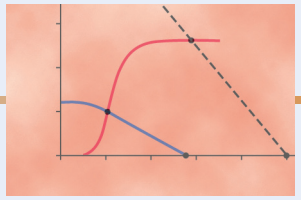

CHAPTER 20

UNIT IV

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 to consider in relation to the circulation because it is the sum of the blood flows to all 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) the 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 average human being who weighs 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. The cardiac index rises rapidly to a level greater than 4 L/min/m^2 at age 10 years and 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 overall 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—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.

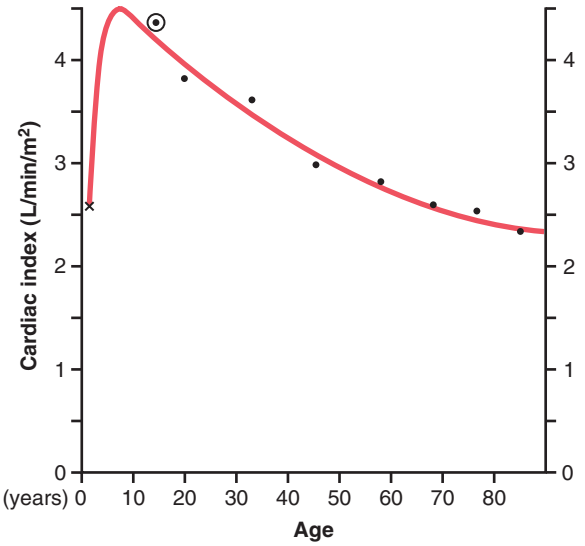

Figure 20-1. Cardiac index for the human being (cardiac output per square meter of surface area) at different ages. *(Modified from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)*

The main reason peripheral factors are usually so important 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 action 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, resulting in 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 to increase the heart rate as much as 10 to 15 percent. In addition, the 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 unstressed conditions, the cardiac output is controlled mainly by peripheral factors that determine venous return. However, as will be discussed later in the chapter, 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 IS THE SUM OF ALL TISSUE BLOOD FLOWS—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 (**Figure 20-2**). 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 20-3** for different levels of exercise. Note that at each increasing level of work output during exercise, oxygen consumption and cardiac output increase in parallel to each other.

To summarize, cardiac output is usually 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.

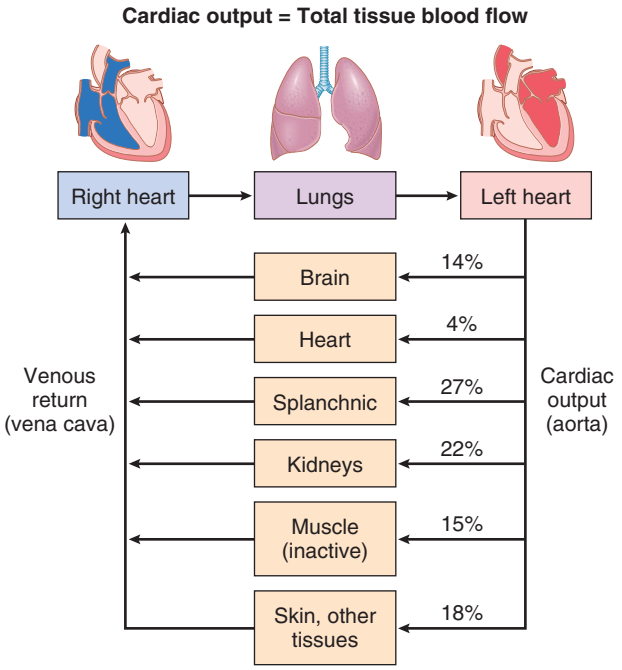

Figure 20-2. Cardiac output is equal to venous return and is the sum of tissue and organ blood flows. Except when the heart is severely weakened and unable to adequately pump the venous return, cardiac output (total tissue blood flow) is determined mainly by the metabolic needs of the tissues and organs of the body.

