19

Integrated Control of the Cardiovascular System

LEARNING OBJECTIVES

Upon completion of this chapter, the student should be able to answer the following questions:

1. What are the four major factors that determine cardiac output? Which two of these factors are said to be "coupling factors," and what is the reason for that description?
2. What is a cardiac function curve, and how is it related to the Frank-Starling mechanism?
3. What is a vascular function curve, and how is it affected by changes in total peripheral resistance, blood volume, and venous tone?
4. Why does the operating point of the cardiovascular system occur at the intersection of the vascular and cardiac function curves?
5. How does evaluation of the cardiac function curve and the vascular function curve enable clinicians to determine the effect of changes in blood volume, vascular tone, and contractility on cardiac output?
6. What mechanisms in the central nervous system, heart, and systemic vasculature allow cardiac output to increase to the necessary levels during vigorous exercise?
7. What are the cardiovascular consequences of hemorrhage, and what are the compensatory mechanisms that tend to restore arterial pressure and cardiac output?

Regulation of Cardiac Output and Blood Pressure

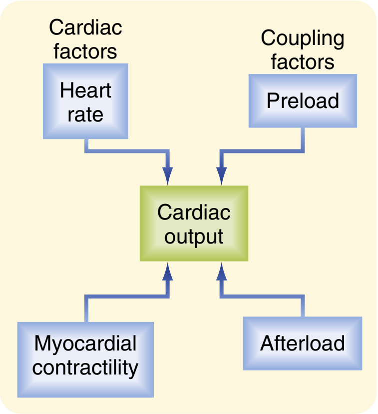
Four factors control cardiac output: heart rate (HR), myocardial contractility, preload, and afterload (Fig. 19.1). HR and myocardial contractility are strictly cardiac factors, although they are controlled by various neural and humoral mechanisms (see Chapters 17 and 18). Preload and afterload (Chapter 16) are factors that are mutually dependent on function of the heart and the vasculature and are important determinants of cardiac output. Preload and afterload are themselves determined by cardiac output and by certain vascular characteristics. Preload and afterload are called *coupling factors* because they constitute a functional coupling between the heart and blood vessels. To understand regulation of cardiac output, the nature of the coupling between the heart and the vascular system must be appreciated.

In this chapter, two kinds of graphed curves are used to analyze interactions between the cardiac and vascular components of the circulatory system. The first curve, the **cardiac function curve,** is an expression of the well-known **Frank-Starling relationship,** and it illustrates the dependence of cardiac output on preload (i.e., central venous or right atrial pressure) (Chapter 16). The cardiac function curve is a characteristic of the heart itself and is usually studied in hearts completely isolated from the rest of the circulation. Later in this chapter, this curve is discussed in association with the other characteristic curve, the **vascular function curve,** to analyze interactions between the heart and the vasculature. The vascular function curve defines the dependence of central venous pressure on cardiac output. This relationship depends only on several vascular system characteristics, including peripheral vascular resistance, arterial and venous compliance, and blood volume. The vascular function curve is entirely independent of the characteristics of the heart. Because of this independence, it can be derived experimentally even if a mechanical pump replaces the heart.

Vascular Function Curve

The vascular function curve defines the changes in central venous pressure (P_v) that are caused by changes in cardiac output. In this curve, P_v is the dependent variable (or response), and cardiac output is the independent variable (or stimulus). These variables are opposite those of the cardiac function curve, in which P_v (or preload) is the independent variable and cardiac output is the dependent variable.

The simplified model of the circulation shown in Fig. 19.2 helps explain how cardiac output determines the level of P_v. In this model, all essential components of the cardiovascular system have been lumped into four basic elements. The right and left sides of the heart, as well as the pulmonary vascular bed, constitute a **pump-oxygenator,** much like an artificial heart-lung machine used to perfuse



• **Fig. 19.1** The four factors (in *blue squares*) that determine cardiac output.

the body during open heart surgery. The high-resistance microcirculation is designated the **peripheral resistance.** Finally, the compliance of the system is subdivided into **arterial compliance (C_a)** and **venous compliance (C_v).** As defined in Chapter 17, the compliance (C) of a blood vessel is the change in volume (ΔV) that is accommodated in that vessel per unit change in transmural pressure (ΔP); that is,

