doing to return the arterial pressure back to normal.

Arterial Pressure Control by the Renal–Body Fluid Mechanism—"Near Infinite Feedback Gain" Feature. Figure 19-3 shows a graphical method that

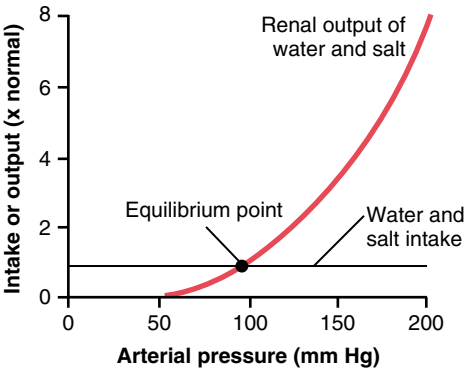


Figure 19-3 Analysis of arterial pressure regulation by equating the "renal output curve" with the "salt and water intake curve." The equilibrium point describes the level to which the arterial pressure will be regulated. (That small portion of the salt and water intake that is lost from the body through nonrenal routes is ignored in this and similar figures in this chapter.)

can be used for analyzing arterial pressure control by the renal–body fluid system. This analysis is based on two separate curves that intersect each other: (1) the renal output curve for water and salt in response to rising arterial pressure, which is the same renal output curve as that shown in Figure 19-1, and (2) the line that represents the net water and salt intake.

Over a long period, the water and salt output must equal the intake. Furthermore, the only place on the graph in Figure 19-3 at which output equals intake is where the two curves intersect, which is called the *equilibrium point.* Now, let us see what happens if the arterial pressure increases above, or decreases below, the equilibrium point.

First, assume that the arterial pressure rises to 150 mm Hg. At this level, the renal output of water and salt is about three times as great as the intake. Therefore, the body loses fluid, the blood volume decreases, and the arterial pressure decreases. Furthermore, this "negative balance" of fluid will not cease until the pressure falls *all the way* back exactly to the equilibrium level. Indeed, even when the arterial pressure is only 1 mm Hg greater than the equilibrium level, there still is slightly more loss of water and salt than intake, so the pressure continues to fall that last 1 mm Hg *until the pressure eventually returns exactly to the equilibrium point.*

If the arterial pressure falls below the equilibrium point, the intake of water and salt is greater than the output. Therefore, body fluid volume increases, blood volume increases, and the arterial pressure rises until once again it returns *exactly* to the equilibrium point. This return of the arterial pressure *always back to the equilibrium point* is the *near infinite feedback gain principle* for control of arterial pressure by the renal–body fluid mechanism.

Two Determinants of the Long-Term Arterial Pressure Level. In Figure 19-3, one can also see that two basic long-term factors determine the long-term arterial pressure level. This can be explained as follows.

As long as the two curves representing (1) renal output of salt and water and (2) intake of salt and water remain exactly as they are shown in Figure 19-3, the mean arterial pressure level will eventually readjust to 100 mm Hg, which is the pressure level depicted by the equilibrium point of this figure. Furthermore, there are only two ways in which the pressure of this equilibrium point can be changed from the 100 mm Hg level. One of these is by shifting the pressure level of the renal output curve for salt and water, and the other is by changing the level of the water and salt intake line. Therefore, expressed simply, the two primary determinants of the long-term arterial pressure level are as follows:

1. The degree of pressure shift of the renal output curve for water and salt
2. The level of the water and salt intake

Operation of these two determinants in the control of arterial pressure is demonstrated in Figure 19-4. In Figure 19-4*A*, some abnormality of the kidneys has caused the renal output curve to shift 50 mm Hg in the high-pressure direction (to the right). Note that the equilibrium point has also shifted to 50 mm Hg higher than normal. Therefore, one can state that if the renal output curve shifts to a new pressure level, the arterial pressure will follow to this new pressure level within a few days.

Figure 19-4*B* shows how a change in the level of salt and water intake also can change the arterial pressure. In this case, the intake level has increased fourfold and the equilibrium point has shifted to a pressure level of 160 mm Hg, 60 mm Hg above the normal level. Conversely, a decrease in the intake level would reduce the arterial pressure.

Thus, it is *impossible to change the long-term mean arterial pressure level* to a new value without changing one or both of the two basic determinants of long-term arterial pressure—either (1) the level of salt and water intake or (2) the degree of shift of the renal function curve along the pressure axis. However, if either of these is changed, one finds the arterial pressure thereafter to be regulated at a new pressure level, the arterial pressure at which the two new curves intersect.

The Chronic Renal Output Curve Is Much Steeper than the Acute Curve. An important characteristic of pressure natriuresis (and pressure diuresis) is that chronic changes in arterial pressure, lasting for days or months, have much greater effect on renal output of salt and water than observed during acute changes in pressure (Figure 19-5). Thus, when the kidneys are functioning normally, the *chronic renal output curve* is much steeper than the acute curve.

The powerful effects of chronic increases in arterial pressure on urine output are because increased pressure not only has direct hemodynamic effects on the kidney to increase excretion, but also indirect effects mediated by nervous and hormonal changes that occur when blood pressure is increased. For example, increased arterial pressure decreases activity of the sympathetic nervous system and various hormones such as angiotensin II and aldosterone that tend to reduce salt and water excretion by the kidneys. Reduced activity of these *antinatriuretic* systems therefore amplifies the effectiveness of pressure natriuresis and diuresis in raising salt and water excretion during chronic increases in arterial pressure (see Chapters 27 and 29 for further discussion).

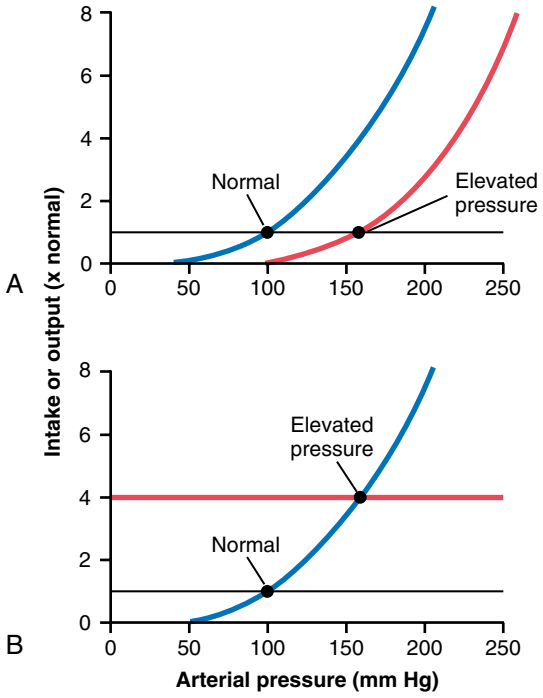


Figure 19-4 Two ways in which the arterial pressure can be increased: *A*, by shifting the renal output curve in the right-hand direction toward a higher pressure level or *B*, by increasing the intake level of salt and water.

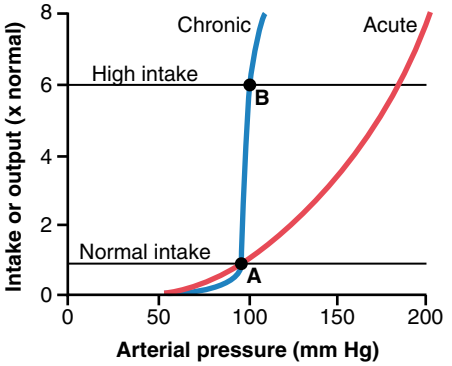


Figure 19-5 Acute and chronic renal output curves. Under steady-state conditions renal output of salt and water is equal to intake of salt and water. *A* and *B* represent the equilibrium points for long-term regulation of arterial pressure when salt intake is normal or six times normal, respectively. Because of the steepness of the chronic renal output curve, increased salt intake causes only small changes in arterial pressure. In persons with impaired kidney function, the steepness of the renal output curve may be reduced, similar to the acute curve, resulting in increased sensitivity of arterial pressure to changes in salt intake.

Conversely, when blood pressure is reduced, the sympathetic nervous system is activated and formation of antinatriuretic hormones is increased, adding to the direct effects of reduced pressure to decrease renal output of salt and water. This combination of direct effects of pressure on the kidneys and indirect effects of pressure on the sympathetic nervous system and various hormone systems make pressure natriuresis and diuresis extremely powerful for long-term control of arterial pressure and body fluid volumes.

The importance of neural and hormonal influences on pressure natriuresis is especially evident during chronic changes in sodium intake. If the kidneys and the nervous and hormonal mechanisms are functioning normally, chronic increases in intakes of salt and water to as high as six times normal are usually associated with only small increases in arterial pressure. Note that the blood pressure equilibrium point B on the curve is nearly the same as point A, the equilibrium point at normal salt intake. Conversely, decreases in salt and water intake to as low as one-sixth normal typically have little effect on arterial pressure. Thus, many persons are said to be *salt insensitive* because large variations in salt intake do not change blood pressure more than a few mm Hg.

Individuals with kidney injury or excessive secretion of antinatriuretic hormones such as angiotensin II or aldosterone, however, may be *salt sensitive* with an attenuated renal output curve similar to the acute curve shown in Figure 19-5. In these cases, even moderate increases in salt intake may cause significant increases in arterial pressure.

Some of the factors include loss of functional nephrons due to kidney injury, or excessive formation of antinatriuretic hormones such as angiotensin II or aldosterone. For example, surgical reduction of kidney mass or injury to the kidney due to hypertension, diabetes, and various kidney diseases all cause blood pressure to be more sensitive to changes in salt intake. In these instances, greater than normal increases in arterial pressure are required to raise renal output sufficiently to maintain a balance between the intake and output of salt and water.

There is some evidence that long-term high salt intake, lasting for several years, may actually damage the kidneys and eventually make blood pressure more salt sensitive. We will discuss salt sensitivity of blood pressure in patients with hypertension later in this chapter.

Failure of Increased Total Peripheral Resistance to Elevate the Long-Term Level of Arterial Pressure if Fluid Intake and Renal Function Do Not Change

Now is the chance for the reader to see whether he or she really understands the renal–body fluid mechanism for arterial pressure control. Recalling the basic equation for arterial pressure—*arterial pressure* equals *cardiac output* times *total peripheral resistance*—it is clear that an increase in total peripheral resistance should elevate the arterial pressure. Indeed, *when the total peripheral resistance is acutely increased,* the arterial pressure does rise immediately. Yet if the kidneys continue to function normally, the acute rise in arterial pressure usually is not maintained. Instead, the arterial pressure returns all the way to normal within a day or so. Why?

The answer to this is the following: Increasing resistance in the blood vessels everywhere else in the body *besides in the kidneys* does not change the equilibrium point for blood pressure control as dictated by the kidneys (see again Figures 19-3 and 19-4). Instead, the kidneys immediately begin to respond to the high arterial pressure, causing pressure diuresis and pressure natriuresis. Within hours, large amounts of salt and water are lost from the body, and this continues until the arterial pressure returns to the pressure level of the equilibrium point. At this point blood pressure is normalized and extracellular fluid volume and blood volume are decreased to levels below normal.

As proof of this principle that changes in total peripheral resistance do not affect the long-term level of arterial pressure if function of the kidneys is still normal, carefully study Figure 19-6. This figure shows the approximate cardiac outputs and the arterial pressures in different clinical conditions in which the *long-term total peripheral resistance* is either much less than or much greater than normal, but kidney excretion of salt and water is normal. Note in all these different clinical conditions that the arterial pressure is also exactly normal.

A word of caution is necessary at this point in our discussion. Many times when the total peripheral resistance increases, *this also increases the intrarenal vascular resistance at the same time,* which alters the function of the kidney and can cause hypertension by shifting the renal

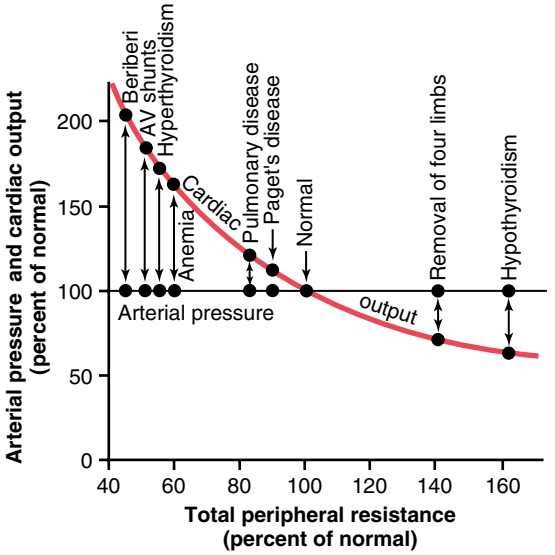


Figure 19-6 Relations of total peripheral resistance to the long-term levels of arterial pressure and cardiac output in different clinical abnormalities. In these conditions, the kidneys were functioning normally. Note that changing the whole-body total peripheral resistance caused equal and opposite changes in cardiac output but in all cases had no effect on arterial pressure. (Redrawn from Guyton AC: Arterial Pressure and Hypertension. Philadelphia: WB Saunders, 1980.)

function curve to a higher pressure level, in the manner shown in Figure 19-4*A*. We see an example of this later in this chapter when we discuss hypertension caused by vasoconstrictor mechanisms. But *it is the increase in renal resistance* that is the culprit, *not the increased total peripheral resistance*—an important distinction.

Increased Fluid Volume Can Elevate Arterial Pressure by Increasing Cardiac Output or Total Peripheral Resistance

The overall mechanism by which increased extracellular fluid volume may elevate arterial pressure, if vascular capacity is not simultaneously increased, is shown in Figure 19-7. The sequential events are (1) increased extracellular fluid volume (2) increases the blood volume, which (3) increases the mean circulatory filling pressure, which (4) increases venous return of blood to the heart, which (5) increases cardiac output, which (6) increases arterial pressure. The increased arterial pressure, in turn, increases real excretion of salt and water and may return extracellular fluid volume to nearly normal if kidney function is normal.

Note especially in this schema the two ways in which an increase in cardiac output can increase the arterial pressure. One of these is the direct effect of increased cardiac output to increase the pressure, and the other is an indirect effect to raise total peripheral vascular resistance

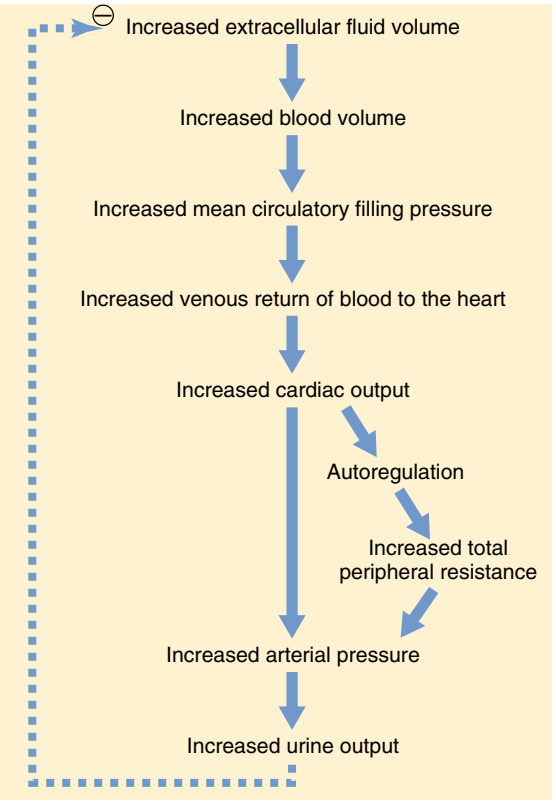


Figure 19-7 Sequential steps by which increased extracellular fluid volume increases the arterial pressure. Note especially that increased cardiac output has both a ***direct effect*** to increase arterial pressure and an ***indirect effect*** by first increasing the total peripheral resistance.

through *autoregulation* of blood flow. The second effect can be explained as follows.

Referring to Chapter 17, let us recall that whenever an excess amount of blood flows through a tissue, the local tissue vasculature constricts and decreases the blood flow back toward normal. This phenomenon is called "autoregulation," which means simply regulation of blood flow by the tissue itself. When increased blood volume increases the cardiac output, the blood flow increases in all tissues of the body, so this autoregulation mechanism constricts blood vessels all over the body. This in turn increases the total peripheral resistance.

Finally, because arterial pressure is equal to *cardiac output* times *total peripheral resistance*, the secondary increase in total peripheral resistance that results from the autoregulation mechanism helps greatly in increasing the arterial pressure. For instance, only a 5 to 10 percent increase in cardiac output can increase the arterial pressure from the normal mean arterial pressure of 100 mm Hg up to 150 mm Hg. In fact, the slight increase in cardiac output is often not measurable.

Importance of Salt (NaCl) in the Renal–Body Fluid Schema for Arterial Pressure Regulation

Although the discussions thus far have emphasized the importance of volume in regulation of arterial pressure, experimental studies have shown that an increase in salt intake is far more likely to elevate the arterial pressure than is an increase in water intake. The reason for this is that pure water is normally excreted by the kidneys almost as rapidly as it is ingested, but salt is not excreted so easily. As salt accumulates in the body, it also indirectly increases the extracellular fluid volume for two basic reasons:

1. When there is excess salt in the extracellular fluid, the osmolality of the fluid increases, and this in turn stimulates the thirst center in the brain, making the person drink extra amounts of water to return the extracellular salt concentration to normal. This increases the extracellular fluid volume.
2. The increase in osmolality caused by the excess salt in the extracellular fluid also stimulates the hypothalamic-posterior pituitary gland secretory mechanism to secrete increased quantities of *antidiuretic hormone*. (This is discussed in Chapter 28.) The antidiuretic hormone then causes the kidneys to reabsorb greatly increased quantities of water from the renal tubular fluid, thereby diminishing the excreted volume of urine but increasing the extracellular fluid volume.

Thus, for these important reasons, the amount of salt that accumulates in the body is the main determinant of the extracellular fluid volume. Because only small increases in extracellular fluid and blood volume can often increase the arterial pressure greatly if the vascular capacity is not simultaneously increased, accumulation of even a small amount of extra salt in the body can lead to considerable elevation of arterial pressure.

As discussed previously, raising salt intake in the absence of impaired kidney function or excessive formation of antinatriuretic hormones usually does not increase arterial pressure much because the kidneys rapidly eliminate the excess salt and blood volume is hardly altered.

Chronic Hypertension (High Blood Pressure) Is Caused by Impaired Renal Fluid Excretion

When a person is said to have chronic *hypertension* (or "high blood pressure"), it is meant that his or her *mean arterial pressure* is greater than the upper range of the accepted normal measure. A *mean* arterial pressure greater than 110 mm Hg (normal is about 90 mm Hg) is considered to be hypertensive. (This level of *mean* pressure occurs when the *diastolic* blood pressure is greater than about 90 mm Hg and the *systolic* pressure is greater than about 135 mm Hg.) In severe hypertension, the *mean* arterial pressure can rise to 150 to 170 mm Hg, with *diastolic* pressure as high as 130 mm Hg and *systolic* pressure occasionally as high as 250 mm Hg.