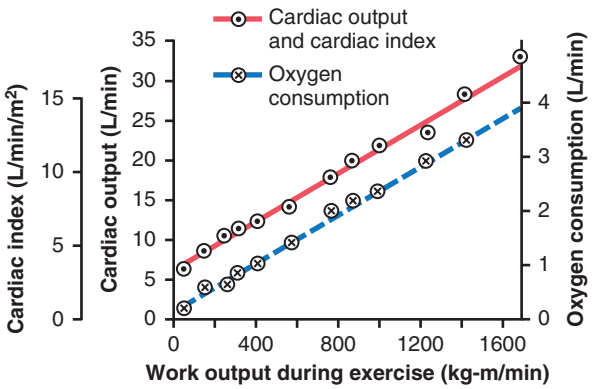

Figure 20-3. Effect of increasing levels of exercise to increase cardiac output (*red solid line*) and oxygen consumption (*blue dashed line*). *(Modified from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)*

Long-Term Cardiac Output Varies Inversely with Total Peripheral Resistance When Arterial Pressure Is Unchanged. **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 vascular resistance, as long as the arterial pressure is unchanged. Note in **Figure 20-4** 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 the total

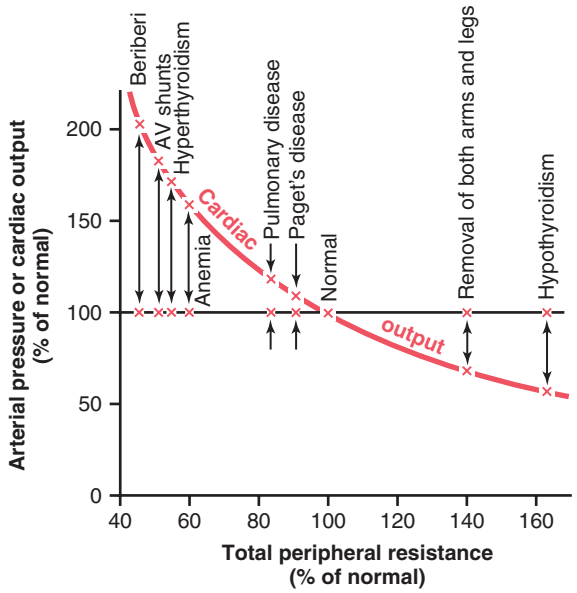

Figure 20-4. Chronic effect of different levels of total peripheral resistance on cardiac output, showing a reciprocal relationship between total peripheral resistance and cardiac output. AV, atrioventricular. *(Modified from Guyton AC: Arterial Pressure and Hypertension. Philadelphia: WB Saunders, 1980.)*

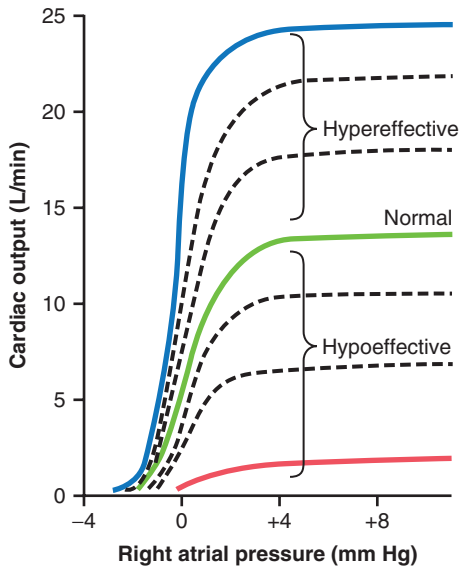

Figure 20-5. Cardiac output curves for the normal heart and for hypoeffective and hypereffective hearts. *(Modified from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)*

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 phenomenon by reconsidering one of the forms of Ohm's law, as expressed in Chapter 14:

$$\text{Cardiac output} = \frac{\text{Arterial pressure}}{\text{Total peripheral resistance}}$$

Thus, 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 20-5 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 a 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 20-5** 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.

Factors That Cause a Hypereffective Heart

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

Nervous Excitation Can 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 20-5**.

Heart Hypertrophy Can Increase Pumping Effectiveness. 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 factor 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 2.5 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 decrease the heart's ability to pump blood are the following:

- Increased arterial pressure against which the heart must pump, such as in severe 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 20-6 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. With nervous control mechanisms intact, 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, 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 fourfold.