Equation 19.1

$$C = \Delta V / \Delta P$$

Venous compliance is approximately 20 times greater than arterial compliance. In the example in Fig. 19.2, the ratio of C_v to C_a is set at 19:1 to simplify calculations.[a]

To show how a change in cardiac output causes an inverse change in P_v, the hypothetical model has certain characteristics that mimic those of an average adult (see Fig. 19.2*A*). The flow generated by the heart (i.e., cardiac output; Q_h) is 5 L/minute; mean arterial pressure (P_a) is 102 mm Hg; and P_v is 2 mm Hg. Peripheral resistance (R) is the ratio of the arteriovenous pressure difference ($P_a - P_v$) to flow (Q_r) through the resistance vessels; this ratio is equal to 20 mm Hg/L/minute.

An arteriovenous pressure difference of 100 mm Hg is sufficient to force a flow rate (Q_r) of 5 L/minute through a peripheral resistance of 20 mm Hg/L/minute (see Fig. 19.2*A*). Under equilibrium conditions, this flow rate (Q_r) is precisely equal to the flow rate (Q_h) pumped by the heart. From heartbeat to heartbeat, the volume of blood in the arteries (V_a) and the volume of blood in the veins (V_v) remain constant because the volume of blood transferred from the veins to the arteries by the heart is equal to the volume of blood that flows from the arteries through the resistance vessels and into the veins.

Effects of Cardiac Arrest on Arterial and Venous Pressure

Fig. 19.2*B* depicts the circulation at the very beginning of an episode of cardiac arrest; that is, $Q_h = 0$. In the instant immediately after arrest of the heart, the volume of blood in the arteries (V_a) and veins (V_v) has not had time to change appreciably. Because arterial pressure and venous pressure depend on V_a and V_v, respectively, these pressures are identical to the respective pressures in Fig. 19.2*A* (i.e., $P_a = 102$ and $P_v = 2$). This arteriovenous pressure gradient of 100 mm Hg forces a flow rate (Q_r) of 5 L/minute through the peripheral resistance of 20 mm Hg/L/minute. Thus although cardiac output (Q_h) at that point is 0 L/minute, the rate of flow through the microcirculation (Q_r) is 5 L/minute because the potential energy stored in the arteries by the preceding pumping action of the heart causes blood to be transferred from arteries to veins. This transfer occurs initially at the control (steady-state) rate, even though the heart can no longer transfer blood from the veins to the arteries.

As cardiac arrest continues, blood flow through the resistance vessels causes the blood volume in the arteries to decrease progressively and the blood volume in the veins to increase progressively at the same absolute rate. Because the arteries and veins are elastic structures, arterial pressure falls gradually, and the venous pressure rises gradually. This process continues until arterial and venous pressures become equal (see Fig. 19.2*C*). Once this condition is reached, the rate of flow (Q_r) from the arteries to the veins through the resistance vessels is 0 L/minute, as is Q_h.

When the effects of cardiac arrest reach this equilibrium state (see Fig. 19.2*C*), the pressure attained in the arteries and veins depends on the relative compliance of these vessels. If arterial compliance (C_a) and venous compliance (C_v) are equal, the decline in P_a is equal to the rise in P_v because the decrease in arterial volume would be equal to the increase in venous volume (according to the principle of conservation of mass). Both P_a and P_v would attain the average of their combined values in Fig. 19.2*A*; that is, $P_a = P_v = (102 + 2)/2 = 52$ mm Hg. However, C_a and C_v in a living person are not equal. Veins are much more compliant than arteries; the compliance ratio (C_v/C_a) is approximately 19, the ratio assumed for the model in Fig. 19.2. When the effects of cardiac arrest reach equilibrium in an intact subject, the pressure in the arteries and veins is much lower than the average value of 52 mm Hg that occurs when C_a and C_v are equal. Hence, transfer of blood from arteries to veins at equilibrium induces a fall in arterial pressure 19 times greater than the concomitant rise in venous pressure. As Fig. 19.2*C* shows, P_v would increase by 5 mm Hg (to 7 mm Hg), whereas P_a would fall by 95 (i.e., 19 × 5) mm Hg (to 7 mm Hg). This equilibrium pressure, which prevails in the absence of flow, is referred to as either **mean circulatory pressure** or **static pressure.** The pressure in the static system reflects the total blood volume in the system and the overall compliance of the system.