Even moderate elevation of arterial pressure leads to shortened life expectancy. At severely high pressures—mean arterial pressures 50 percent or more above normal—a person can expect to live no more than a few more years unless appropriately treated. The lethal effects of hypertension are caused mainly in three ways:

1. Excess workload on the heart leads to early heart failure and coronary heart disease, often causing death as a result of a heart attack.
2. The high pressure frequently damages a major blood vessel in the brain, followed by death of major portions of the brain; this is a *cerebral infarct.* Clinically it is called a "stroke." Depending on which part of the brain is involved, a stroke can cause paralysis, dementia, blindness, or multiple other serious brain disorders.
3. High pressure almost always causes injury in the kidneys, producing many areas of renal destruction and, eventually, kidney failure, uremia, and death.

Lessons learned from the type of hypertension called "volume-loading hypertension" have been crucial in understanding the role of the renal–body fluid volume mechanism for arterial pressure regulation. Volume-loading hypertension means hypertension caused by excess accumulation of extracellular fluid in the body, some examples of which follow.

Experimental Volume-Loading Hypertension Caused by Reduced Renal Mass Along with Simultaneous Increase in Salt Intake. Figure 19-8 shows a typical experiment demonstrating volume-loading hypertension in a group of dogs with 70 percent of their kidney mass removed. At the first circled point on the curve, the two poles of one of the kidneys were removed, and at the second circled point, the entire opposite kidney was removed, leaving the animals with only 30 percent of normal renal mass. Note that removal of this amount of kidney mass increased the arterial pressure an average of only 6 mm Hg. Then, the dogs were given salt solution to drink instead of water. Because *salt* solution fails to quench the thirst, the dogs drank two to four times the normal amounts of volume, and within a few days, their average arterial pressure rose to about 40 mm Hg above normal. After 2 weeks, the dogs were given tap water again instead of salt solution; the pressure returned to normal within 2 days. Finally, at the end of the experiment, the dogs were given salt solution again, and this time the pressure

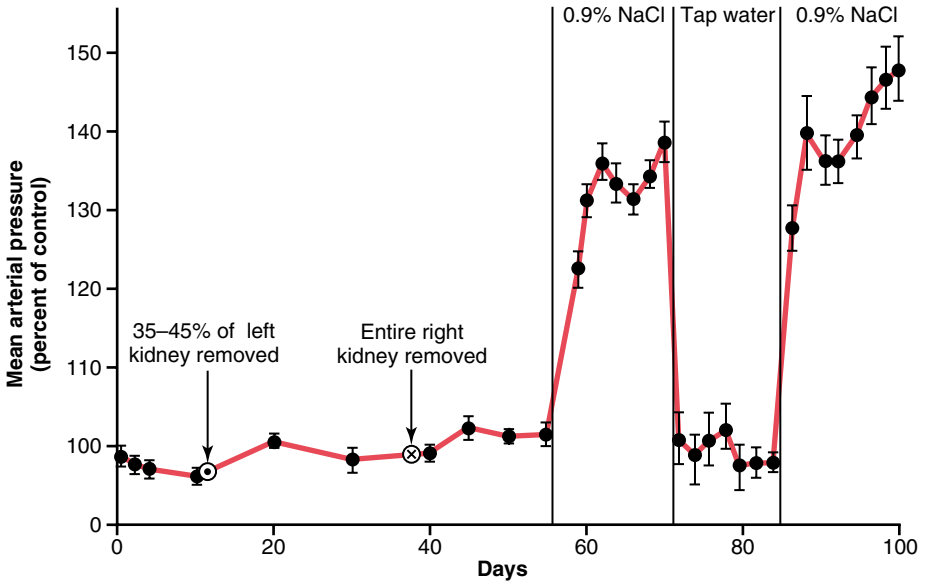


Figure 19-8 Average effect on arterial pressure of drinking 0.9 percent saline solution instead of water in four dogs with 70 percent of their renal tissue removed. (Redrawn from Langston JB, Guyton AC, Douglas BH, et al: Effect of changes in salt intake on arterial pressure and renal function in partially nephrectomized dogs. Circ Res 12:508, 1963. By permission of the American Heart Association, Inc.)

rose much more rapidly to an even higher level because the dogs had already learned to tolerate the salt solution and therefore drank much more. Thus, this experiment demonstrates volume-loading hypertension.

If the reader considers again the basic determinants of long-term arterial pressure regulation, he or she can immediately understand why hypertension occurred in the volume-loading experiment of Figure 19-8. First, reduction of the kidney mass to 30 percent of normal greatly reduced the ability of the kidneys to excrete salt and water. Therefore, salt and water accumulated in the body and in a few days raised the arterial pressure high enough to excrete the excess salt and water intake.

Sequential Changes in Circulatory Function During the Development of Volume-Loading Hypertension. It is especially instructive to study the sequential changes in circulatory function during progressive development of volume-loading hypertension. Figure 19-9 shows these sequential changes. A week or so before the point labeled "0" days, the kidney mass had already been decreased to only 30 percent of normal. Then, at this point, the intake of salt and water was increased to about six times normal and kept at this high intake thereafter. The acute effect was to increase extracellular fluid volume, blood volume, and cardiac output to 20 to 40 percent above normal. Simultaneously, the arterial pressure began to rise but not nearly so much at first as did the fluid volumes and cardiac output. The reason for this slower rise in pressure can be discerned by studying the total peripheral resistance curve, which shows an initial *decrease* in total peripheral resistance. This decrease was caused by the baroreceptor mechanism discussed in Chapter 18, which tried to prevent the rise in pressure. However, after 2 to 4 days, the baroreceptors adapted (reset) and were no longer able to prevent the rise in pressure. At this time, the arterial pressure had risen almost to its full height because of the increase in cardiac output, even though the total peripheral resistance was still almost at the normal level.

After these early acute changes in the circulatory variables had occurred, more prolonged secondary changes occurred during the next few weeks. Especially important was a *progressive increase in total peripheral resistance,* while at the same time *the cardiac output decreased almost all the way back to normal,* mainly as a result of *the long-term blood flow autoregulation* mechanism that is discussed in detail in Chapter 17 and earlier in this chapter. That is, after the cardiac output had risen to a high level and had initiated the hypertension, the excess blood flow through the tissues then caused progressive constriction of the local arterioles, thus returning the local blood flows in all the body tissues and also the cardiac output almost all the way back to normal, while simultaneously causing a *secondary increase in total peripheral resistance.*

Note, too, that the extracellular fluid volume and blood volume returned almost all the way back to normal along with the decrease in cardiac output. This resulted from two factors: First, the increase in arteriolar resistance decreased the capillary pressure, which allowed the fluid in the tissue spaces to be absorbed back into the blood. Second, the elevated arterial pressure now caused the kidneys to excrete the excess volume of fluid that had initially accumulated in the body.

Last, let us take stock of the final state of the circulation several weeks after the initial onset of volume loading. We find the following effects:

1. Hypertension
2. Marked increase in total peripheral resistance
3. Almost complete return of the extracellular fluid volume, blood volume, and cardiac output back to normal

Therefore, we can divide volume-loading hypertension into two separate sequential stages: The first stage results from increased fluid volume causing increased cardiac output. This increase in cardiac output mediates the hypertension. The second stage in volume-loading hypertension is characterized by high blood pressure and high total peripheral resistance but return of the cardiac output so near to normal that the usual measuring techniques frequently cannot detect an abnormally elevated cardiac output.

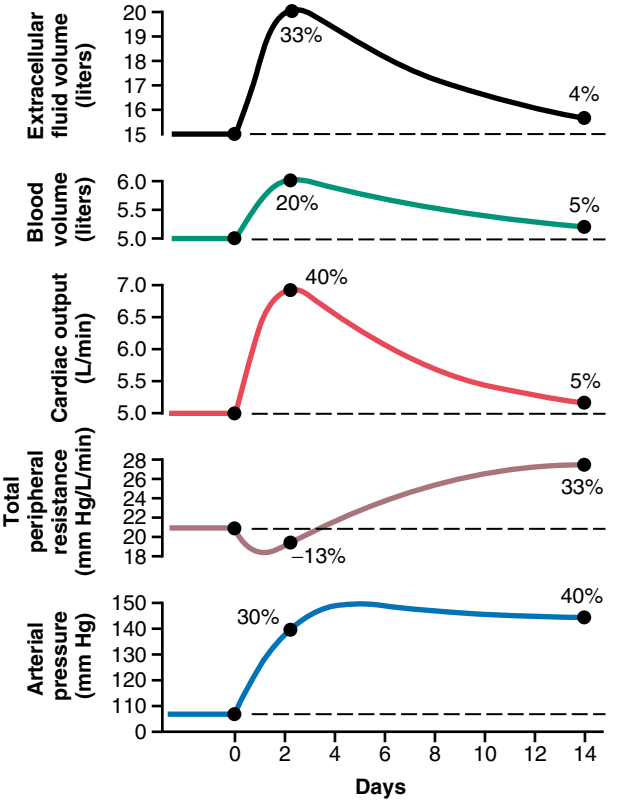


Figure 19-9 Progressive changes in important circulatory system variables during the first few weeks of ***volume-loading hypertension.*** Note especially the initial increase in cardiac output as the basic cause of the hypertension. Subsequently, the autoregulation mechanism returns the cardiac output almost to normal while simultaneously causing a ***secondary increase in total peripheral resistance.*** (Modified from Guyton AC: Arterial Pressure and Hypertension. Philadelphia: WB Saunders, 1980.)

Thus, the increased total peripheral resistance in volume-loading hypertension occurs after the hypertension has developed and, therefore, is secondary to the hypertension rather than being the cause of the hypertension.

Volume-Loading Hypertension in Patients Who Have No Kidneys but Are Being Maintained on an Artificial Kidney

When a patient is maintained on an artificial kidney, it is especially important to keep the patient's body fluid volume at a normal level—that is, it is important to remove an appropriate amount of water and salt each time the patient is dialyzed. If this is not done and extracellular fluid volume is allowed to increase, hypertension almost invariably develops in exactly the same way as shown in Figure 19-9. That is, the cardiac output increases at first and causes hypertension. Then the autoregulation mechanism returns the cardiac output back toward normal while causing a secondary increase in total peripheral resistance. Therefore, in the end, the hypertension is a high peripheral resistance type of hypertension.

Hypertension Caused by Primary Aldosteronism

Another type of volume-loading hypertension is caused by excess aldosterone in the body or, occasionally, by excesses of other types of steroids. A small tumor in one of the adrenal glands occasionally secretes large quantities of aldosterone, which is the condition called "primary aldosteronism." As discussed in Chapters 27 and 29, aldosterone increases the rate of reabsorption of salt and water by the tubules of the kidneys, thereby reducing the loss of these in the urine while at the same time causing an increase in blood volume and extracellular fluid volume. Consequently, hypertension occurs. And, if salt intake is increased at the same time, the hypertension becomes even greater. Furthermore, if the condition persists for months or years, the excess arterial pressure often causes pathological changes in the kidneys that make the kidneys retain even more salt and water in addition to that caused directly by the aldosterone. Therefore, the hypertension often finally becomes lethally severe.

Here again, in the early stages of this type of hypertension, the cardiac output is increased, but in later stages, the cardiac output generally returns almost to normal while the total peripheral resistance becomes secondarily elevated, as explained earlier in the chapter for primary volume-loading hypertension.

The Renin-Angiotensin System: Its Role in Arterial Pressure Control

Aside from the capability of the kidneys to control arterial pressure through changes in extracellular fluid volume, the kidneys also have another powerful mechanism for controlling pressure. It is the renin-angiotensin system.

Renin is a protein enzyme released by the kidneys when the arterial pressure falls too low. In turn, it raises the arterial pressure in several ways, thus helping to correct the initial fall in pressure.

Components of the Renin-Angiotensin System

Figure 19-10 shows the functional steps by which the renin-angiotensin system helps to regulate arterial pressure.

Renin is synthesized and stored in an inactive form called *prorenin* in the *juxtaglomerular cells* (JG cells) of the kidneys. The JG cells are modified smooth muscle cells located *in the walls of the afferent arterioles immediately proximal to the glomeruli*. When the arterial pressure falls, intrinsic reactions in the kidneys themselves cause many of the prorenin molecules in the JG cells to split and release renin. Most of the renin enters the renal blood and then passes out of the kidneys to circulate throughout the entire body. However, small amounts of the renin do remain in the local fluids of the kidney and initiate several intrarenal functions.

Renin itself is an enzyme, not a vasoactive substance. As shown in the schema of Figure 19-10, renin acts enzymatically on another plasma protein, a globulin called *renin substrate* (or *angiotensinogen*), to release a 10-amino acid peptide, *angiotensin I*. Angiotensin I has mild vasoconstrictor properties but not enough to cause significant changes in circulatory function. The renin persists in the blood for 30 minutes to 1 hour and continues to cause formation of still more angiotensin I during this entire time.

Within a few seconds to minutes after formation of angiotensin I, two additional amino acids are split from

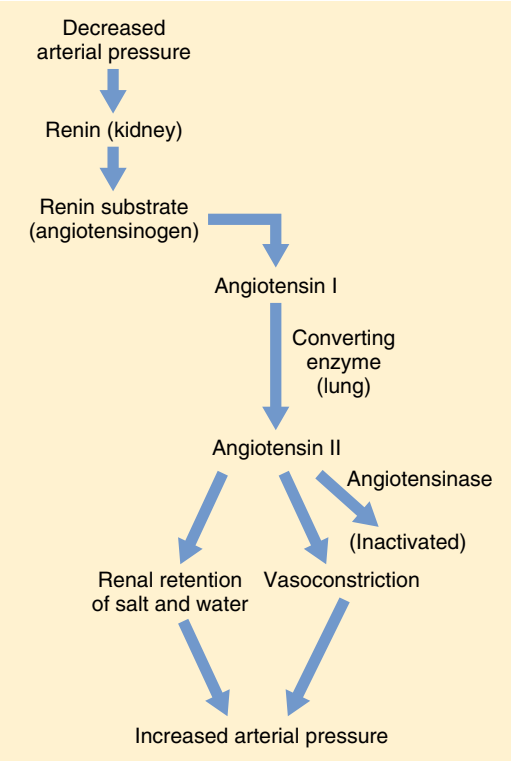


Figure 19-10 Renin-angiotensin vasoconstrictor mechanism for arterial pressure control.

the angiotensin I to form the 8-amino acid peptide *angiotensin II*. This conversion occurs to a great extent in the lungs while the blood flows through the small vessels of the lungs, catalyzed by an enzyme called *angiotensin converting enzyme* that is present in the endothelium of the lung vessels. Other tissues such as the kidneys and blood vessels also contain converting enzyme and therefore form angiotensin II locally.

Angiotensin II is an extremely powerful vasoconstrictor, and it also affects circulatory function in other ways as well. However, it persists in the blood only for 1 or 2 minutes because it is rapidly inactivated by multiple blood and tissue enzymes collectively called *angiotensinases*.

During its persistence in the blood, angiotensin II has two principal effects that can elevate arterial pressure. The first of these, *vasoconstriction in many areas of the body,* occurs rapidly. Vasoconstriction occurs intensely in the arterioles and much less so in the veins. Constriction of the arterioles increases the total peripheral resistance, thereby raising the arterial pressure, as demonstrated at the bottom of the schema in Figure 19-10. Also, the mild constriction of the veins promotes increased venous return of blood to the heart, thereby helping the heart pump against the increasing pressure.

The second principal means by which angiotensin II increases the arterial pressure is to *decrease excretion of both salt and water* by the kidneys. This slowly increases the extracellular fluid volume, which then increases the arterial pressure during subsequent hours and days. This long-term effect, acting through the extracellular fluid volume mechanism, is even more powerful than the acute vasoconstrictor mechanism in eventually raising the arterial pressure.

Rapidity and Intensity of the Vasoconstrictor Pressure Response to the Renin-Angiotensin System

Figure 19-11 shows a typical experiment demonstrating the effect of hemorrhage on the arterial pressure under two separate conditions: (1) with the renin-angiotensin system functioning and (2) without the system functioning (the system was interrupted by a renin-blocking antibody). Note that after hemorrhage—enough to cause acute decrease of the arterial pressure to 50 mm Hg—the arterial pressure rose back to 83 mm Hg when the renin-angiotensin system was functional. Conversely, it rose to only 60 mm Hg when the renin-angiotensin system was blocked. This shows that the renin-angiotensin system is powerful enough to return the arterial pressure at least halfway back to normal within a few minutes after severe hemorrhage. Therefore, sometimes it can be of lifesaving service to the body, especially in circulatory shock.

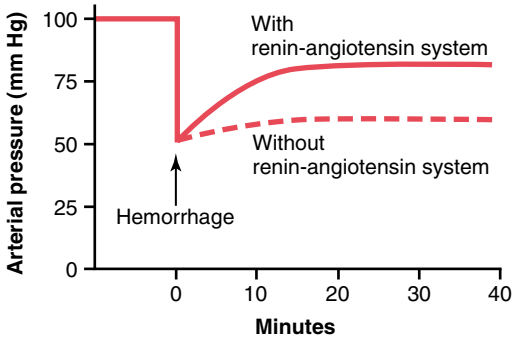


Figure 19-11 Pressure-compensating effect of the renin-angiotensin vasoconstrictor system after severe hemorrhage. (Drawn from experiments by Dr. Royce Brough.)

Note also that the renin-angiotensin vasoconstrictor system requires about 20 minutes to become fully active. Therefore, it is somewhat slower to act for blood pressure control than are the nervous reflexes and the sympathetic norepinephrine-epinephrine system.

Effect of Angiotensin II in the Kidneys to Cause Renal Retention of Salt and Water—An Important Means for Long-Term Control of Arterial Pressure

Angiotensin II causes the kidneys to retain both salt and water in two major ways:

1. Angiotensin II acts directly on the kidneys to cause salt and water retention.
2. Angiotensin II causes the adrenal glands to secrete aldosterone, and the aldosterone in turn increases salt and water reabsorption by the kidney tubules.

Thus, whenever excess amounts of angiotensin II circulate in the blood, the entire long-term renal–body fluid mechanism for arterial pressure control automatically becomes set to a higher arterial pressure level than normal.

Mechanisms of the Direct Renal Effects of Angiotensin II to Cause Renal Retention of Salt and Water. Angiotensin has several direct renal effects that make the kidneys retain salt and water. One major effect is to constrict the renal arterioles, thereby diminishing blood flow through the kidneys. The slow flow of blood reduces the pressure in the peritubular capillaries, which causes rapid reabsorption of fluid from the tubules. Angiotensin II also has important direct actions on the tubular cells themselves to increase tubular reabsorption of sodium and water. The total result of all these effects is significant, sometimes decreasing urine output to less than one fifth of normal.

Stimulation of Aldosterone Secretion by Angiotensin II, and the Effect of Aldosterone to Increase Salt and Water Retention by the Kidneys. Angiotensin II is also one of the most powerful stimulators of aldosterone secretion by the adrenal glands, as we shall discuss in relation to body fluid regulation in Chapter 29 and in relation to adrenal gland function in Chapter 77. Therefore, when the renin-angiotensin system becomes activated, the rate of aldosterone secretion usually also increases; and an important subsequent function of aldosterone is to cause marked increase in sodium reabsorption by the kidney tubules, thus increasing the total body extracellular

fluid sodium. This increased sodium then causes water retention, as already explained, increasing the extracellular fluid volume and leading secondarily to still more long-term elevation of the arterial pressure.