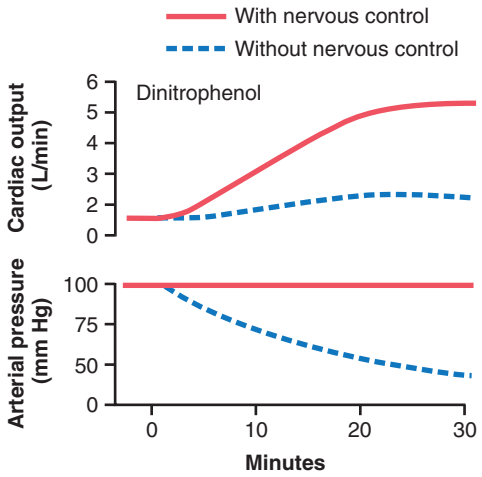

Figure 20-6. Experiment in a dog to demonstrate the importance of nervous maintenance of the arterial pressure as a prerequisite for cardiac output control. Note that with pressure control, the metabolic stimulant *dinitrophenol* increases cardiac output greatly; without pressure control, the arterial pressure falls and the cardiac output rises very little. *(Drawn from experiments by Dr. M. Banet.)*

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 increase venous return and cardiac output above normal, the nervous system plays a key 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 above normal, which serves to increase the cardiac output an extra 30 to 100 percent.

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 abnormal cardiac outputs are shown in Figure 20-7.

High Cardiac Output Caused by Reduced Total Peripheral Resistance

The left side of Figure 20-7 identifies conditions that commonly cause cardiac outputs that are 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

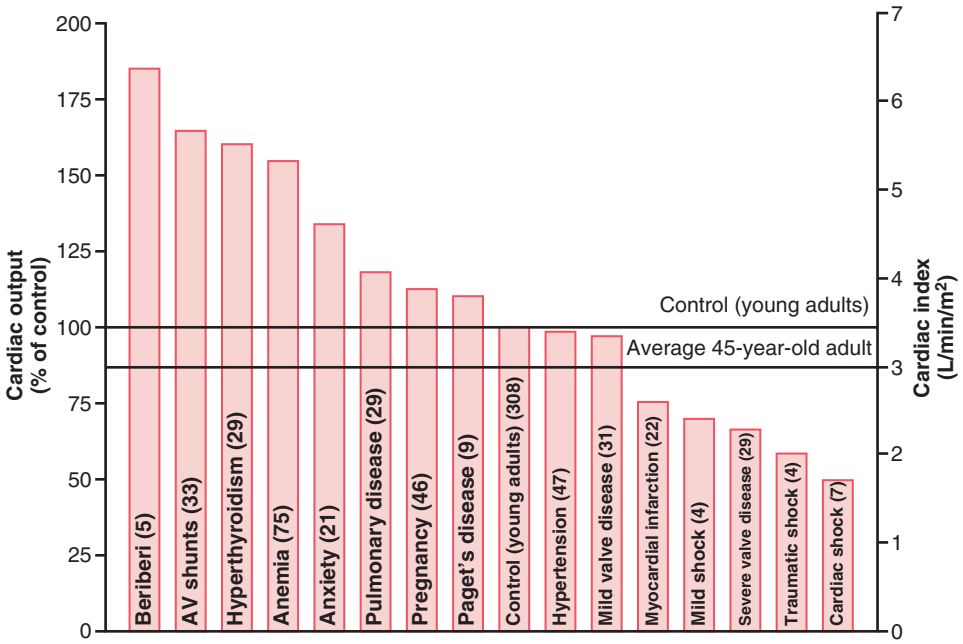

Figure 20-7. Cardiac output in different pathological conditions. The numbers in parentheses indicate number of patients studied in each condition. AV, atrioventricular. *(Modified from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)*

of the heart itself, which we will explain subsequently. 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 (AV) fistula (shunt).* Earlier, we pointed out that whenever a fistula (also called an *AV shunt*) occurs between a major artery and a major vein, large amounts of blood flow directly from the artery into the vein. This also greatly decreases the total peripheral resistance and, likewise, increases the venous return and cardiac output.
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, total peripheral resistance decreases markedly because of local tissue blood flow control reactions throughout the body; consequently, venous return and cardiac output often increase to 40 to 80 percent above normal.
4. *Anemia.* In anemia, two peripheral effects greatly decrease total peripheral resistance. One of these effects is reduced viscosity of the blood, resulting from the decreased concentration of red blood cells. The other effect is diminished delivery of oxygen to the tissues, which causes local vasodilation. As a consequence, cardiac output increases greatly.

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

Low Cardiac Output

Figure 20-7 shows at the far right several conditions that cause abnormally low cardiac output. These conditions fall into two categories: (1) abnormalities that decrease pumping effectiveness of the heart and (2) those that decrease venous return.

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 condition 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 conditions are shown on the right in Figure 20-7, 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 condition is discussed 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, often from hemorrhage. 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.* Acute venous dilation 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 dilation 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 as rapidly as normal.
3. *Obstruction of the large veins.* On rare occasions, the large veins leading into the heart become obstructed, and 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, a reduction in the size of the skeletal muscles usually occurs. This reduction, 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 the tissue metabolic rate is reduced, as occurs in skeletal muscle during prolonged bed rest, the oxygen consumption and nutrition needs of the tissues will also be lower, which 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 is a peripheral factor or a cardiac factor, if ever the cardiac output falls below the level required for adequate nutrition of the tissues, the person is said to experience *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 20-5**. 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.

Effect of External Pressure Outside the Heart on Cardiac Output Curves. **Figure 20-8** 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.

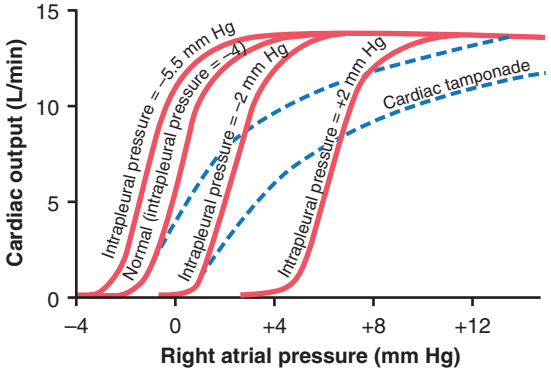

Figure 20-8. Cardiac output curves at different levels of intrapleural pressure and at different degrees of cardiac tamponade. *(Modified from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)*

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 20-8** 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.

Combinations of Different Patterns of Cardiac Output Curves. **Figure 20-9** 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 an 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) because of 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.

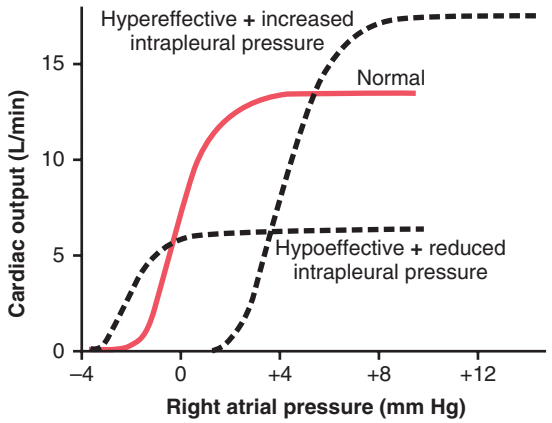

Figure 20-9. Combinations of two major patterns of cardiac output curves showing the effect of alterations in both extracardiac pressure and effectiveness of the heart as a pump. *(Modified from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)*

VENOUS RETURN CURVES

The entire systemic circulation 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 the following three principal factors that affect venous return to the heart from the systemic circulation:

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 20-10** 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 any increase in back pressure causes blood to dam up in the systemic circulation 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