Thus both the direct effect of angiotensin on the kidney and its effect acting through aldosterone are important in long-term arterial pressure control. However, research in our laboratory has suggested that the direct effect of angiotensin on the kidneys is perhaps three or more times as potent as the indirect effect acting through aldosterone—even though the indirect effect is the one most widely known.

Quantitative Analysis of Arterial Pressure Changes Caused by Angiotensin II. Figure 19-12 shows a quantitative analysis of the effect of angiotensin in arterial pressure control. This figure shows two renal output curves, as well as a line depicting a normal level of sodium intake. The left-hand renal output curve is that measured in dogs whose renin-angiotensin system had been blocked by an angiotensin-converting enzyme inhibitor drug that blocks the conversion of angiotensin I to angiotensin II. The right-hand curve was measured in dogs infused continuously with angiotensin II at a level about 2.5 times the normal rate of angiotensin formation in the blood. Note the shift of the renal output curve toward higher pressure levels under the influence of angiotensin II. This shift is caused by both the direct effects of angiotensin II on the kidney and the indirect effect acting through aldosterone secretion, as explained earlier.

Finally, note the two equilibrium points, one for zero angiotensin showing an arterial pressure level of 75 mm Hg, and one for elevated angiotensin showing a pressure level of 115 mm Hg. Therefore, the effect of angiotensin to cause renal retention of salt and water can have a powerful effect in promoting chronic elevation of the arterial pressure.

Role of the Renin-Angiotensin System in Maintaining a Normal Arterial Pressure Despite Large Variations in Salt Intake

One of the most important functions of the renin-angiotensin system is to allow a person to eat either very small or very large amounts of salt without causing great changes in either extracellular fluid volume or arterial pressure. This function is explained by the schema in Figure 19-13, which shows that the initial effect of increased salt intake is to elevate the extracellular fluid volume, in turn elevating the arterial pressure. Then, the increased arterial pressure causes increased blood flow through the kidneys, as well as other effects, which reduce the rate of secretion of renin to a much lower level and lead sequentially to decreased renal retention of salt and water, return of the extracellular fluid volume almost to normal, and, finally, return of the arterial pressure also almost to normal. Thus, the renin-angiotensin system is an automatic feedback mechanism that helps maintain the arterial pressure at or near the normal level even when salt intake is increased. Or, when salt intake is decreased below normal, exactly opposite effects take place.

To emphasize the efficacy of the renin-angiotensin system in controlling arterial pressure, when the system functions normally, the pressure rises no more than 4 to 6 mm Hg in response to as much as a 50-fold increase in salt intake. Conversely, when the renin-angiotensin system is blocked, the same increase in salt intake sometimes causes the pressure to rise 10 times the normal increase, often as much as 50 to 60 mm Hg.

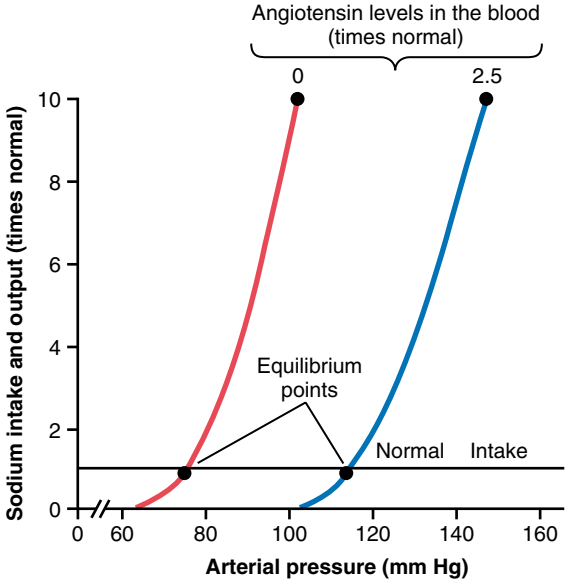


Figure 19-12 Effect of two angiotensin II levels in the blood on the renal output curve, showing regulation of the arterial pressure at an equilibrium point of 75 mm Hg when the angiotensin II level is low and at 115 mm Hg when the angiotensin II level is high.

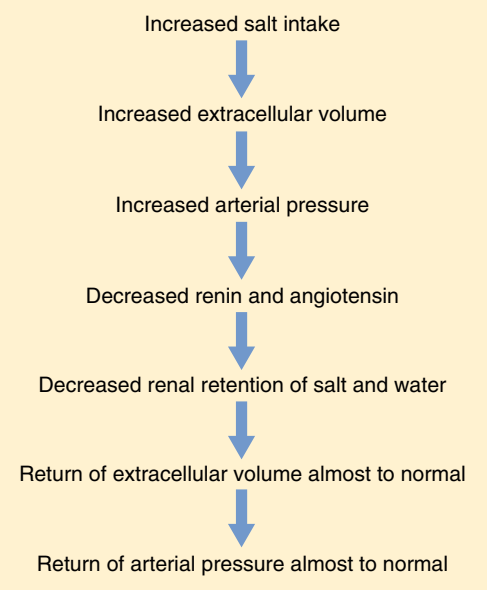


Figure 19-13 Sequential events by which increased salt intake increases the arterial pressure, but feedback decrease in activity of the renin angiotensin system returns the arterial pressure almost to the normal level.

Types of Hypertension in Which Angiotensin Is Involved: Hypertension Caused by a Renin-Secreting Tumor or by Infusion of Angiotensin II

Occasionally a tumor of the renin-secreting juxtaglomerular cells *(the JG cells)* occurs and secretes tremendous quantities of renin; in turn, equally large quantities of angiotensin II are formed. In all patients in whom this has occurred, severe hypertension has developed. Also, when large amounts of angiotensin II are infused continuously for days or weeks into animals, similar severe long-term hypertension develops.

We have already noted that angiotensin II can increase the arterial pressure in two ways:

1. By constricting the arterioles throughout the entire body, thereby increasing the total peripheral resistance and arterial pressure; this effect occurs within seconds after one begins to infuse angiotensin.
2. By causing the kidneys to retain salt and water; over a period of days, this, too, causes hypertension and is the principal cause of the long-term continuation of the elevated pressure.

"One-Kidney" Goldblatt Hypertension. When one kidney is removed and a constrictor is placed on the renal artery of the remaining kidney, as shown in Figure 19-14, the immediate effect is greatly reduced pressure in the renal artery beyond the constrictor, as demonstrated by the dashed curve in the figure. Then, within seconds or minutes, the systemic arterial pressure begins to rise and continues to rise for several days. The pressure usually rises rapidly for the first hour or so, and this is followed by a slower additional rise during the next several days. When the *systemic* arterial pressure reaches its new stable pressure level, the *renal* arterial pressure (the dashed curve in the figure) will have returned almost all the way back to normal. The hypertension produced in this way is called *"one-kidney" Goldblatt hypertension* in honor of Dr. Harry Goldblatt, who first studied the important quantitative features of hypertension caused by renal artery constriction.

The early rise in arterial pressure in Goldblatt hypertension is caused by the renin-angiotensin vasoconstrictor mechanism. That is, because of poor blood flow through the kidney after acute constriction of the renal artery, large quantities of renin are secreted by the kidney, as demonstrated by the lowermost curve in Figure 19-14, and this increases angiotensin II and aldosterone in the blood. The angiotensin in turn raises the arterial pressure acutely. The secretion of renin rises to a peak in an hour or so but returns nearly to normal in 5 to 7 days because the *renal* arterial pressure by that time has also risen back to normal, so the kidney is no longer ischemic.

The second rise in arterial pressure is caused by retention of salt and water by the constricted kidney (that is also stimulated by angiotensin II and aldosterone). In 5 to 7 days, the body fluid volume will have increased enough

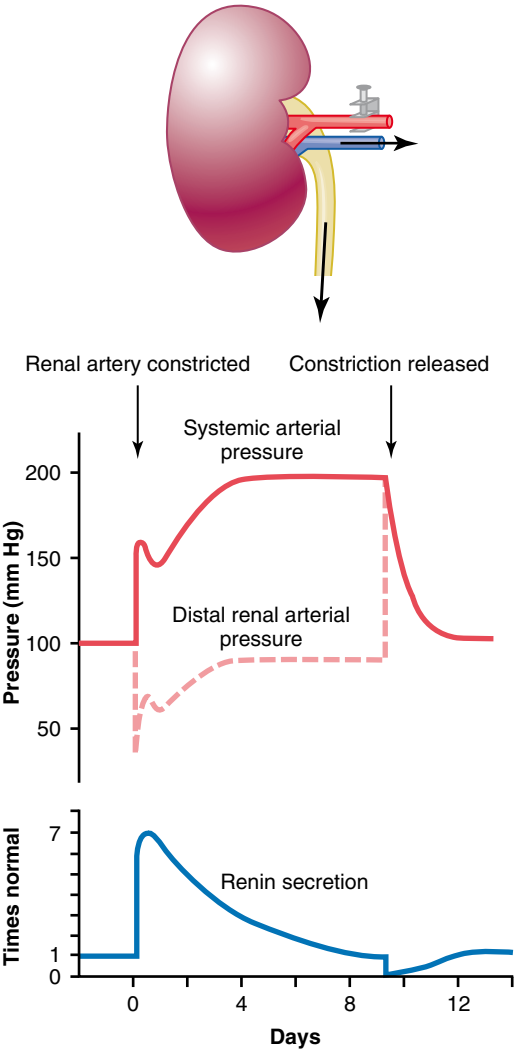


Figure 19-14 Effect of placing a constricting clamp on the renal artery of one kidney after the other kidney has been removed. Note the changes in systemic arterial pressure, renal artery pressure distal to the clamp, and rate of renin secretion. The resulting hypertension is called "one-kidney" Goldblatt hypertension.

to raise the arterial pressure to its new sustained level. The quantitative value of this sustained pressure level is determined by the degree of constriction of the renal artery. That is, the aortic pressure must rise high enough so that renal arterial pressure distal to the constrictor is enough to cause normal urine output.

A similar scenario occurs in patients with stenosis of the renal artery of a single remaining kidney, as sometimes occurs after a person receives a kidney transplant. Also, functional or pathological increases in resistance of the renal arterioles, due to atherosclerosis or excessive levels of vasoconstrictors, can cause hypertension through the same mechanisms as constriction of the main renal artery.

"Two-Kidney" Goldblatt Hypertension. Hypertension also can result when the artery to only one kidney is constricted while the artery to the other kidney

is normal. This hypertension results from the following mechanism: The constricted kidney secretes renin and also retains salt and water because of decreased renal arterial pressure in this kidney. Then the "normal" opposite kidney retains salt and water because of the renin produced by the ischemic kidney. This renin causes formation of angiotension II and aldosterone, both of which circulate to the opposite kidney and cause it also to retain salt and water. Thus, both kidneys, but for different reasons, become salt and water retainers. Consequently, hypertension develops.

The clinical counterpart of "two-kidney Goldblatt" hypertension occurs when there is stenosis of a single renal artery, for example caused by atherosclerosis, in a person who has two kidneys.

Hypertension Caused by Diseased Kidneys That Secrete Renin Chronically. Often, patchy areas of one or both kidneys are diseased and become ischemic because of local vascular constrictions, whereas other areas of the kidneys are normal. When this occurs, almost identical effects occur as in the two-kidney type of Goldblatt hypertension. That is, the patchy ischemic kidney tissue secretes renin, and this in turn, acting through the formation of angiotensin II, causes the remaining kidney mass also to retain salt and water. Indeed, one of the most common causes of renal hypertension, especially in older persons, is such patchy ischemic kidney disease.

Other Types of Hypertension Caused by Combinations of Volume Loading and Vasoconstriction

Hypertension in the Upper Part of the Body Caused by Coarctation of the Aorta. One out of every few thousand babies is born with pathological constriction or blockage of the aorta at a point beyond the aortic arterial branches to the head and arms but proximal to the renal arteries, a condition called coarctation of the aorta. When this occurs, blood flow to the lower body is carried by multiple, small collateral arteries in the body wall, with much vascular resistance between the upper aorta and the lower aorta. As a consequence, the arterial pressure in the upper part of the body may be 40 to 50 percent higher than that in the lower body.

The mechanism of this upper-body hypertension is almost identical to that of one-kidney Goldblatt hypertension. That is, when a constrictor is placed on the aorta above the renal arteries, the blood pressure in both kidneys at first falls, renin is secreted, angiotensin and aldosterone are formed, and hypertension occurs in the upper body. The arterial pressure in the lower body at the level of the kidneys rises approximately to normal, but high pressure persists in the upper body. The kidneys are no longer ischemic, so secretion of renin and formation of angiotensin and aldosterone return to normal. Likewise, in coarctation of the aorta, the arterial pressure in the lower body is usually almost normal, whereas the pressure in the upper body is far higher than normal.

Role of Autoregulation in the Hypertension Caused by Aortic Coarctation. A significant feature of hypertension caused by aortic coarctation is that blood flow in the arms, where the pressure may be 40 to 60 percent above normal, is almost exactly normal. Also, blood flow in the legs, where the pressure is not elevated, is almost exactly normal. How could this be, with the pressure in the upper body 40 to 60 percent greater than in the lower body? The answer is not that there are differences in vasoconstrictor substances in the blood of the upper and lower body, because the same blood flows to both areas. Likewise, the nervous system innervates both areas of the circulation similarly, so there is no reason to believe that there is a difference in nervous control of the blood vessels. The only reasonable answer is that *long-term autoregulation develops so nearly completely* that the local blood flow control mechanisms have compensated almost 100 percent for the differences in pressure. The result is that, in both the high-pressure area and the low-pressure area, the local blood flow is controlled almost exactly in accord with the needs of the tissue and not in accord with the level of the pressure. One of the reasons these observations are so important is that they demonstrate how nearly complete the long-term autoregulation process can be.

Hypertension in Preeclampsia (Toxemia of Pregnancy). Approximately 5 to 10 percent of expectant mothers develop a syndrome called *preeclampsia* (also called *toxemia of pregnancy*). One of the manifestations of preeclampsia is hypertension that usually subsides after delivery of the baby. Although the precise causes of preeclampsia are not completely understood, ischemia of the placenta and subsequent release by the placenta of toxic factors are believed to play a role in causing many of the manifestations of this disorder, including hypertension in the mother. Substances released by the ischemic placenta, in turn, cause dysfunction of vascular endothelial cells throughout the body, including the blood vessels of the kidneys. This *endothelial dysfunction decreases release of nitric oxide* and other vasodilator substances, causing vasoconstriction, decreased rate of fluid filtration from the glomeruli into the renal tubules, impaired renal-pressure natriuresis, and development of hypertension.

Another pathological abnormality that may contribute to hypertension in preeclampsia is thickening of the kidney glomerular membranes (perhaps caused by an autoimmune process), which also reduces the rate of glomerular fluid filtration. For obvious reasons, the arterial pressure level required to cause normal formation of urine becomes elevated, and the long-term level of arterial pressure becomes correspondingly elevated. These patients are especially prone to extra degrees of hypertension when they have excess salt intake.

Neurogenic Hypertension. *Acute neurogenic hypertension* can be caused by strong *stimulation of the sympathetic nervous system.* For instance, when a person becomes excited for any reason or at times during states of anxiety, the sympathetic system becomes excessively stimulated, peripheral vasoconstriction occurs everywhere in the body, and *acute* hypertension ensues.

Acute Neurogenic Hypertension Caused by Sectioning the Baroreceptor Nerves. Another type of *acute* neurogenic hypertension occurs when the nerves leading from the baroreceptors are cut or when the tractus solitarius

hypertension is caused mainly by increased renal tubular reabsorption of salt and water due to increased sympathetic nerve activity and increased levels of angiotensin II and aldosterone. However, if hypertension is not effectively treated, there may also be vascular damage in the kidneys that can reduce the glomerular filtration rate and increase the severity of the hypertension. Eventually uncontrolled hypertension associated with obesity can lead to severe vascular injury and complete loss of kidney function.

Graphical Analysis of Arterial Pressure Control in Essential Hypertension. Figure 19-15 is a graphical analysis of essential hypertension. The curves of this figure are called *sodium-loading renal function curves* because the arterial pressure in each instance is increased very slowly, over many days or weeks, by gradually increasing the level of sodium intake. The sodium-loading type of curve can be determined by increasing the level of sodium intake to a new level every few days, then waiting for the renal output of sodium to come into balance with the intake, and at the same time recording the changes in arterial pressure.

When this procedure is used in essential hypertensive patients, two types of curves, shown to the right in Figure 19-15, can be recorded in essential hypertensive patients, one called (1) *salt-insensitive* hypertension and the other (2) *salt-sensitive* hypertension. Note in both instances that the curves are shifted to the right, to a higher pressure level than for normal people. Now, let us plot on this same graph (1) a normal level of salt intake and (2) a high level of salt intake representing 3.5 times the normal intake. In the case of the person with salt-insensitive essential hypertension, the arterial pressure does not increase significantly when changing from normal salt intake to high salt intake. Conversely, in those patients who have salt-sensitive essential hypertension, the high salt intake significantly exacerbates the hypertension.

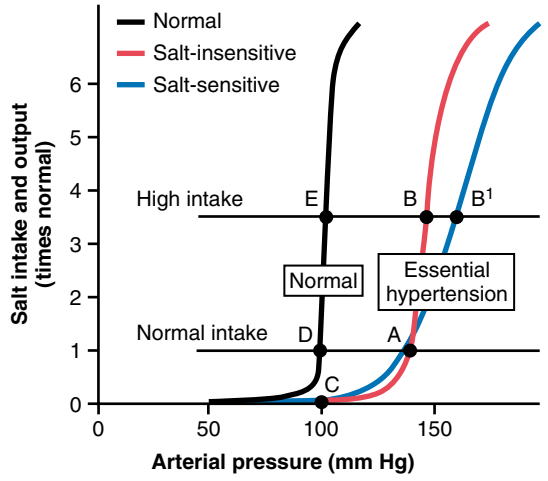


Figure 19-15 Analysis of arterial pressure regulation in (1) non-salt-sensitive essential hypertension and (2) salt-sensitive essential hypertension. (Redrawn from Guyton AC, Coleman TG, Young DB, et al: Salt balance and long-term blood pressure control. Annu Rev Med 31:15, 1980. With permission, from the *Annual Review of Medicine,* © 1980, by Annual Reviews http://www.AnnualReviews.org.)

Two additional points should be emphasized: (1) Salt sensitivity of blood pressure is not an all-or-none characteristic—it is a quantitative characteristic, with some individuals being more salt sensitive than others. (2) Salt sensitivity of blood pressure is not a fixed characteristic; instead, blood pressure usually becomes more salt sensitive as a person ages, especially after 50 or 60 years of age.

The reason for the difference between salt-insensitive essential hypertension and salt-sensitive hypertension is presumably related to structural or functional differences in the kidneys of these two types of hypertensive patients. For example, salt-sensitive hypertension may occur with different types of chronic renal disease due to gradual loss of the functional units of the kidneys (the *nephrons*) or to normal aging as discussed in Chapter 31. Abnormal function of the renin-angiotensin system can also cause blood pressure to become salt sensitive, as discussed previously in this chapter.

Treatment of Essential Hypertension. Current guidelines for treating hypertension recommend, as a first step, lifestyle modifications that are aimed at increasing physical activity and weight loss in most patients. Unfortunately, many patients are unable to lose weight, and pharmacological treatment with antihypertensive drugs must be initiated.

Two general classes of drugs are used to treat hypertension: (1) *vasodilator drugs* that increase renal blood flow and (2) *natriuretic or diuretic drugs* that decrease tubular reabsorption of salt and water.

Vasodilator drugs usually cause vasodilation in many other tissues of the body, as well as in the kidneys. Different ones act in one of the following ways: (1) by inhibiting sympathetic nervous signals to the kidneys or by blocking the action of the sympathetic transmitter substance on the renal vasculature and renal tubules, (2) by directly relaxing the smooth muscle of the renal vasculature, or (3) by blocking the action of the renin-angiotensin system on the renal vasculature or renal tubules.

Those drugs that reduce reabsorption of salt and water by the renal tubules include especially drugs that block active transport of sodium through the tubular wall; this blockage in turn also prevents the reabsorption of water, as explained earlier in the chapter. These natriuretic or diuretic drugs are discussed in greater detail in Chapter 31.

Summary of the Integrated, Multifaceted System for Arterial Pressure Regulation

By now, it is clear that arterial pressure is regulated not by a single pressure controlling system but instead by several interrelated systems, each of which performs a specific function. For instance, when a person bleeds severely

is destroyed in each side of the medulla oblongata (these are the areas where the nerves from the carotid and aortic baroreceptors connect in the brain stem). The sudden cessation of normal nerve signals from the baroreceptors has the same effect on the nervous pressure control mechanisms as a sudden reduction of the arterial pressure in the aorta and carotid arteries. That is, loss of the normal inhibitory effect on the vasomotor center caused by normal baroreceptor nervous signals allows the vasomotor center suddenly to become extremely active and the mean arterial pressure to increase from 100 mm Hg to as high as 160 mm Hg. The pressure returns to nearly normal within about 2 days because the response of the vasomotor center to the absent baroreceptor signal fades away, which is called central "resetting" of the baroreceptor pressure control mechanism. Therefore, the neurogenic hypertension caused by sectioning the baroreceptor nerves is mainly an acute type of hypertension, not a chronic type.

Genetic Causes of Hypertension. Spontaneous hereditary hypertension has been observed in several strains of animals, including different strains of rats, rabbits, and at least one strain of dogs. In the strain of rats that has been studied to the greatest extent, the Okamoto spontaneously hypertensive rat strain, there is evidence that in early development of the hypertension, the sympathetic nervous system is considerably more active than in normal rats. In the later stages of this type of hypertension, structural changes have been observed in the nephrons of the kidneys: (1) increased preglomerular renal arterial resistance and (2) decreased permeability of the glomerular membranes. These structural changes could also contribute to the long-term continuance of the hypertension. In other strains of hypertensive rats, impaired renal function also has been observed.

In humans, several different gene mutations have been identified that can cause hypertension. These forms of hypertension are called *monogenic hypertension* because they are caused by mutation of a single gene. An interesting feature of these genetic disorders is that they all cause excessive salt and water reabsorption by the renal tubules. In some cases the increased reabsorption is due to gene mutations that directly increase transport of sodium or chloride in the renal tubular epithelial cells. In other instances, the gene mutations cause increased synthesis or activity of hormones that stimulate renal tubular salt and water reabsorption. Thus, in all monogenic hypertensive disorders discovered thus far, the final common pathway to hypertension appears to be increased salt reabsorption and expansion of extracellular fluid volume. Monogenic hypertension, however, is rare and all of the known forms together account for less than 1% of human hypertension.

"Primary (Essential) Hypertension"

About 90 to 95 percent of all people who have hypertension are said to have "primary hypertension," also widely known as "essential hypertension" by many clinicians. These terms mean simply that *the hypertension is of unknown origin,* in contrast to those forms of hypertension that are *secondary* to known causes, such as renal artery stenosis or monogenic forms of hypertension.

In most patients, *excess weight gain* and *sedentary lifestyle* appear to play a major role in causing hypertension. The majority of patients with hypertension are overweight, and studies of different populations suggest that excess weight gain and obesity may account for as much as 65 to 75 percent of the risk for developing primary hypertension. Clinical studies have clearly shown the value of weight loss for reducing blood pressure in most patients with hypertension. In fact, clinical guidelines for treating hypertension recommend increased physical activity and weight loss as a first step in treating most patients with hypertension.

Some of the characteristics of primary hypertension caused by excess weight gain and obesity include:

1. *Cardiac output is increased* due, in part, to the additional blood flow required for the extra adipose tissue. However, blood flow in the heart, kidneys, gastrointestinal tract, and skeletal muscle also increases with weight gain due to increased metabolic rate and growth of the organs and tissues in response to their increased metabolic demands. As the hypertension is sustained for many months and years, total peripheral vascular resistance may be increased.
2. *Sympathetic nerve activity, especially in the kidneys, is increased in overweight patients.* The causes of increased sympathetic activity in obesity are not fully understood, but recent studies suggest that hormones, such as *leptin,* released from fat cells may directly stimulate multiple regions of the hypothalamus, which, in turn, have an excitatory influence on the vasomotor centers of the brain medulla.
3. *Angiotensin II and aldosterone levels are increased twofold to threefold in many obese patients.* This may be caused partly by increased sympathetic nerve stimulation, which increases renin release by the kidneys and therefore formation of angiotensin II, which, in turn, stimulates the adrenal gland to secrete aldosterone.
4. *The renal-pressure natriuresis mechanism is impaired, and the kidneys will not excrete adequate amounts of salt and water unless the arterial pressure is high or unless kidney function is somehow improved.* In other words, if the mean arterial pressure in the essential hypertensive person is 150 mm Hg, acute reduction of the mean arterial pressure artificially to the normal value of 100 mm Hg (but without otherwise altering renal function except for the decreased pressure) will cause almost total anuria, and the person will retain salt and water until the pressure rises back to the elevated value of 150 mm Hg. Chronic reductions in arterial pressure with effective antihypertensive therapies, however, usually do not cause marked salt and water retention by the kidneys because these therapies also improve renal-pressure natriuresis, as discussed later.

Experimental studies in obese animals and obese patients suggest that impaired renal-pressure natriuresis in obesity

so that the pressure falls suddenly, two problems confront the pressure control system. The first is survival, that is, to return the arterial pressure immediately to a high enough level that the person can live through the acute episode. The second is to return the blood volume and arterial eventually to their normal levels so that the circulatory system can reestablish full normality, not merely back to the levels required for survival.

In Chapter 18, we saw that the first line of defense against acute changes in arterial pressure is the nervous control system. In this chapter, we have emphasized a second line of defense achieved mainly by kidney mechanisms for long-term control of arterial pressure. However, there are other pieces to the puzzle. Figure 19-16 helps to put these together.

Figure 19-16 shows the approximate immediate (seconds and minutes) and long-term (hours and days) control responses, expressed as feedback gain, of eight arterial pressure control mechanisms. These mechanisms can be divided into three groups: (1) those that react rapidly, within seconds or minutes; (2) those that respond over an intermediate time period, minutes or hours; and (3) those that provide long-term arterial pressure regulation, days, months, and years. Let us see how they fit together as a total, integrated system for pressure control.

Rapidly Acting Pressure Control Mechanisms, Acting Within Seconds or Minutes. The rapidly acting pressure control mechanisms are almost entirely acute nervous reflexes or other nervous responses. Note in Figure 19-16 the three mechanisms that show responses within seconds. They are (1) the baroreceptor feedback mechanism, (2) the central nervous system ischemic mechanism, and (3) the chemoreceptor mechanism. Not only do these mechanisms begin to react within seconds, but they are also powerful. After any acute fall in pressure, as might be caused by severe hemorrhage, the nervous mechanisms combine (1) to cause constriction of the veins and transfer of blood into the heart, (2) to cause increased heart rate and contractility of the heart to provide greater pumping capacity by the heart, and (3) to cause constriction of most peripheral arterioles to impede flow of blood out of the arteries; all these effects occur almost instantly to raise the arterial pressure back into a survival range.

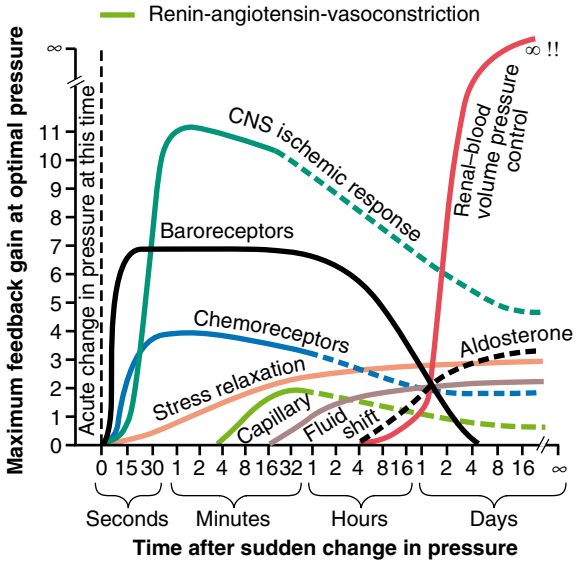


Figure 19-16 Approximate potency of various arterial pressure control mechanisms at different time intervals after onset of a disturbance to the arterial pressure. Note especially the infinite gain (∞) of the renal body fluid pressure control mechanism that occurs after a few weeks' time. (Redrawn from Guyton AC: Arterial Pressure and Hypertension. Philadelphia: WB Saunders, 1980.)

When the pressure suddenly rises too high, as might occur in response to rapid transfusion of excess blood, the same control mechanisms operate in the reverse direction, again returning the pressure back toward normal.

Pressure Control Mechanisms That Act After Many Minutes. Several pressure control mechanisms exhibit significant responses only after a few minutes following acute arterial pressure change. Three of these, shown in Figure 19-16, are (1) the renin-angiotensin vasoconstrictor mechanism, (2) stress-relaxation of the vasculature, and (3) shift of fluid through the tissue capillary walls in and out of the circulation to readjust the blood volume as needed.

We have already described at length the role of the renin-angiotensin vasoconstrictor system to provide a semiacute means for increasing the arterial pressure when this is necessary. The *stress-relaxation mechanism* is demonstrated by the following example: When the pressure in the blood vessels becomes too high, they become stretched and keep on stretching more and more for minutes or hours; as a result, the pressure in the vessels falls toward normal. This continuing stretch of the vessels, called *stress-relaxation,* can serve as an intermediate-term pressure "buffer."

The *capillary fluid shift mechanism* means simply that any time capillary pressure falls too low, fluid is absorbed from the tissues through the capillary membranes and into the circulation, thus building up the blood volume and increasing the pressure in the circulation. Conversely, when the capillary pressure rises too high, fluid is lost out of the circulation into the tissues, thus reducing the blood volume, as well as virtually all the pressures throughout the circulation.

These three intermediate mechanisms become mostly activated within 30 minutes to several hours. During this time, the nervous mechanisms usually become less and less effective, which explains the importance of these nonnervous, intermediate time pressure control measures.

Long-Term Mechanisms for Arterial Pressure Regulation. The goal of this chapter has been to explain the role of the kidneys in long-term control of arterial pressure. To the far right in Figure 19-16 is shown the renal–blood volume pressure control mechanism (which is the same as the renal–body fluid pressure control

mechanism), demonstrating that it takes a few hours to begin showing significant response. Yet it eventually develops a feedback gain for control of arterial pressure nearly equal to infinity. This means that this mechanism can eventually return the arterial pressure nearly *all the way* back, not merely partway back, to that pressure level that provides normal output of salt and water by the kidneys. By now, the reader should be familiar with this concept, which has been the major point of this chapter.

Many factors can affect the pressure-regulating level of the renal–body fluid mechanism. One of these, shown in Figure 19-16, is aldosterone. A decrease in arterial pressure leads within minutes to an increase in aldosterone secretion, and over the next hour or days, this plays an important role in modifying the pressure control characteristics of the renal–body fluid mechanism.

Especially important is interaction of the renin-angiotensin system with the aldosterone and renal fluid mechanisms. For instance, a person's salt intake varies tremendously from one day to another. We have seen in this chapter that the salt intake can decrease to as little as one-tenth normal or can increase to 10 to 15 times normal and yet the regulated level of the mean arterial pressure will change only a few mm Hg if the renin-angiotensin-aldosterone system is fully operative. But, without a functional renin-angiotensin-aldosterone system, blood pressure becomes very sensitive to changes in salt intake.

Thus, arterial pressure control begins with the life-saving measures of the nervous pressure controls, then continues with the sustaining characteristics of the intermediate pressure controls, and, finally, is stabilized at the long-term pressure level by the renal–body fluid mechanism. This long-term mechanism in turn has multiple interactions with the renin-angiotensin-aldosterone system, the nervous system, and several other factors that provide special blood pressure control capabilities for special purposes.

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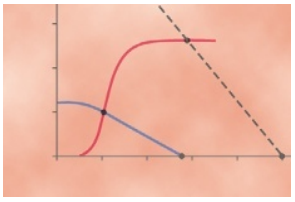
Cardiac Output, Venous Return, and Their Regulation



Cardiac output is the quantity of blood pumped into the aorta each minute by the heart. This is also the quantity of blood that flows through the circulation. Cardiac output is one of the most important factors that we have to consider in relation to the circulation because it is the sum of the blood flows to all of the tissues of the body.

Venous return is the quantity of blood flowing from the veins into the right atrium each minute. The venous return and the cardiac output must equal each other except for a few heartbeats at a time when blood is temporarily stored in or removed from the heart and lungs.

Normal Values for Cardiac Output at Rest and During Activity

Cardiac output varies widely with the level of activity of the body. The following factors, among others, directly affect cardiac output: (1) the basic level of body metabolism, (2) whether the person is exercising, (3) the person's age, and (4) size of the body.

For *young, healthy men,* resting cardiac output averages about 5.6 L/min. For *women,* this value is about 4.9 L/min. When one considers the factor of age as well—because with increasing age, body activity and mass of some tissues (e.g., skeletal muscle) diminish—the average cardiac output for the resting adult, in round numbers, is often stated to be about 5 L/min.

Cardiac Index

Experiments have shown that the cardiac output increases approximately in proportion to the surface area of the body. Therefore, cardiac output is frequently stated in terms of the *cardiac index,* which is the *cardiac output per square meter of body surface area.* The normal human being weighing 70 kilograms has a body surface area of about 1.7 square meters, which means that the normal average cardiac index for adults is about 3 L/min/m^2 of body surface area.

Effect of Age on Cardiac Output. Figure 20-1 shows the cardiac output, expressed as cardiac index, at different ages. Rising rapidly to a level greater than 4 L/min/m^2 at age 10 years, the cardiac index declines to about 2.4 L/min/m^2 at age 80 years. We explain later in the chapter that the cardiac output is regulated throughout life almost directly in proportion to the overall bodily metabolic activity. Therefore, the declining cardiac index is indicative of declining activity or declining muscle mass with age.

Control of Cardiac Output by Venous Return—Role of the Frank-Starling Mechanism of the Heart

When one states that cardiac output is controlled by venous return, this means that it is not the heart itself that is normally the primary controller of cardiac output. Instead, it is the various factors of the peripheral circulation that affect flow of blood into the heart from the veins, called *venous return,* that are the primary controllers.

The main reason peripheral factors are usually more important than the heart itself in controlling cardiac output is that the heart has a built-in mechanism that normally allows it to pump automatically whatever amount of blood that flows into the right atrium from the veins. This mechanism, called the *Frank-Starling law of the heart,* was discussed in Chapter 9. Basically, this law states that when increased quantities of blood flow into the heart, the increased blood stretches the walls of the heart chambers. As a result of the stretch, the cardiac muscle contracts with increased force, and this empties the extra blood that has entered from the systemic circulation. Therefore, the blood that flows into the heart is automatically pumped without delay into the aorta and flows again through the circulation.

Another important factor, discussed in Chapter 10, is that stretching the heart causes the heart to pump faster—at an increased heart rate. That is, stretch of the *sinus node* in the wall of the right atrium has a direct effect on the rhythmicity of the node itself to increase heart rate as much as 10 to 15 percent. In addition, the

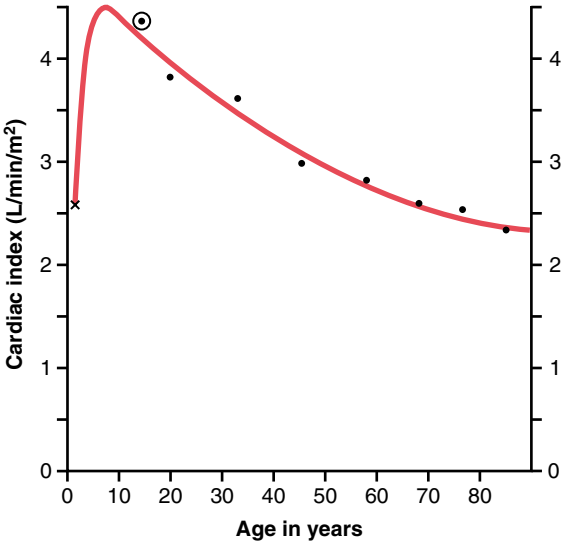


Figure 20-1 *Cardiac index* for the human being (cardiac output per square meter of surface area) at different ages. (Redrawn from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)

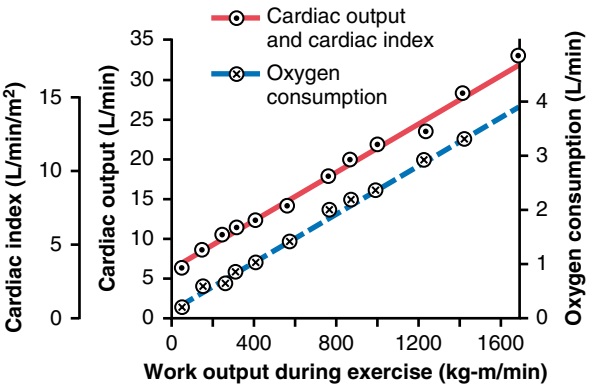


Figure 20-2 Effect of increasing levels of exercise to increase cardiac output (*red solid line*) and oxygen consumption (*blue dashed line*). (Redrawn from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)

stretched right atrium initiates a nervous reflex called the *Bainbridge reflex,* passing first to the vasomotor center of the brain and then back to the heart by way of the sympathetic nerves and vagi, also to increase the heart rate.

Under most normal unstressful conditions, the cardiac output is controlled almost entirely by peripheral factors that determine venous return. However, we discuss later in the chapter that if the returning blood does become more than the heart can pump, then the heart becomes the limiting factor that determines cardiac output.

Cardiac Output Regulation Is the Sum of Blood Flow Regulation in All the Local Tissues of the Body—Tissue Metabolism Regulates Most Local Blood Flow

The venous return to the heart is the sum of all the local blood flows through all the individual tissue segments of the peripheral circulation. Therefore, it follows that cardiac output regulation is the sum of all the local blood flow regulations.

The mechanisms of local blood flow regulation were discussed in Chapter 17. In most tissues, blood flow increases mainly in proportion to each tissue's metabolism. For instance, local blood flow almost always increases when tissue oxygen consumption increases; this effect is demonstrated in Figure 20-2 for different levels of exercise. Note that at each increasing level of work output during exercise, the oxygen consumption and the cardiac output increase in parallel to each other.