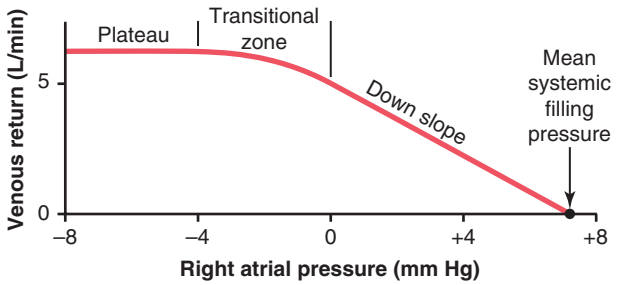

Figure 20-10. Normal *venous return curve*. The plateau is caused by *collapse* of the large veins entering the chest when the right atrial pressure falls below atmospheric pressure. Note also that venous return becomes zero when the right atrial pressure rises to equal the mean systemic filling pressure.

a pressure of 7 mm Hg, which, by definition, is the *mean systemic filling pressure*.

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 reaches 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 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, 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 20-11** 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

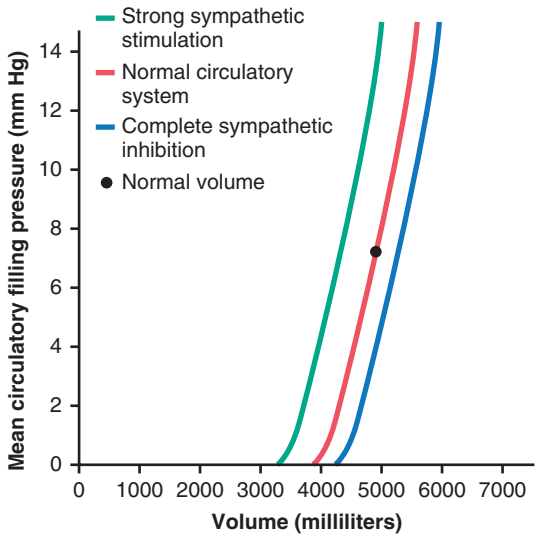

Figure 20-11. Effect of changes in total blood volume on the *mean circulatory filling pressure* (i.e., "volume-pressure curves" for the entire circulatory system). These curves also show the effects of strong sympathetic stimulation and complete sympathetic inhibition.

the normal value of 7 mm Hg. Similarly, at still higher volumes, the mean circulatory filling pressure increases almost linearly.

Sympathetic Nervous Stimulation Increases Mean Circulatory Filling Pressure. The *green curve* and *blue curve* in **Figure 20-11** show the effects, respectively, of high and low levels of sympathetic nervous activity on the mean circulatory filling pressure. 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. Note in **Figure 20-11** how steep the curves are, which means that even slight changes in blood volume or 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

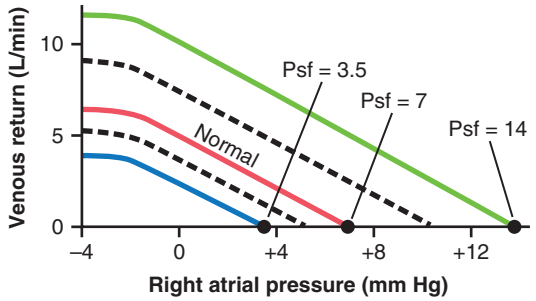

Figure 20-12. Venous return curves showing the normal curve when the mean systemic filling pressure *(Psf)* is 7 mm Hg and the effect of altering the Psf to either 3.5 or 14 mm Hg. *(Modified from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)*

the heart, so the pressures in the systemic circulation can be measured independently from those in the pulmonary circulation. The *mean systemic filling pressure*, although almost impossible to measure in the living animal, *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 20-12 shows the effects on the venous return curve caused by increasing or decreasing Psf. Note that the normal Psf is 7 mm Hg. Then, for the uppermost curve in the figure, Psf has been increased to 14 mm Hg, and for the lowermost curve, it has been decreased to 3.5 mm Hg. These curves demonstrate that the greater the Psf (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 Psf, the more the curve shifts *downward* and *to the left.*

Expressing this another way, the greater the degree to which the system is filled, the easier it is for blood to flow into the heart. The lesser the degree to which the system is filled, the more difficult it is for blood to flow into the heart.