To summarize, cardiac output is determined by the sum of all the various factors throughout the body that control local blood flow. All the local blood flows summate to form the venous return, and the heart automatically pumps this returning blood back into the arteries to flow around the system again.

Effect of Total Peripheral Resistance on the Long-Term Cardiac Output Level. Figure 20-3 is the same as Figure 19-6. It is repeated here to illustrate an extremely important principle in cardiac output control: Under many conditions, the long-term cardiac output level varies reciprocally with changes in total peripheral resistance, as long as the arterial pressure is unchanged. Note in Figure 20-3 that when the total peripheral resistance is exactly normal (at the 100 percent mark in the figure), the cardiac output is also normal. Then, when

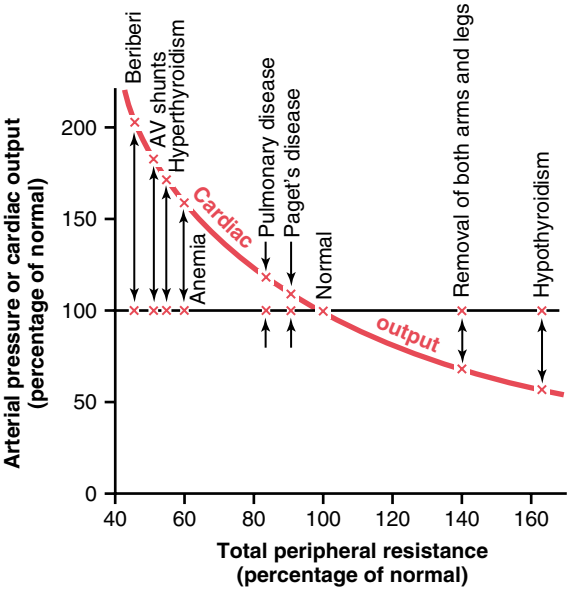


Figure 20-3 Chronic effect of different levels of total peripheral resistance on cardiac output, showing a reciprocal relationship between total peripheral resistance and cardiac output. (Redrawn from Guyton AC: Arterial Pressure and Hypertension. Philadelphia: WB Saunders, 1980.)

the total peripheral resistance increases above normal, the cardiac output falls; conversely, when the total peripheral resistance decreases, the cardiac output increases. One can easily understand this by reconsidering one of the forms of Ohm's law, as expressed in Chapter 14:

$$\text{Cardiac Output} = \frac{\text{Arterial Pressure}}{\text{Total Peripheral Resistance}}$$

The meaning of this formula, and of Figure 20-3, is simply the following: Any time the long-term level of total peripheral resistance changes (but no other functions of the circulation change), the cardiac output changes quantitatively in exactly the opposite direction.

The Heart Has Limits for the Cardiac Output That It Can Achieve

There are definite limits to the amount of blood that the heart can pump, which can be expressed quantitatively in the form of *cardiac output curves.*

Figure 20-4 demonstrates the *normal cardiac output curve,* showing the cardiac output per minute at each level of right atrial pressure. This is one type of *cardiac function curve,* which was discussed in Chapter 9. Note that the plateau level of this normal cardiac output curve is about 13 L/min, 2.5 times the normal cardiac output of about 5 L/min. This means that the normal human heart, functioning without any special stimulation, can pump an amount of venous return up to about 2.5 times the normal venous return before the heart becomes a limiting factor in the control of cardiac output.

Shown in Figure 20-4 are several other cardiac output curves for hearts that are not pumping normally. The uppermost curves are for *hypereffective hearts* that are pumping better than normal. The lowermost curves are for *hypoeffective hearts* that are pumping at levels below normal.

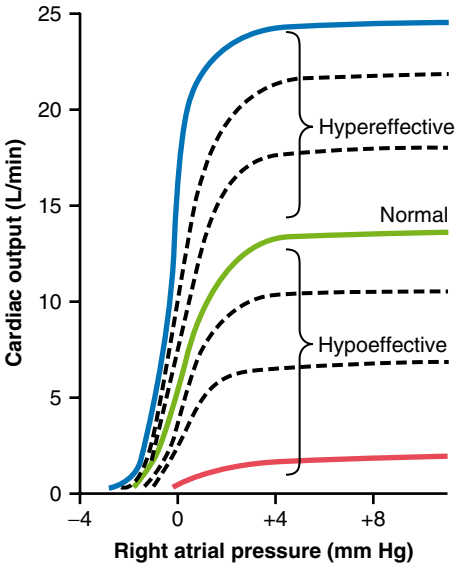


Figure 20-4 Cardiac output curves for the normal heart and for hypoeffective and hypereffective hearts. (Redrawn from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)

Factors That Cause a Hypereffective Heart

Two types of factors can make the heart a better pump than normal: (1) nervous stimulation and (2) hypertrophy of the heart muscle.

Effect of Nervous Excitation to Increase Heart Pumping. In Chapter 9, we saw that a combination of (1) sympathetic *stimulation* and (2) parasympathetic *inhibition* does two things to increase the pumping effectiveness of the heart: (1) It greatly increases the heart rate—sometimes, in young people, from the normal level of 72 beats/min up to 180 to 200 beats/min—and (2) it increases the strength of heart contraction (which is called increased "contractility") to twice its normal strength. Combining these two effects, maximal nervous excitation of the heart can raise the plateau level of the cardiac output curve to almost twice the plateau of the normal curve, as shown by the 25-L/min level of the uppermost curve in Figure 20-4.

Increased Pumping Effectiveness Caused by Heart Hypertrophy. A long-term increased workload, but not so much excess load that it damages the heart, causes the heart muscle to increase in mass and contractile strength in the same way that heavy exercise causes skeletal muscles to hypertrophy. For instance, it is common for the hearts of marathon runners to be increased in mass by 50 to 75 percent. This increases the plateau level of the cardiac output curve, sometimes 60 to 100 percent, and therefore allows the heart to pump much greater than usual amounts of cardiac output.

When one combines nervous excitation of the heart and hypertrophy, as occurs in marathon runners, the total effect can allow the heart to pump as much 30 to 40 L/min, about 2½ times the level that can be achieved in the average person; this increased level of pumping is one of the most important factors in determining the runner's running time.

Factors That Cause a Hypoeffective Heart

Any factor that decreases the heart's ability to pump blood causes hypoeffectivity. Some of the factors that can do this are the following:

- Increased arterial pressure against which the heart must pump, such as in hypertension
- Inhibition of nervous excitation of the heart
- Pathological factors that cause abnormal heart rhythm or rate of heartbeat
- Coronary artery blockage, causing a "heart attack"
- Valvular heart disease
- Congenital heart disease
- Myocarditis, an inflammation of the heart muscle
- Cardiac hypoxia

Role of the Nervous System in Controlling Cardiac Output

Importance of the Nervous System in Maintaining Arterial Pressure When Peripheral Blood Vessels Are Dilated and Venous Return and Cardiac Output Increase

Figure 20-5 shows an important difference in cardiac output control with and without a functioning autonomic nervous system. The solid curves demonstrate the effect in the normal dog of intense dilation of the peripheral blood vessels caused by administering the drug dinitrophenol, which increased the metabolism of virtually all tissues of the body about fourfold. Note that with nervous control to keep the arterial pressure from falling, dilating all the peripheral blood vessels caused almost no change in arterial pressure but increased the cardiac output almost fourfold. However, after autonomic control of the nervous system had been blocked, none of the normal circulatory reflexes for maintaining the arterial pressure could function. Vasodilation of the vessels with dinitrophenol (dashed curves) then caused a profound fall in arterial pressure to about one-half normal, and the cardiac output rose only 1.6-fold instead of 4-fold.

Thus, maintenance of a normal arterial pressure by the nervous reflexes, by mechanisms explained in Chapter 18, is essential to achieve high cardiac outputs when the peripheral tissues dilate their vessels to increase the venous return.

Effect of the Nervous System to *Increase* the Arterial Pressure During Exercise. During exercise, intense increase in metabolism in active skeletal muscles acts directly on the muscle arterioles to relax them and to allow adequate oxygen and other nutrients needed to sustain muscle contraction. Obviously, this greatly decreases the total peripheral resistance, which normally would decrease the arterial pressure as well. However, the nervous system immediately compensates. The same brain activity that sends motor signals to the muscles sends simultaneous signals into the autonomic nervous centers of the brain to excite circulatory activity, causing large vein constriction, increased heart rate, and increased contractility of the heart. All these changes acting together increase the arterial pressure above normal, which in turn forces still more blood flow through the active muscles.

In summary, when local tissue blood vessels dilate and thereby increase venous return and cardiac output above normal, the nervous system plays an exceedingly important role in preventing the arterial pressure from falling to disastrously low levels. In fact, during exercise, the nervous system goes even further, providing additional signals to raise the arterial pressure even above normal, which serves to increase the cardiac output an extra 30 to 100 percent.

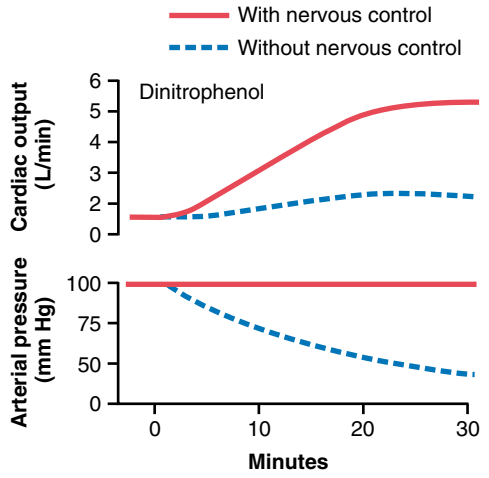


Figure 20-5 Experiment in a dog to demonstrate the importance of nervous maintenance of the arterial pressure as a prerequisite for cardiac output control. Note that with pressure control, the metabolic stimulant ***dinitrophenol*** increases cardiac output greatly; without pressure control, the arterial pressure falls and the cardiac output rises very little. (Drawn from experiments by Dr. M. Banet.)

Pathologically High or Low Cardiac Outputs

In healthy humans, the average cardiac outputs are surprisingly constant from one person to another. However, multiple clinical abnormalities can cause either high or low cardiac outputs. Some of the more important of these are shown in Figure 20-6.

High Cardiac Output Caused by Reduced Total Peripheral Resistance

The left side of Figure 20-6 identifies conditions that commonly cause cardiac outputs higher than normal. One of the distinguishing features of these conditions is that *they all result from chronically reduced total peripheral resistance.* None of them result from excessive excitation of the heart itself, which we will explain subsequently. For the present, let us look at some of the conditions that can decrease the peripheral resistance and at the same time increase the cardiac output to above normal.

1. *Beriberi.* This disease is caused by insufficient quantity of the vitamin *thiamine (vitamin B_1)* in the diet. Lack of this vitamin causes diminished ability of the tissues to use some cellular nutrients, and the local tissue blood flow mechanisms in turn cause marked compensatory peripheral vasodilation. Sometimes the total peripheral resistance decreases to as little as one-half normal. Consequently, the long-term levels of venous return and cardiac output also often increase to twice normal.
2. *Arteriovenous fistula (shunt).* Earlier, we pointed out that whenever a fistula (also called an *AV shunt*) occurs between a major artery and a major vein, tremendous amounts of blood flow directly from the artery into the vein. This, too, greatly decreases the total peripheral resistance and, likewise, increases the venous return and cardiac output.

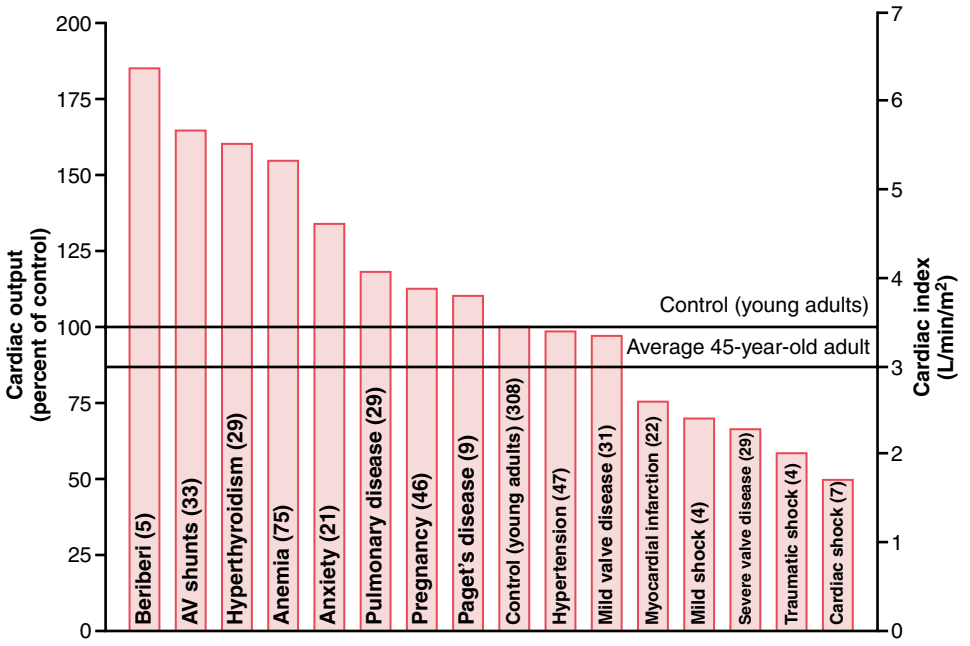


Figure 20-6 Cardiac output in different pathological conditions. The numbers in parentheses indicate number of patients studied in each condition. (Redrawn from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)

3. *Hyperthyroidism.* In hyperthyroidism, the metabolism of most tissues of the body becomes greatly increased. Oxygen usage increases, and vasodilator products are released from the tissues. Therefore, the total peripheral resistance decreases markedly because of the local tissue blood flow control reactions throughout the body; consequently, the venous return and cardiac output often increase to 40 to 80 percent above normal.
4. *Anemia.* In anemia, two peripheral effects greatly decrease the total peripheral resistance. One of these is reduced viscosity of the blood, resulting from the decreased concentration of red blood cells. The other is diminished delivery of oxygen to the tissues, which causes local vasodilation. As a consequence, the cardiac output increases greatly.

Any other factor that decreases the total peripheral resistance chronically also increases the cardiac output if arterial pressure does not decrease too much.

Low Cardiac Output

Figure 20-6 shows at the far right several conditions that cause abnormally low cardiac output. These conditions fall into two categories: (1) those abnormalities that cause the pumping effectiveness of the heart to fall too low and (2) those that cause venous return to fall too low.

Decreased Cardiac Output Caused by Cardiac Factors. Whenever the heart becomes severely damaged, regardless of the cause, its limited level of pumping may fall below that needed for adequate blood flow to the tissues. Some examples of this include (1) *severe coronary blood vessel blockage and consequent myocardial infarction,* (2) *severe valvular heart disease,* (3) *myocarditis,* (4) *cardiac tamponade,* and (5) *cardiac metabolic derangements.* The effects of several of these are shown on the right in Figure 20-6, demonstrating the low cardiac outputs that result.

When the cardiac output falls so low that the tissues throughout the body begin to suffer nutritional deficiency, the condition is called *cardiac shock.* This is discussed fully in Chapter 22 in relation to cardiac failure.

Decrease in Cardiac Output Caused by Noncardiac Peripheral Factors—Decreased Venous Return. Anything that interferes with venous return also can lead to decreased cardiac output. Some of these factors are the following:

1. *Decreased blood volume.* By far, the most common noncardiac peripheral factor that leads to decreased cardiac output is decreased blood volume, resulting most often from hemorrhage. It is clear why this condition decreases the cardiac output: Loss of blood decreases the filling of the vascular system to such a low level that there is not enough blood in the peripheral vessels to create peripheral vascular pressures high enough to push the blood back to the heart.
2. *Acute venous dilation.* On some occasions, the peripheral veins become acutely vasodilated. This results most often when the sympathetic nervous system suddenly becomes inactive. For instance, fainting often results from sudden loss of sympathetic nervous system activity, which causes the peripheral capacitative vessels, especially the veins, to dilate markedly. This decreases the filling pressure of the vascular system because the blood volume can no longer create adequate pressure in the now flaccid peripheral blood vessels. As a result, the blood "pools" in the vessels and does not return to the heart.

3. *Obstruction of the large veins.* On rare occasions, the large veins leading into the heart become obstructed, so the blood in the peripheral vessels cannot flow back into the heart. Consequently, the cardiac output falls markedly.
4. *Decreased tissue mass, especially decreased skeletal muscle mass.* With normal aging or with prolonged periods of physical inactivity, there is usually a reduction in the size of the skeletal muscles. This, in turn, decreases the total oxygen consumption and blood flow needs of the muscles, resulting in decreases in skeletal muscle blood flow and cardiac output.
5. *Decreased metabolic rate of the tissues.* If tissue metabolic rate is reduced, such as occurs in skeletal muscle during prolonged bed rest, the oxygen consumption and nutrition needs of the tissues will also be lower. This decreases blood flow to the tissues, resulting in reduced cardiac output. Other conditions, such as *hypothyroidism,* may also reduce metabolic rate and therefore tissue blood flow and cardiac output.

Regardless of the cause of low cardiac output, whether it be a peripheral factor or a cardiac factor, if ever the cardiac output falls below that level required for adequate nutrition of the tissues, the person is said to suffer *circulatory shock.* This condition can be lethal within a few minutes to a few hours. Circulatory shock is such an important clinical problem that it is discussed in detail in Chapter 24.

A More Quantitative Analysis of Cardiac Output Regulation

Our discussion of cardiac output regulation thus far is adequate for understanding the factors that control cardiac output in most simple conditions. However, to understand cardiac output regulation in especially stressful situations, such as the extremes of exercise, cardiac failure, and circulatory shock, a more complex quantitative analysis is presented in the following sections.

To perform the more quantitative analysis, it is necessary to distinguish separately the two primary factors concerned with cardiac output regulation: (1) the pumping ability of the heart, as represented by *cardiac output curves,* and (2) the peripheral factors that affect flow of blood from the veins into the heart, as represented by *venous return curves.* Then one can put these curves together in a quantitative way to show how they interact with each other to determine cardiac output, venous return, and right atrial pressure at the same time.

Cardiac Output Curves Used in the Quantitative Analysis

Some of the cardiac output curves used to depict quantitative heart pumping effectiveness have already been shown in Figure 20-4. However, an additional set of curves is required to show the effect on cardiac output caused by changing external pressures on the outside of the heart, as explained in the next section.