When the "Pressure Gradient for Venous Return" Is Zero, There Is No Venous Return. When the right atrial pressure rises to equal the Psf, 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 peripheral vessels back to the right atrium. However, when the right atrial pressure falls progressively lower than the Psf, blood flow to the heart increases proportionately, as one can see by studying any of the venous return curves in Figure 20-12. That is, *the greater the difference between the Psf 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 Psf 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. However, 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 overcomes 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 is determined 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, Psf 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 20-13 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 Psf, venous return becomes zero at all levels of resistance to venous return because there is no pressure gradient to cause flow of blood. Therefore, *the highest level to which the right atrial pressure can rise,* regardless of how much the heart might fail, is equal to the Psf.

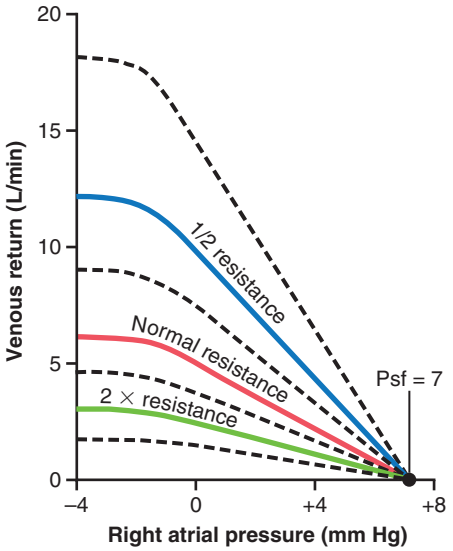

Figure 20-13. Venous return curves depicting the effect of altering the resistance to venous return. Psf, mean systemic filling pressure. *(Modified from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)*

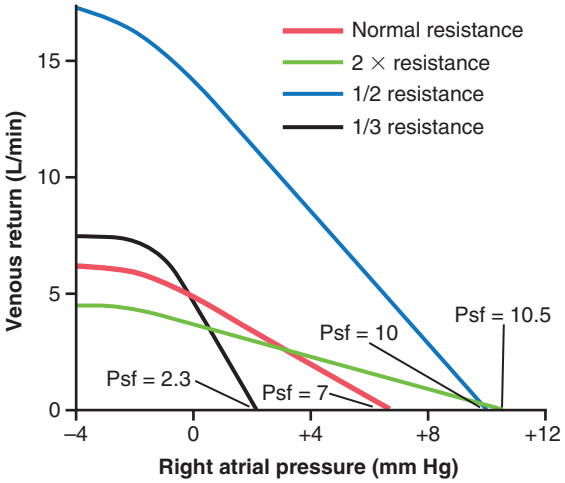

Figure 20-14. Combinations of the major patterns of venous return curves, showing the effects of simultaneous changes in mean systemic filling pressure *(Psf)* and in resistance to venous return. *(Modified from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)*

Combinations of Venous Return Curve Patterns. Figure 20-14 shows the effects on the venous return curve caused by simultaneous changes in Psf and resistance to venous return, demonstrating that both these factors can operate simultaneously.

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 requirement 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.

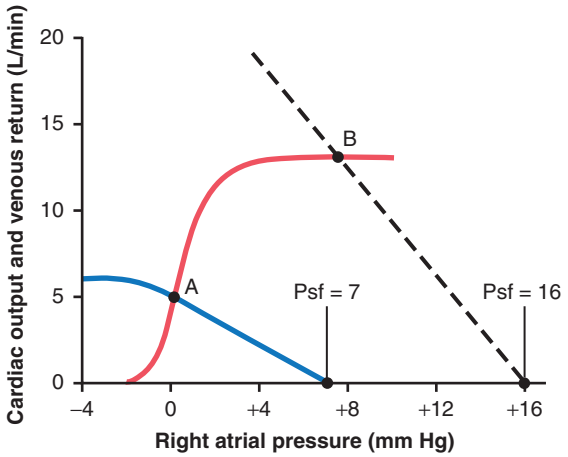

Figure 20-15. The two solid curves demonstrate an analysis of cardiac output and right atrial pressure when the cardiac output (*red line*) and venous return (*blue line*) curves are normal. Transfusion of blood equal to 20 percent of the blood volume causes the venous return curve to become the dashed curve; as a result, the cardiac output and right atrial pressure shift from point *A* to point *B*. Psf, mean systemic filling pressure.