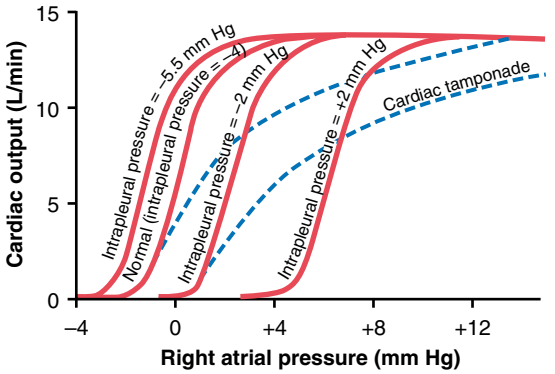


Figure 20-7 Cardiac output curves at different levels of intrapleural pressure and at different degrees of cardiac tamponade. (Redrawn from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)

Effect of External Pressure Outside the Heart on Cardiac Output Curves. Figure 20-7 shows the effect of changes in external cardiac pressure on the cardiac output curve. The normal external pressure is equal to the normal intrapleural pressure (the pressure in the chest cavity), which is –4 mm Hg. Note in the figure that a rise in intrapleural pressure, to –2 mm Hg, shifts the entire cardiac output curve to the right by the same amount. This shift occurs because to fill the cardiac chambers with blood requires an extra 2 mm Hg right atrial pressure to overcome the increased pressure on the outside of the heart. Likewise, an increase in intrapleural pressure to +2 mm Hg requires a 6 mm Hg increase in right atrial pressure from the normal –4 mm Hg, which shifts the entire cardiac output curve 6 mm Hg to the right.

Some of the factors that can alter the external pressure on the heart and thereby shift the cardiac output curve are the following:

1. *Cyclical changes of intrapleural pressure during respiration,* which are about ±2 mm Hg during normal breathing but can be as much as ±50 mm Hg during strenuous breathing.
2. *Breathing against a negative pressure,* which shifts the curve to a more negative right atrial pressure (to the left).
3. *Positive pressure breathing,* which shifts the curve to the right.
4. *Opening the thoracic cage,* which increases the intrapleural pressure to 0 mm Hg and shifts the cardiac output curve to the right 4 mm Hg.
5. *Cardiac tamponade,* which means accumulation of a large quantity of fluid in the pericardial cavity around the heart with resultant increase in external cardiac pressure and shifting of the curve to the right. Note in Figure 20-7 that cardiac tamponade shifts the upper parts of the curves farther to the right than the lower parts because the external "tamponade" pressure rises to higher values as the chambers of the heart fill to increased volumes during high cardiac output.

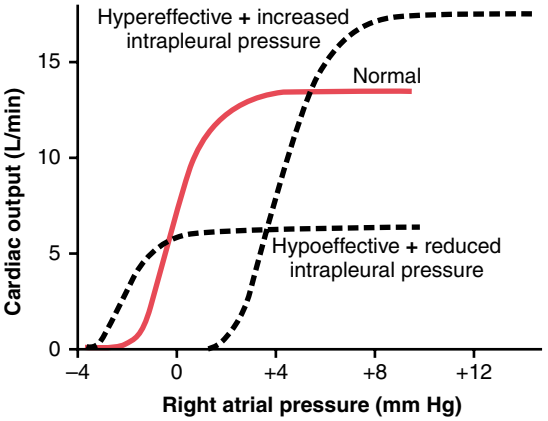


Figure 20-8 Combinations of two major patterns of cardiac output curves showing the effect of alterations in both extracardiac pressure and effectiveness of the heart as a pump. (Redrawn from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)

Combinations of Different Patterns of Cardiac Output Curves. Figure 20-8 shows that the final cardiac output curve can change as a result of simultaneous changes in (a) external cardiac pressure and (b) effectiveness of the heart as a pump. For example, the combination of a hypereffective heart and increased intrapleural pressure would lead to increased maximum level of cardiac output due to the increased pumping capability of the heart but the cardiac output curve would be shifted to the right (to higher atrial pressures) due to the increased intrapleural pressure. Thus, by knowing what is happening to the external pressure, as well as to the capability of the heart as a pump, one can express the momentary ability of the heart to pump blood by a single cardiac output curve.

Venous Return Curves

There remains the entire systemic circulation that must be considered before total analysis of cardiac regulation can be achieved. To analyze the function of the systemic circulation, we first remove the heart and lungs from the circulation of an animal and replace them with a pump and artificial oxygenator system. Then, different factors, such as blood volume, vascular resistances, and central venous pressure in the right atrium, are altered to determine how the systemic circulation operates in different circulatory states. In these studies, one finds three principal factors that affect venous return to the heart from the systemic circulation. They are as follows:

1. *Right atrial pressure,* which exerts a backward force on the veins to impede flow of blood from the veins into the right atrium.
2. Degree of filling of the systemic circulation (measured by the *mean systemic filling pressure*), which forces the systemic blood toward the heart (this is the pressure measured everywhere in the systemic circulation when all flow of blood is stopped and is discussed in detail later).
3. *Resistance to blood flow* between the peripheral vessels and the right atrium.

These factors can all be expressed quantitatively by the *venous return curve,* as we explain in the next sections.

Normal Venous Return Curve

In the same way that the cardiac output curve relates pumping of blood by the heart to right atrial pressure, the *venous return curve relates venous return also to right atrial pressure*—that is, the venous flow of blood into the heart from the systemic circulation at different levels of right atrial pressure.

The curve in Figure 20-9 is the *normal* venous return curve. This curve shows that when heart pumping capability becomes diminished and causes the right atrial pressure to rise, the backward force of the rising atrial pressure on the veins of the systemic circulation decreases venous return of blood to the heart. *If all nervous circulatory reflexes are prevented from acting,* venous return decreases to zero when the right atrial pressure rises to about +7 mm Hg. Such a slight rise in right atrial pressure causes a drastic decrease in venous return because the systemic circulation is a distensible bag, so any increase in back pressure causes blood to dam up in this bag instead of returning to the heart.

At the same time that the right atrial pressure is rising and causing venous stasis, pumping by the heart also approaches zero because of decreasing venous return. Both the arterial and the venous pressures come to equilibrium when all flow in the systemic circulation ceases at a pressure of 7 mm Hg, which, by definition, is the *mean systemic filling pressure (Psf).*

Plateau in the Venous Return Curve at Negative Atrial Pressures Caused by Collapse of the Large Veins. When the right atrial pressure falls *below* zero—that is, below atmospheric pressure—further increase in venous return almost ceases. And by the time the right atrial pressure has fallen to about –2 mm Hg, the venous return will have reached a plateau. It remains at this plateau level even though the right atrial pressure falls to –20 mm Hg, –50 mm Hg, or even further. This plateau is caused by *collapse of the veins* entering the chest. Negative pressure

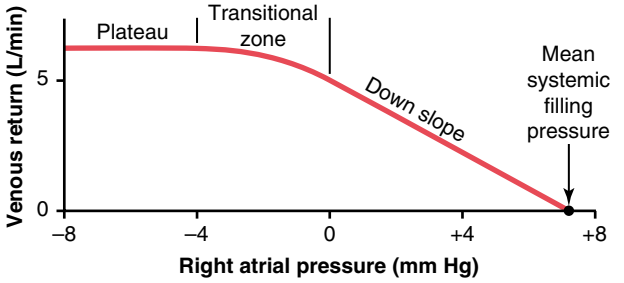


Figure 20-9 Normal *venous return curve*. The plateau is caused by *collapse* of the large veins entering the chest when the right atrial pressure falls below atmospheric pressure. Note also that venous return becomes zero when the right atrial pressure rises to equal the mean systemic filling pressure.

in the right atrium sucks the walls of the veins together where they enter the chest, which prevents any additional flow of blood from the peripheral veins. Consequently, even very negative pressures in the right atrium cannot increase venous return significantly above that which exists at a normal atrial pressure of 0 mm Hg.

Mean Circulatory Filling Pressure and Mean Systemic Filling Pressure, and Their Effect on Venous Return

When heart pumping is stopped by shocking the heart with electricity to cause ventricular fibrillation or is stopped in any other way, flow of blood everywhere in the circulation ceases a few seconds later. Without blood flow, the pressures everywhere in the circulation become equal. This equilibrated pressure level is called the *mean circulatory filling pressure.*

Effect of Blood Volume on Mean Circulatory Filling Pressure. The greater the volume of blood in the circulation, the greater is the mean circulatory filling pressure because extra blood volume stretches the walls of the vasculature. The *red curve* in Figure 20-10 shows the approximate normal effect of different levels of blood volume on the mean circulatory filling pressure. Note that at a blood volume of about 4000 milliliters, the mean circulatory filling pressure is close to zero because this is the "unstressed volume" of the circulation, but at a volume of 5000 milliliters, the filling pressure is the normal value of 7 mm Hg. Similarly, at still higher volumes, the mean circulatory filling pressure increases almost linearly.

Effect of Sympathetic Nervous Stimulation of the Circulation on Mean Circulatory Filling Pressure. The *green curve* and *blue curve* in Figure 20-10 show the effects, respectively, of high and low levels of sympathetic nervous activity on the mean circulatory filling pressure.

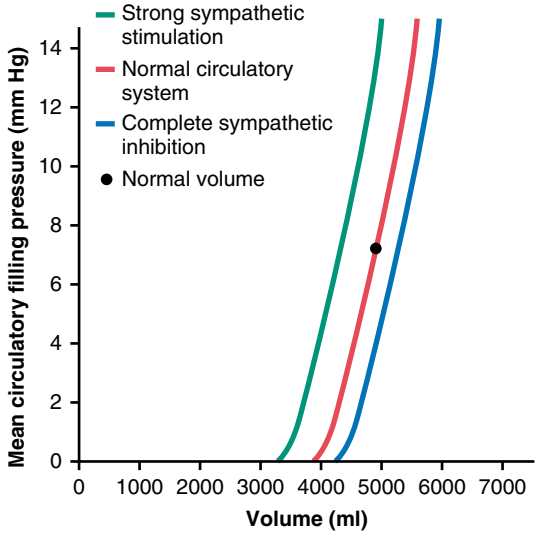


Figure 20-10 Effect of changes in total blood volume on the *mean circulatory filling pressure* (i.e., "volume-pressure curves" for the entire circulatory system). These curves also show the effects of strong sympathetic stimulation and complete sympathetic inhibition.

Strong sympathetic stimulation constricts all the systemic blood vessels, as well as the larger pulmonary blood vessels and even the chambers of the heart. Therefore, the capacity of the system decreases so that at each level of blood volume, the mean circulatory filling pressure is increased. At normal blood volume, maximal sympathetic stimulation increases the mean circulatory filling pressure from 7 mm Hg to about 2.5 times that value, or about 17 mm Hg.

Conversely, complete inhibition of the sympathetic nervous system relaxes both the blood vessels and the heart, decreasing the mean circulatory filling pressure from the normal value of 7 mm Hg down to about 4 mm Hg. Before leaving Figure 20-10, note specifically how steep the curves are. This means that even slight changes in blood volume or slight changes in the capacity of the system caused by various levels of sympathetic activity can have large effects on the mean circulatory filling pressure.

Mean Systemic Filling Pressure and Its Relation to Mean Circulatory Filling Pressure. The *mean systemic filling pressure,* Psf, is slightly different from the mean circulatory filling pressure. It is the pressure measured everywhere *in the systemic circulation* after blood flow has been stopped by clamping the large blood vessels at the heart, so the pressures in the systemic circulation can be measured independently from those in the pulmonary circulation. The mean systemic pressure, although almost impossible to measure in the living animal, is the important pressure for determining venous return. *The mean systemic filling pressure, however, is almost always nearly equal to the mean circulatory filling pressure* because the pulmonary circulation has less than one eighth as much capacitance as the systemic circulation and only about one tenth as much blood volume.

Effect on the Venous Return Curve of Changes in Mean Systemic Filling Pressure. Figure 20-11 shows the effects on the venous return curve caused by increasing or decreasing the mean systemic filling pressure (Psf). Note in Figure 20-11 that the normal mean systemic filling pressure is 7 mm Hg. Then, for the uppermost curve

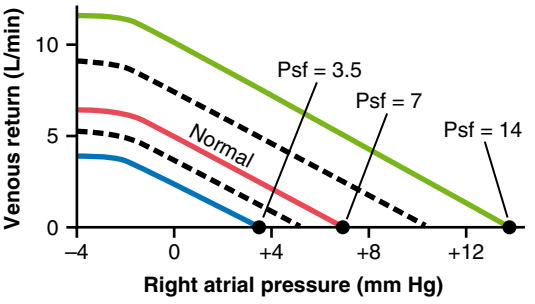


Figure 20-11 Venous return curves showing the normal curve when the mean systemic filling pressure (Psf) is 7 mm Hg and the effect of altering the Psf to either 3.5 or 14 mm Hg. (Redrawn from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)

in the figure, the mean systemic filling pressure has been increased to 14 mm Hg, and for the lowermost curve, has been decreased to 3.5 mm Hg. These curves demonstrate that the greater the mean systemic filling pressure (which also means the greater the "tightness" with which the circulatory system is filled with blood), the more the venous return curve shifts *upward* and *to the right.* Conversely, the lower the mean systemic filling pressure, the more the curve shifts *downward* and *to the left.*

To express this another way, the greater the system is filled, the easier it is for blood to flow into the heart. The less the filling, the more difficult it is for blood to flow into the heart.

"Pressure Gradient for Venous Return"—When This Is Zero, There Is No Venous Return. When the right atrial pressure rises to equal the mean systemic filling pressure, there is no longer any pressure difference between the peripheral vessels and the right atrium. Consequently, there can no longer be any blood flow from any peripheral vessels back to the right atrium. However, when the right atrial pressure falls progressively lower than the mean systemic filling pressure, the flow to the heart increases proportionately, as one can see by studying any of the venous return curves in Figure 20-11. That is, *the greater the difference between the mean systemic filling pressure and the right atrial pressure, the greater becomes the venous return.* Therefore, the difference between these two pressures is called the *pressure gradient for venous return.*

Resistance to Venous Return

In the same way that mean systemic filling pressure represents a pressure pushing venous blood from the periphery toward the heart, there is also resistance to this venous flow of blood. It is called the *resistance to venous return.* Most of the resistance to venous return occurs in the veins, although some occurs in the arterioles and small arteries as well.

Why is venous resistance so important in determining the resistance to venous return? The answer is that when the resistance in the veins increases, blood begins to be dammed up, mainly in the veins themselves. But the venous pressure rises very little because the veins are highly distensible. Therefore, this rise in venous pressure is not very effective in overcoming the resistance, and blood flow into the right atrium decreases drastically. Conversely, when arteriolar and small artery resistances increase, blood accumulates in the arteries, which have a capacitance only one thirtieth as great as that of the veins. Therefore, even slight accumulation of blood in the arteries raises the pressure greatly—30 times as much as in the veins—and this high pressure does overcome much of the increased resistance. Mathematically, it turns out that about two thirds of the so-called "resistance to venous return" is determined by venous resistance, and about one third by the arteriolar and small artery resistance.

Venous return can be calculated by the following formula:

$$VR = \frac{Psf - PRA}{RVR}$$

in which *VR* is venous return, *Psf* is mean systemic filling pressure, *PRA* is right atrial pressure, and *RVR* is resistance to venous return. In the healthy human adult, the values for these are as follows: venous return equals 5 L/min, mean systemic filling pressure equals 7 mm Hg, right atrial pressure equals 0 mm Hg, and resistance to venous return equals 1.4 mm Hg per L/min of blood flow.

Effect of Resistance to Venous Return on the Venous Return Curve. Figure 20-12 demonstrates the effect of different levels of resistance to venous return on the venous return curve, showing that a *decrease* in this resistance to one-half normal allows twice as much flow of blood and, therefore, *rotates the curve upward* to twice as great a slope. Conversely, an *increase* in resistance to twice normal *rotates the curve downward* to one half as great a slope.

Note also that when the right atrial pressure rises to equal the mean systemic filling pressure, venous return becomes zero at all levels of resistance to venous return because when there is no pressure gradient to cause flow of blood, it makes no difference what the resistance is in the circulation; the flow is still zero. Therefore, *the highest level to which the right atrial pressure can rise,* regardless of how much the heart might fail, is equal to the mean systemic filling pressure.

Combinations of Venous Return Curve Patterns. Figure 20-13 shows effects on the venous return curve caused by simultaneous changes in mean systemic pressure (Psf) and resistance to venous return, demonstrating that both these factors can operate simultaneously.

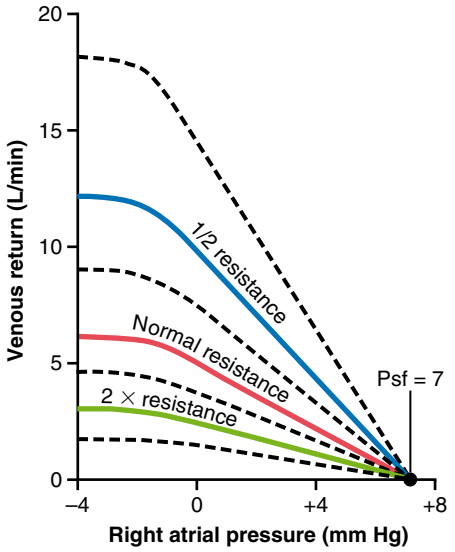


Figure 20-12 Venous return curves depicting the effect of altering the "resistance to venous return." Psf, mean systemic filling pressure. (Redrawn from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)

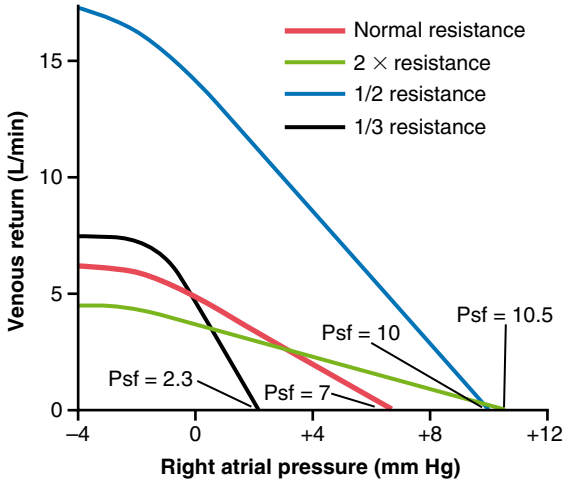


Figure 20-13 Combinations of the major patterns of venous return curves, showing the effects of simultaneous changes in mean systemic filling pressure (Psf) and in "resistance to venous return." (Redrawn from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)

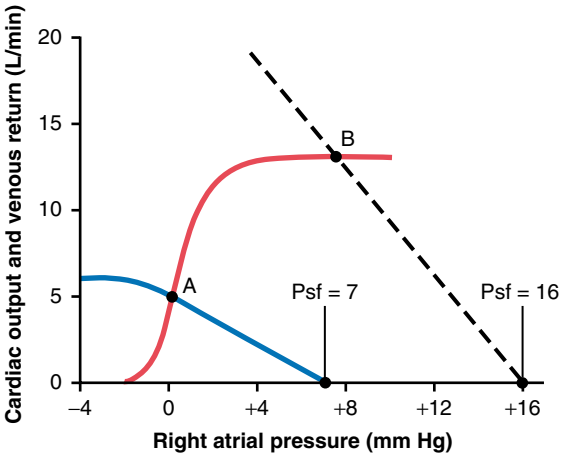


Figure 20-14 The two *solid curves* demonstrate an analysis of cardiac output and right atrial pressure when the cardiac output (*red line*) and venous return (*blue line*) curves are normal. Transfusion of blood equal to 20 percent of the blood volume causes the venous return curve to become the *dashed curve;* as a result, the cardiac output and right atrial pressure shift from point *A* to point *B.* Psf, mean systemic filling pressure.