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 ability 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 state of flow in the form of a venous return curve; and (3) "equate" these curves against each other, as shown in Figure 20-15.

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 20-15. Immediately upon infusing the large quantity of extra blood, the increased filling of the system causes the 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 20-15** 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.

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 Psf.*
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 Psf to return 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*, and (2) in the systemic circulation, it *increases the Psf* because of contraction of the peripheral vessels, especially the veins, and it *increases the resistance to venous return.*

In **Figure 20-16**, 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 Psf to 17 mm Hg (depicted by the point at which the venous return curve reaches the zero venous return level). 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,* until other compensatory effects occur within seconds or minutes to return cardiac output to nearly normal.

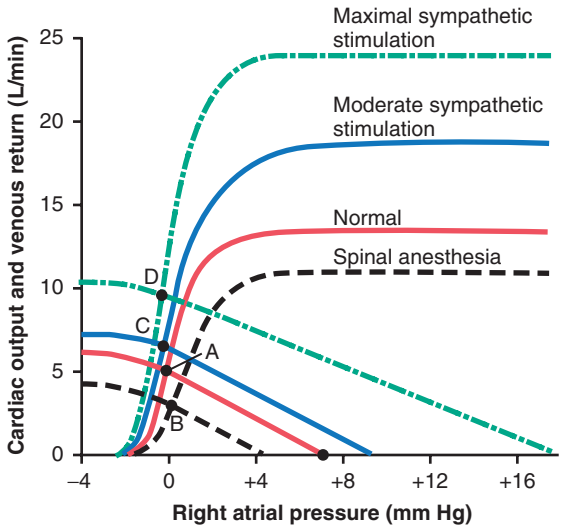

Figure 20-16. Analysis of the effect on cardiac output of (1) moderate sympathetic stimulation (from point *A* to point *C*), (2) maximal sympathetic stimulation (point D), and (3) sympathetic inhibition caused by total spinal anesthesia (point *B*). *(Modified from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)*

Effect of Sympathetic Inhibition on Cardiac Output. The sympathetic nervous system can be blocked by inducing *total spinal anesthesia* or by using a drug, such as *hexamethonium,* that blocks transmission of nerve signals through the autonomic ganglia. The lowermost curves in **Figure 20-16** show the effect of sympathetic inhibition caused by total spinal anesthesia, demonstrating that (1) the *Psf 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 20-17** shows various stages of circulatory changes that occur after opening a large AV 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*

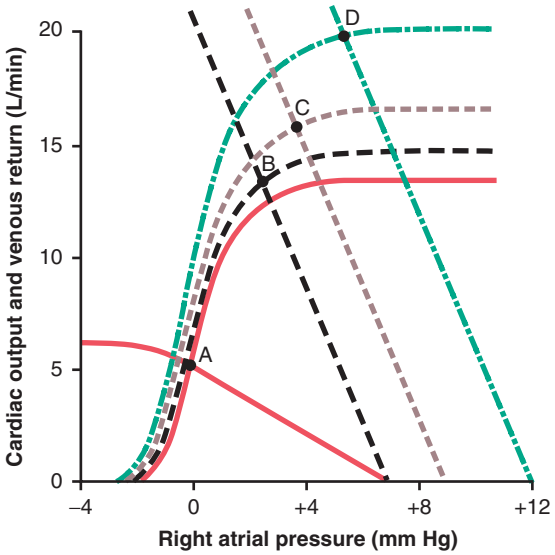

Figure 20-17. Analysis of successive changes in cardiac output and right atrial pressure in a human being after a large arteriovenous (AV) fistula is suddenly opened. The stages of the analysis, as shown by the equilibrium points, are *A,* normal conditions; *B,* immediately after opening the AV fistula; *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. *(Modified from Guyton AC, Jones CE, Coleman TB: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.)*

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 Psf (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 rises 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 transiently reduced kidney output of urine, causing salt and water retention. The Psf 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 that is now 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.