Analysis of Cardiac Output and Right Atrial Pressure Using Simultaneous Cardiac Output and Venous Return Curves

In the complete circulation, the heart and the systemic circulation must operate together. This means that (1) the venous return from the systemic circulation must equal the cardiac output from the heart and (2) the right atrial pressure is the same for both the heart and the systemic circulation.

Therefore, one can predict the cardiac output and right atrial pressure in the following way: (1) Determine the momentary pumping ability of the heart and depict this in the form of a cardiac output curve; (2) determine the momentary state of flow from the systemic circulation into the heart and depict this in the form of a venous return curve; and (3) "equate" these curves against each other, as shown in Figure 20-14.

Two curves in the figure depict the *normal cardiac output curve* (red line) and the *normal venous return curve* (blue line). There is only one point on the graph, point A, at which the venous return equals the cardiac output and at which the right atrial pressure is the same for both the heart and the systemic circulation. Therefore, in the normal circulation, the right atrial pressure, cardiac output, and venous return are all depicted by point A, called the *equilibrium point,* giving a normal value for cardiac output of 5 L/min and a right atrial pressure of 0 mm Hg.

Effect of Increased Blood Volume on Cardiac Output. A sudden increase in blood volume of about 20 percent increases the cardiac output to about 2.5 to 3 times normal. An analysis of this effect is shown in Figure 20-14. Immediately on infusing the large quantity of extra blood, the increased filling of the system causes the mean systemic filling pressure (Psf) to increase to 16 mm Hg, which shifts the venous return curve to the right. At the same time, the increased blood volume distends the blood vessels, thus reducing their resistance and thereby reducing the resistance to venous return, which rotates the curve upward. As a result of these two effects, the venous return curve of Figure 20-14 is shifted to the right. This new curve equates with the cardiac output curve at point B, showing that the cardiac output and venous return increase 2.5 to 3 times, and that the right atrial pressure rises to about +8 mm Hg.

Further Compensatory Effects Initiated in Response to Increased Blood Volume. The greatly increased cardiac output caused by increased blood volume lasts for only a few minutes because several compensatory effects immediately begin to occur: (1) The increased cardiac output *increases the capillary pressure* so that fluid begins to transude out of the capillaries into the tissues, thereby returning the blood volume toward normal. (2) The increased pressure in the veins causes the veins to continue distending gradually by the mechanism called *stress-relaxation,* especially causing the venous blood reservoirs, such as the liver and spleen, to distend, thus *reducing the mean systemic pressure.* (3) The excess blood flow through the peripheral tissues causes autoregulatory increase in the peripheral vascular resistance, thus increasing the *resistance to venous return.* These factors cause the mean systemic filling pressure to return back toward normal and the resistance vessels of the systemic circulation to constrict. Therefore, gradually, over a period of 10 to 40 minutes, the cardiac output returns almost to normal.

Effect of Sympathetic Stimulation on Cardiac Output. Sympathetic stimulation affects both the heart and the systemic circulation: (1) It *makes the heart a stronger pump.* (2) In the systemic circulation, it *increases*

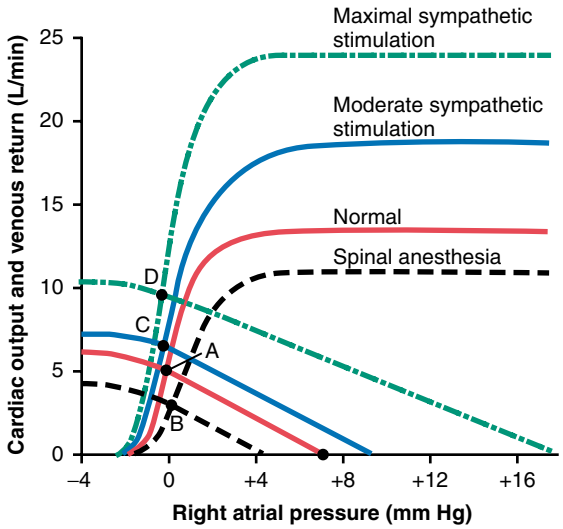


Figure 20-15 Analysis of the effect on cardiac output of (1) moderate sympathetic stimulation (from point *A* to point *C*), (2) maximal sympathetic stimulation (point D), and (3) sympathetic inhibition caused by total spinal anesthesia (point *B*). (Redrawn from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)

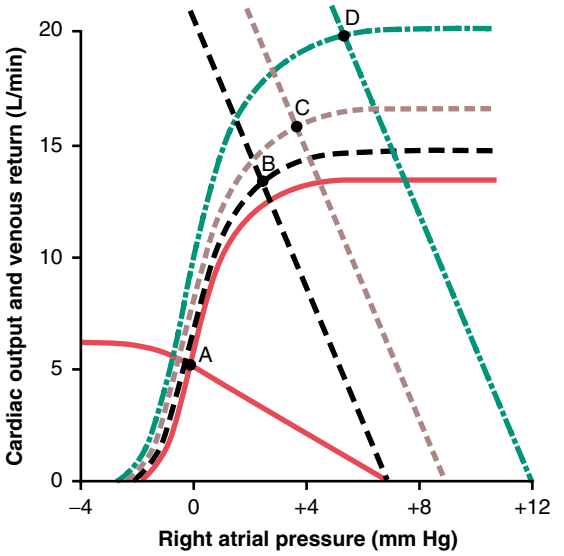


Figure 20-16 Analysis of successive changes in cardiac output and right atrial pressure in a human being after a large arteriovenous (AV) fistula is suddenly opened. The stages of the analysis, as shown by the equilibrium points, are *A*, normal conditions; *B*, immediately after opening the AV fistula; *C*, 1 minute or so after the sympathetic reflexes have become active; and *D*, several weeks after the blood volume has increased and the heart has begun to hypertrophy. (Redrawn from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)

the mean systemic filling pressure because of contraction of the peripheral vessels, especially the veins, and it *increases the resistance to venous return.*

In Figure 20-15, the *normal* cardiac output and venous return curves are depicted; these equate with each other at point A, which represents a normal venous return and cardiac output of 5 L/min and a right atrial pressure of 0 mm Hg. Note in the figure that maximal sympathetic stimulation (green curves) increases the mean systemic filling pressure to 17 mm Hg (depicted by the point at which the venous return curve reaches the zero venous return level). And the sympathetic stimulation also increases pumping effectiveness of the heart by nearly 100 percent. As a result, the cardiac output rises from the normal value at equilibrium point A to about double normal at equilibrium point D—and yet *the right atrial pressure hardly changes.* Thus, different degrees of sympathetic stimulation can increase the cardiac output progressively to about twice normal *for short periods of time,* until other compensatory effects occur within seconds or minutes.

Effect of Sympathetic Inhibition on Cardiac Output. The sympathetic nervous system can be blocked by inducing *total spinal anesthesia* or by using some drug, such as *hexamethonium,* that blocks transmission of nerve signals through the autonomic ganglia. The lowermost curves in Figure 20-15 show the effect of sympathetic inhibition caused by total spinal anesthesia, demonstrating that (1) the *mean systemic filling pressure falls to about 4 mm Hg* and (2) the *effectiveness of the heart as a pump decreases to about 80 percent of normal.* The cardiac output falls from point A to point B, which is a decrease to about 60 percent of normal.

Effect of Opening a Large Arteriovenous Fistula. Figure 20-16 shows various stages of circulatory changes that occur after opening a large arteriovenous fistula, that is, after making an opening directly between a large artery and a large vein.

1. The two red curves crossing at point A show the normal condition.
2. The curves crossing at point B show the circulatory condition *immediately after opening the large fistula.* The principal effects are (1) a sudden and precipitous rotation of the venous return curve upward caused by the *large decrease in resistance to venous return* when blood is allowed to flow with almost no impediment directly from the large arteries into the venous system, bypassing most of the resistance elements of the peripheral circulation, and (2) a *slight increase in the level of the cardiac output curve* because opening the fistula decreases the peripheral resistance and allows an acute fall in arterial pressure against which the heart can pump more easily. The net result, depicted by point B, is an *increase in cardiac output from 5 L/min up to 13 L/min* and *an increase in right atrial pressure to about +3 mm Hg.*
3. Point C represents the effects about 1 minute later, after the sympathetic nerve reflexes have restored the arterial pressure almost to normal and caused two other effects: (1) an increase in the mean systemic filling pressure (because of constriction of all veins and arteries) from 7 to 9 mm Hg, thus shifting the venous return

curve 2 mm Hg to the right, and (2) further elevation of the cardiac output curve because of sympathetic nervous excitation of the heart. The cardiac output now rises to almost 16 L/min, and the right atrial pressure to about 4 mm Hg.

4. Point D shows the effect after several more weeks. By this time, the blood volume has increased because the slight reduction in arterial pressure and the sympathetic stimulation have both reduced kidney output of urine. The mean systemic filling pressure has now risen to +12 mm Hg, shifting the venous return curve another 3 mm Hg to the right. Also, the prolonged increased workload on the heart has caused the heart muscle to hypertrophy slightly, raising the level of the cardiac output curve still further. Therefore, point D shows a cardiac output now of almost 20 L/min and a right atrial pressure of about 6 mm Hg.

Other Analyses of Cardiac Output Regulation. In Chapter 21, analysis of cardiac output regulation during exercise is presented, and in Chapter 22, analyses of cardiac output regulation at various stages of congestive heart failure are shown.

Methods for Measuring Cardiac Output

In animal experiments, one can cannulate the aorta, pulmonary artery, or great veins entering the heart and measure the cardiac output using any type of flowmeter. An electromagnetic or ultrasonic flowmeter can also be placed on the aorta or pulmonary artery to measure cardiac output.

In the human, except in rare instances, cardiac output is measured by indirect methods that do not require surgery. Two of the methods that have been used for experimental studies are the *oxygen Fick method* and the *indicator dilution method.*

Cardiac output can also be estimated by *echocardiography,* a method that uses ultrasound waves from a transducer placed on the chest wall or passed into the patient's esophagus to measure the size of the heart's chambers, as well as the velocity of blood flowing from the left ventricle into the aorta. Stroke volume is calculated from the velocity of blood flowing into the aorta and the aorta cross-sectional area determined from the aorta diameter that is measured by ultrasound imaging. Cardiac output is then calculated from the product of the stroke volume and the heart rate.

Pulsatile Output of the Heart as Measured by an Electromagnetic or Ultrasonic Flowmeter

Figure 20-17 shows a recording in a dog of blood flow in the root of the aorta made using an electromagnetic flowmeter. It demonstrates that the blood flow rises rapidly to a peak during systole, and then at the end of systole reverses for a fraction of a second. This reverse flow causes the aortic valve to close and the flow to return to zero.

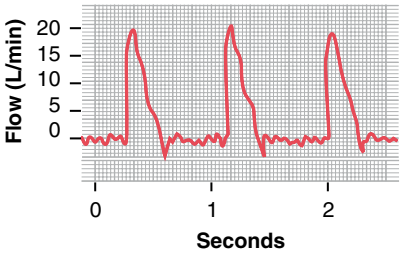


Figure 20-17 Pulsatile blood flow in the root of the aorta recorded using an electromagnetic flowmeter.

Measurement of Cardiac Output Using the Oxygen Fick Principle

The Fick principle is explained by Figure 20-18. This figure shows that 200 milliliters of oxygen are being absorbed from the lungs into the pulmonary blood each minute. It also shows that the blood entering the right heart has an oxygen concentration of 160 milliliters per liter of blood, whereas that leaving the left heart has an oxygen concentration of 200 milliliters per liter of blood. From these data, one can calculate that each liter of blood passing through the lungs absorbs 40 milliliters of oxygen.

Because the total quantity of oxygen absorbed into the blood from the lungs each minute is 200 milliliters, dividing 200 by 40 calculates a total of five 1-liter portions of blood that must pass through the pulmonary circulation each minute to absorb this amount of oxygen. Therefore, the quantity of blood flowing through the lungs each minute is 5 liters, which is also a measure of the cardiac output. Thus, the cardiac output can be calculated by the following formula:

$$\text{Cardiac output (L/min)} = \frac{\text{O}_2 \text{ absorbed per minute by the lungs (ml/min)}}{\text{Arteriovenous O}_2 \text{ difference (ml/L of blood)}}$$

In applying this Fick procedure for measuring cardiac output in the human being, *mixed venous blood* is usually obtained through a catheter inserted up the brachial vein of the forearm, through the subclavian vein, down to the right atrium, and, finally, into the right ventricle or

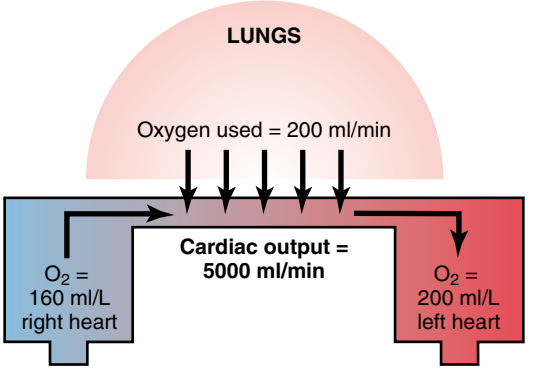


Figure 20-18 Fick principle for determining cardiac output.

pulmonary artery. And *systemic arterial blood* can then be obtained from any systemic artery in the body. The *rate of oxygen absorption* by the lungs is measured by the rate of disappearance of oxygen from the respired air, using any type of oxygen meter.

Indicator Dilution Method for Measuring Cardiac Output

To measure cardiac output by the so-called "indicator dilution method," a small amount of *indicator,* such as a dye, is injected into a large systemic vein or, preferably, into the right atrium. This passes rapidly through the right side of the heart, then through the blood vessels of the lungs, through the left side of the heart, and, finally, into the systemic arterial system. The concentration of the dye is recorded as the dye passes through one of the peripheral arteries, giving a curve as shown in Figure 20-19. In each of these instances, 5 milligrams of Cardio-Green dye was injected at zero time. In the top recording, none of the dye passed into the arterial tree until about 3 seconds after the injection, but then the arterial concentration of the dye rose rapidly to a maximum in about 6 to 7 seconds. After that, the concentration fell rapidly, but before the concentration reached zero, some of the dye had already circulated all the way through some of the peripheral systemic vessels and returned through the heart for a second time. Consequently, the dye concentration in the artery began to rise again. For the purpose of calculation, it is necessary to *extrapolate* the early down-slope of the curve to the zero point, as shown by the dashed portion of each curve. In this way, the *extrapolated time-concentration curve* of the dye in the systemic artery without recirculation can be measured in its first portion and estimated reasonably accurately in its latter portion.

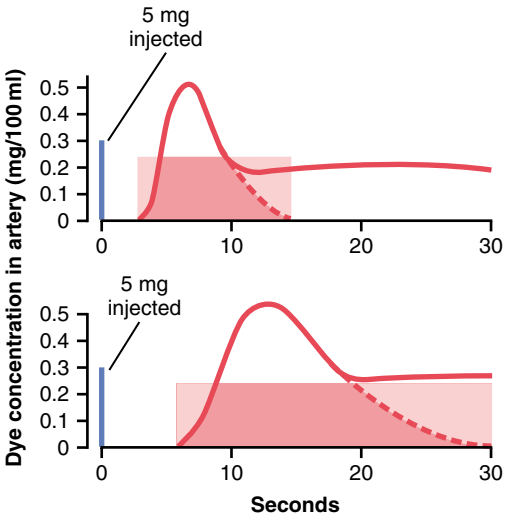


Figure 20-19 *Extrapolated dye concentration curves* used to calculate two separate cardiac outputs by the dilution method. (The rectangular areas are the calculated average concentrations of dye in the arterial blood for the durations of the respective extrapolated curves.)

Once the extrapolated time-concentration curve has been determined, one then calculates the mean concentration of dye in the arterial blood for the duration of the curve. For instance, in the top example of Figure 20-19, this was done by measuring the area under the entire initial and extrapolated curve and then averaging the concentration of dye for the duration of the curve; one can see from the shaded rectangle straddling the curve in the upper figure that the average concentration of dye was 0.25 mg/dl of blood and that the duration of this average value was 12 seconds. A total of 5 milligrams of dye had been injected at the beginning of the experiment. For blood carrying only 0.25 milligram of dye in each 100 milliliters to carry the entire 5 milligrams of dye through the heart and lungs in 12 seconds, a total of 20 portions each with 100 milliliters of blood would have passed through the heart during the 12 seconds, which would be the same as a cardiac output of 2 L/12 sec, or 10 L/min. We leave it to the reader to calculate the cardiac output from the bottom *extrapolated* curve of Figure 20-19. To summarize, the cardiac output can be determined using the following formula:

$$\text{Cardiac output (ml/min)} = \frac{\text{Milligrams of dye injected} \times 60}{\left(\begin{array}{c}\text{Average concentration of dye}\\ \text{in each milliliter of blood}\\ \text{for the duration of the curve}\end{array}\right) \times \left(\begin{array}{c}\text{Duration of}\\ \text{the curve}\\ \text{in seconds}\end{array}\right)}$$

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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

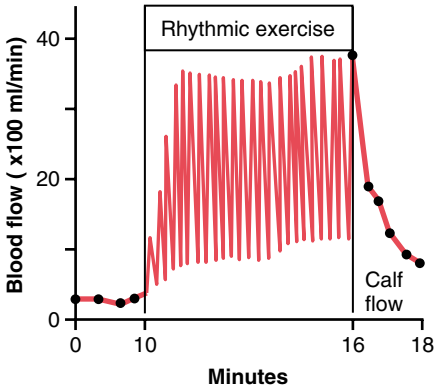

Figure 21-1 Effects of muscle exercise on blood flow in the calf of a leg during strong rhythmical contraction. The blood flow was much less during contractions than between contractions. (Adapted from Barcroft H, Dornhorst AC: The blood flow through the human calf during rhythmic exercise. J Physiol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

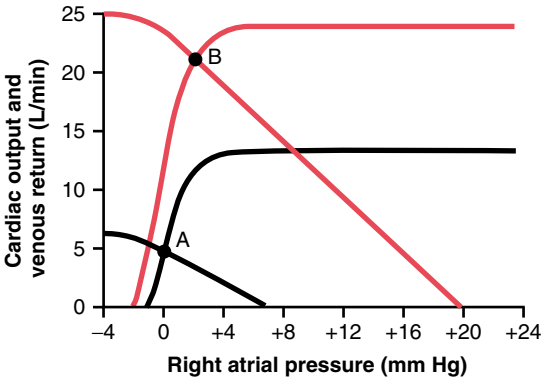

Figure 21-2 Graphical analysis of change in cardiac output and right atrial pressure with onset of strenuous exercise. *Black curves*, normal circulation. *Red curves*, heavy exercise.

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.

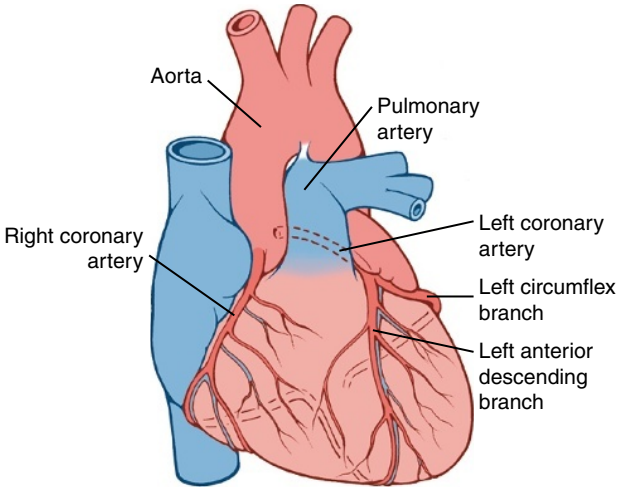

Figure 21-3 The coronary arteries.

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.

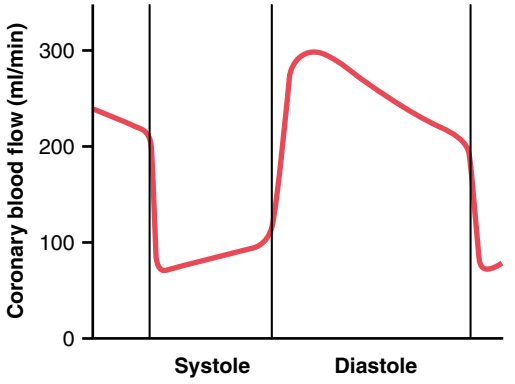

Figure 21-4 Phasic flow of blood through the coronary capillaries of the human left ventricle during cardiac systole and diastole (as extrapolated from measured flows in dogs).

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.

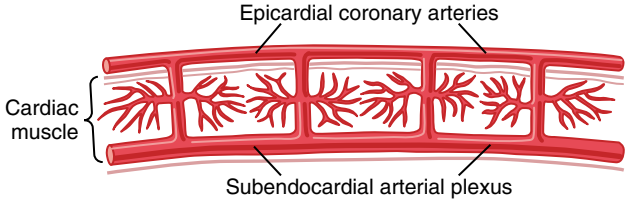

Figure 21-5 Diagram of the epicardial, intramuscular, and subendocardial coronary vasculature.

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.

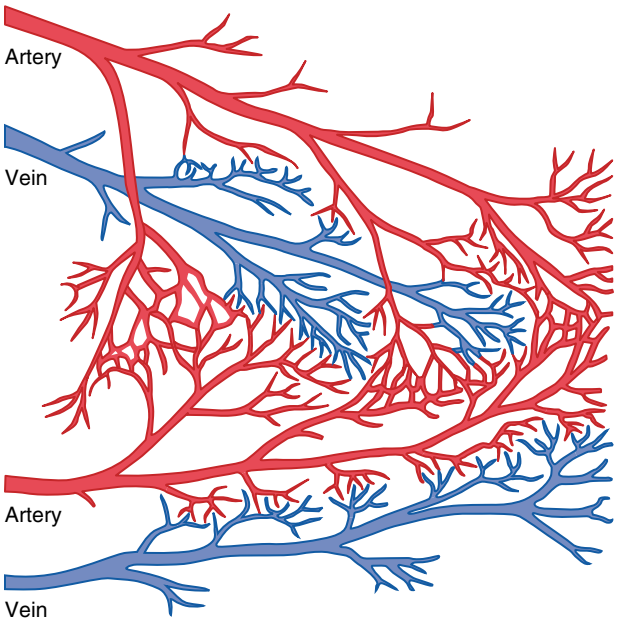

Figure 21-6 Minute anastomoses in the normal coronary arterial system.

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.

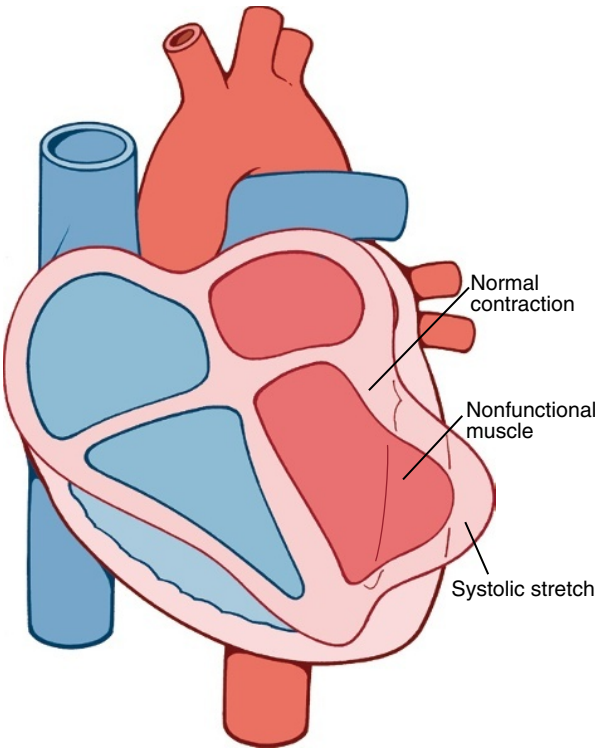

Figure 21-7 Systolic stretch in an area of ischemic cardiac muscle.

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.

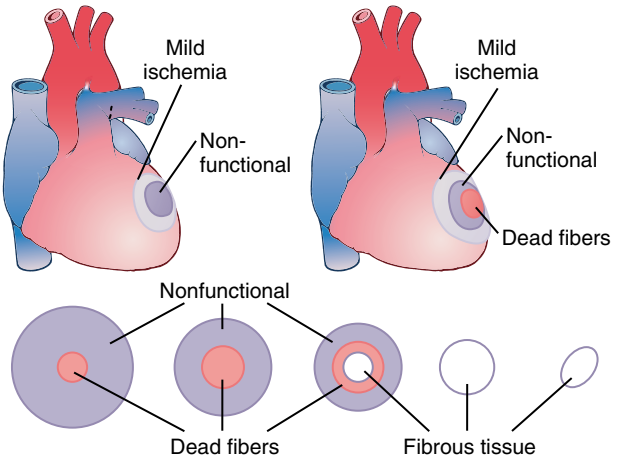

Figure 21-8 *Top,* Small and large areas of coronary ischemia. *Bottom,* Stages of recovery from myocardial infarction.

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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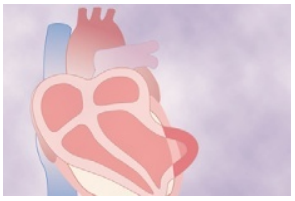
CHAPTER 22

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.

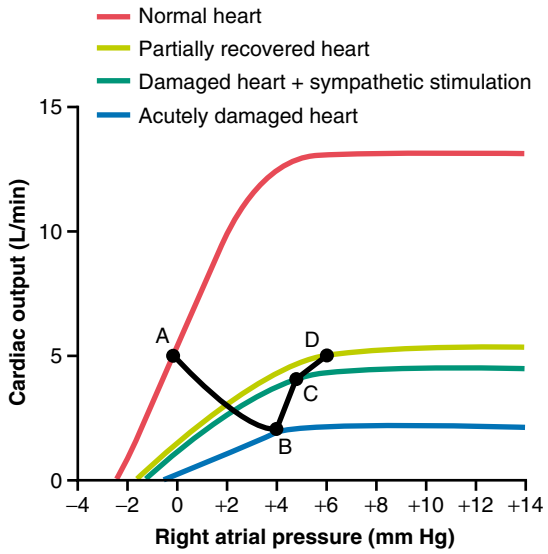


Figure 22-1 Progressive changes in the cardiac output curve after acute myocardial infarction. Both the cardiac output and right atrial pressure change progressively from point A to point D (illustrated by the black line) over a period of seconds, minutes, days, and weeks.

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

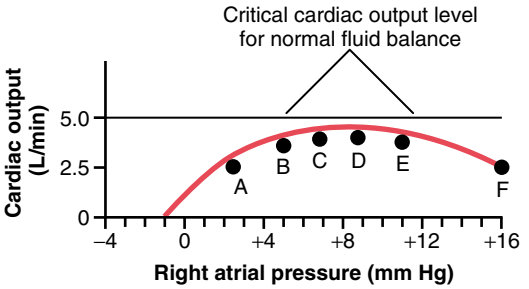


Figure 22-2 Greatly depressed cardiac output that indicates decompensated heart disease. Progressive fluid retention raises the right atrial pressure over a period of days, and the cardiac output progresses from point A to point F, until death occurs.

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.

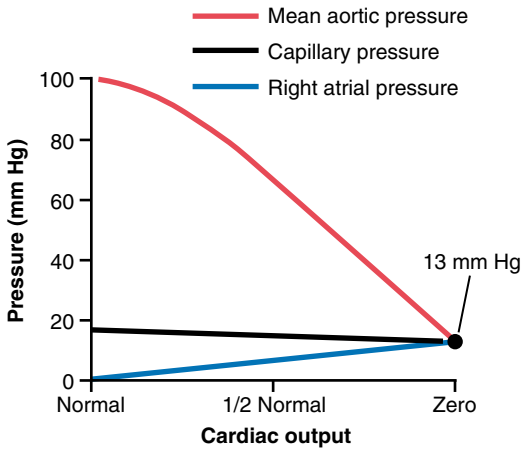


Figure 22-3 Progressive changes in mean aortic pressure, peripheral tissue capillary pressure, and right atrial pressure as the cardiac output falls from normal to zero.

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

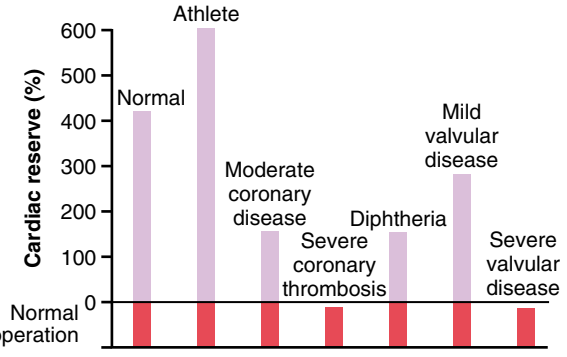


Figure 22-4 Cardiac reserve in different conditions, showing less than zero reserve for two of the conditions.

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.

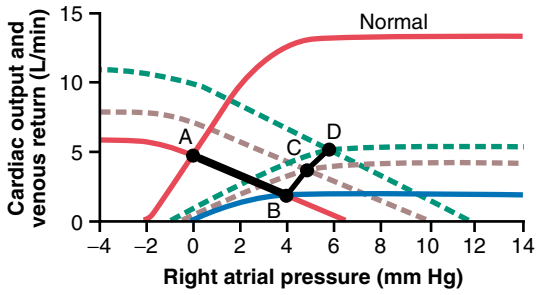


Figure 22-5 Progressive changes in cardiac output and right atrial pressure during different stages of cardiac failure.

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

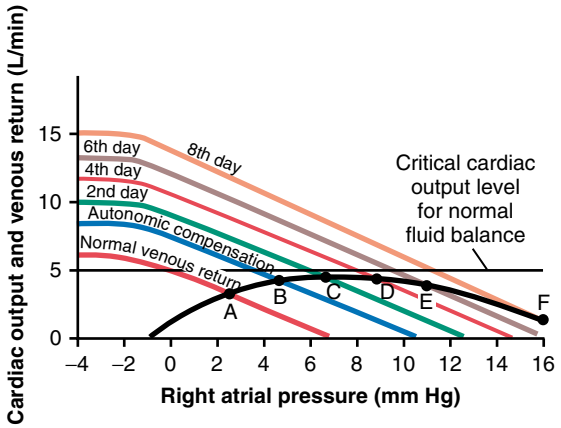


Figure 22-6 Graphical analysis of decompensated heart disease showing progressive shift of the venous return curve to the right as a result of continued fluid retention.

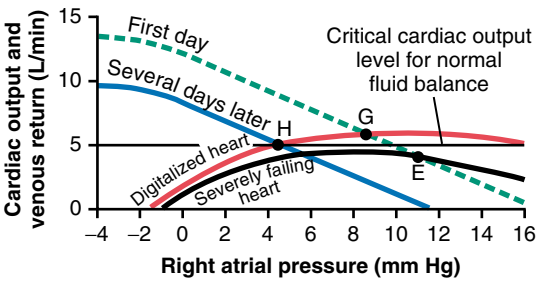


Figure 22-7 Treatment of decompensated heart disease showing the effect of digitalis in elevating the cardiac output curve, this in turn causing increased urine output and progressive shift of the venous return curve to the left.

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

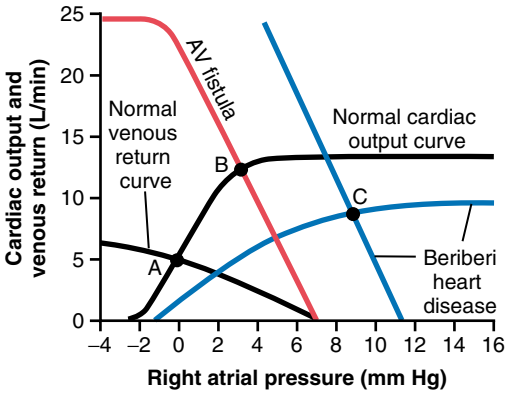


Figure 22-8 Graphical analysis of two types of conditions that can cause high-output cardiac failure: (1) arteriovenous (AV) fistula and (2) beriberi heart disease.

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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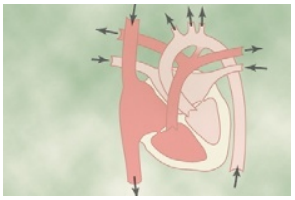
Heart Valves and Heart Sounds; Valvular and Congenital Heart Defects



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-

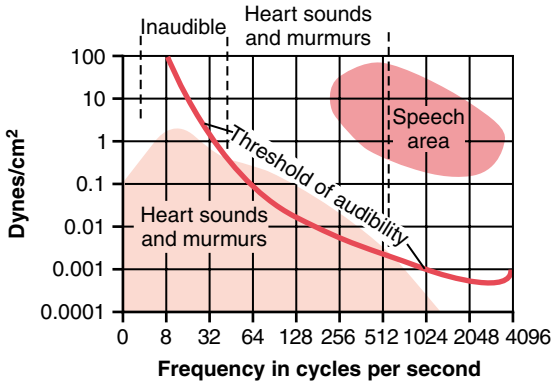


Figure 23-1 Amplitude of different-frequency vibrations in the heart sounds and heart murmurs in relation to the threshold of audibility, showing that the range of sounds that can be heard is between 40 and 520 cycles/sec. (Modified from Butterworth JS, Chassin JL, McGrath JJ: Cardiac Auscultation, 2nd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

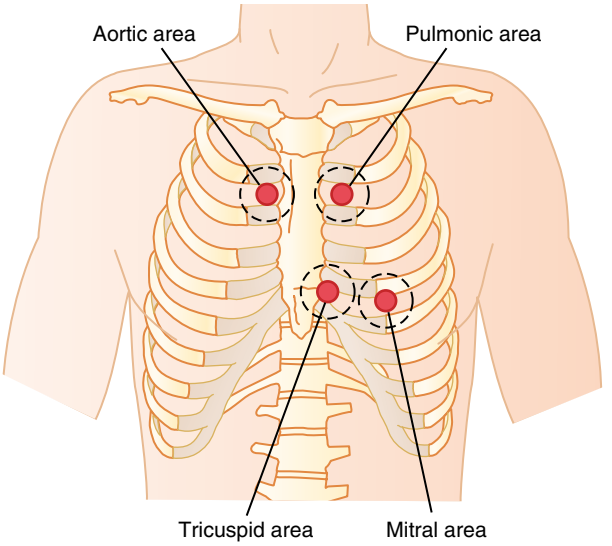


Figure 23-2 Chest areas from which sound from each valve is best heard.

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

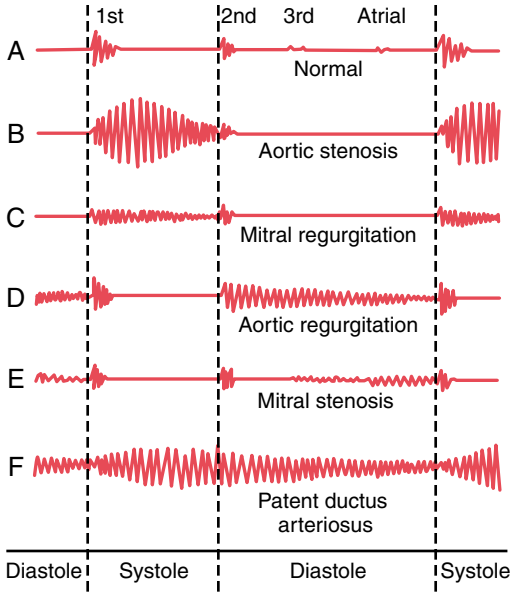


Figure 23-3 Phonocardiograms from normal and abnormal hearts.

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.

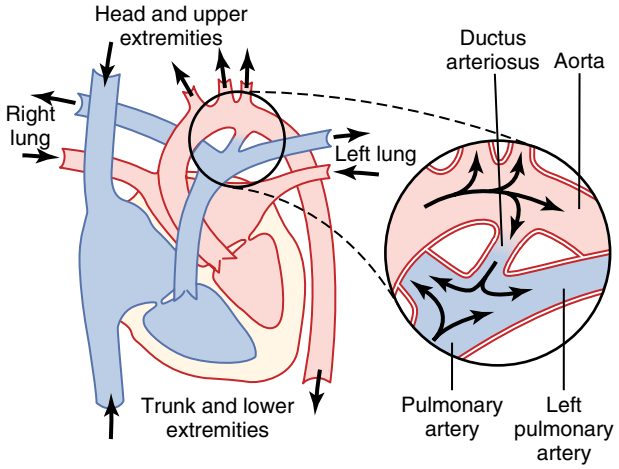


Figure 23-4 Patent ductus arteriosus, showing by the blue color that venous blood changes into oxygenated blood at different points in the circulation. The right-hand diagram shows backflow of blood from the aorta into the pulmonary artery and then through the lungs for a second time.

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.

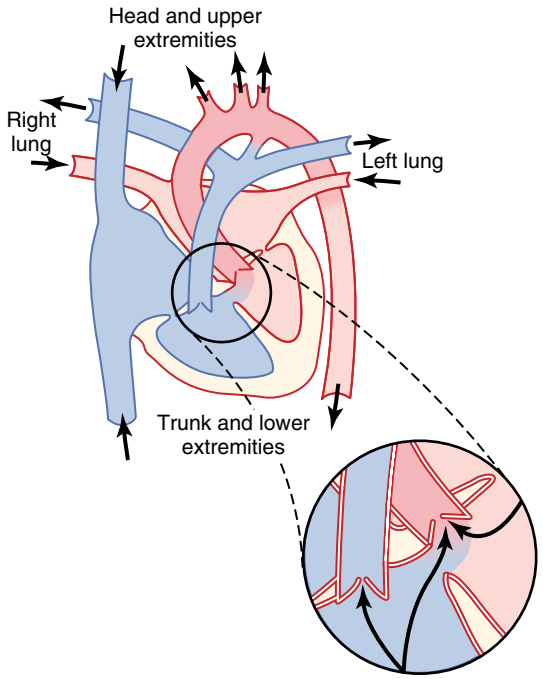


Figure 23-5 Tetralogy of Fallot, showing by the blue color that most of the venous blood is shunted from the right ventricle into the aorta without passing through the lungs.

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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