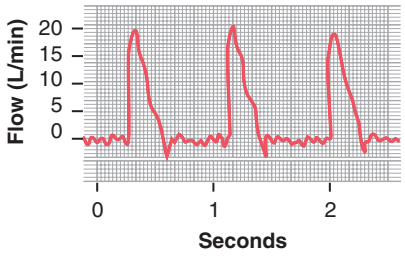

Figure 20-18. Pulsatile blood flow in the root of the aorta recorded using an electromagnetic flowmeter.

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 a flowmeter. An electromagnetic or ultrasonic flowmeter can also be placed on the aorta or pulmonary artery to measure cardiac output.

In humans, 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 MEASURED BY AN ELECTROMAGNETIC OR ULTRASONIC FLOWMETER

Figure 20-18 shows a recording in a dog of blood flow in the root of the aorta; this recording was 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 it reverses for a fraction of a second. This reverse flow causes the aortic valve to close and the flow to return to zero.

MEASUREMENT OF CARDIAC OUTPUT USING THE OXYGEN FICK PRINCIPLE

The Fick principle is explained by **Figure 20-19**. This figure shows that 200 milliliters of oxygen are being

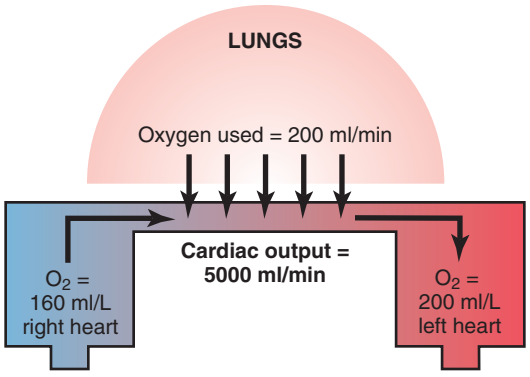

Figure 20-19. Fick principle for determining cardiac output.

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 ml/L of blood, whereas that leaving the left heart has an oxygen concentration of 200 ml/L 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:

$$\text{Cardiac output (L/min)} = \frac{O_2 \text{ absorbed per minute by the lungs (ml/min)}}{\text{Arteriovenous } O_2 \text{ difference (ml/L of blood)}}$$

In applying this Fick procedure for measuring cardiac output in humans, *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 pulmonary artery. *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 "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 indicator 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

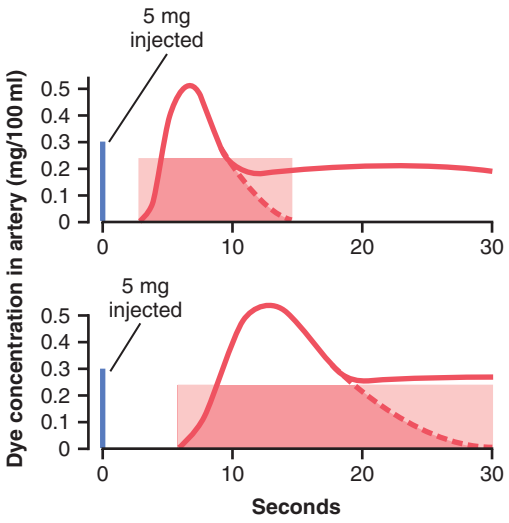

Figure 20-20. Extrapolated dye concentration curves used to calculate two separate cardiac outputs by the dilution method. (The rectangular areas are the calculated average concentrations of dye in the arterial blood for the durations of the respective extrapolated curves.)

Figure 20-20. In each of these instances, 5 milligrams of Cardiogreen dye were 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.

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 20-20**, this calculation 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 20-20**. To summarize, the cardiac output can be determined using the following formula:

$$\text{Cardiac output (ml/min)} = \frac{\text{Milligrams of dye injected} \times 60}{\begin{pmatrix}\text{Average concentration of dye}\\ \text{in each milliliter of blood}\\ \text{for the duration of the curve}\end{pmatrix} \times \begin{pmatrix}\text{Duration of}\\ \text{the curve}\\ \text{in seconds}\end{pmatrix}}$$

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