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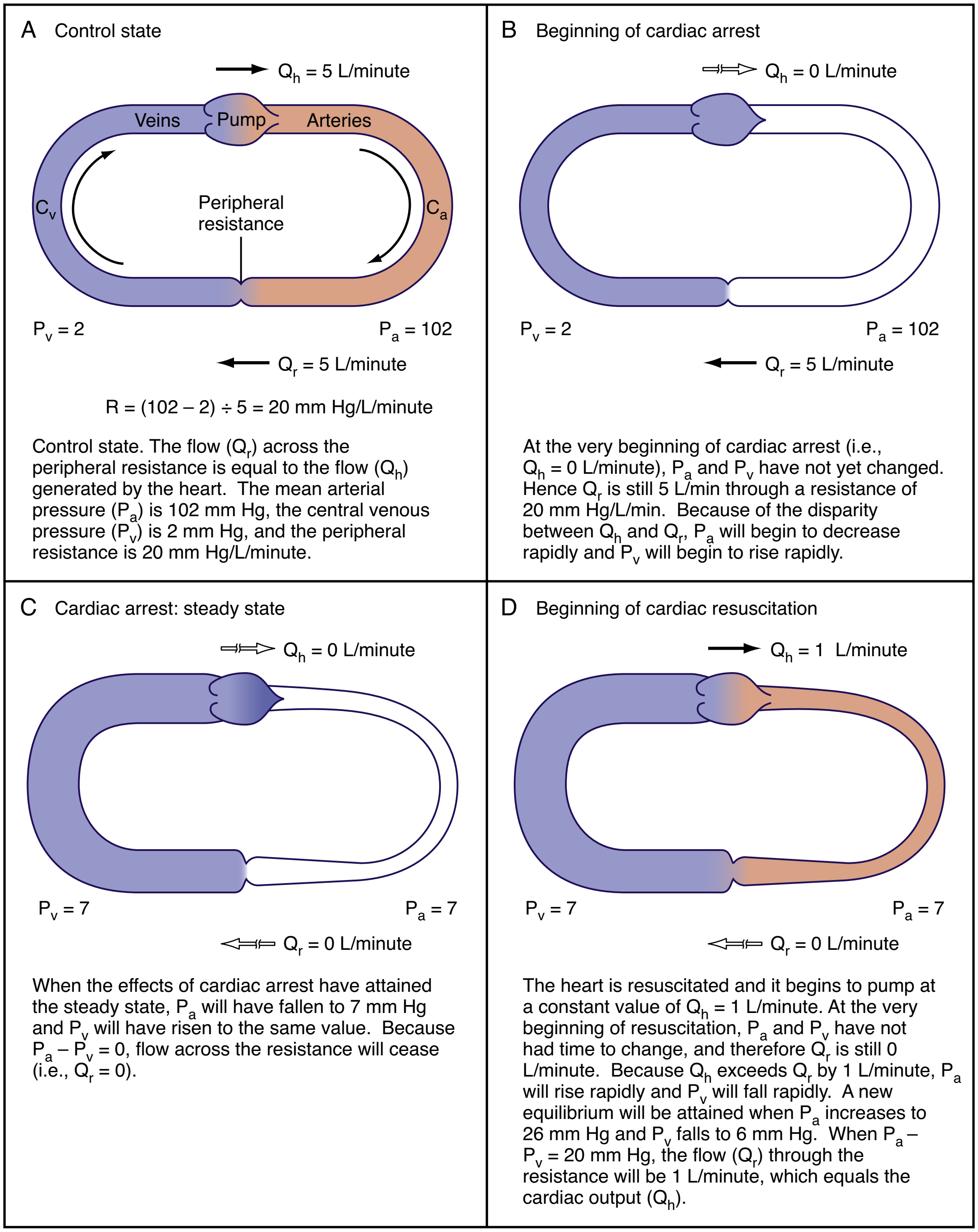
[a] Thus if it were necessary to add *x* mL of blood to the arterial system to produce a 1-mm Hg increase in arterial pressure, 19*x* mL of blood would need to be added to the venous system to raise venous pressure by the same amount.



Control state. The flow (Q_r) across the peripheral resistance is equal to the flow (Q_h) generated by the heart. The mean arterial pressure (P_a) is 102 mm Hg, the central venous pressure (P_v) is 2 mm Hg, and the peripheral resistance is 20 mm Hg/L/minute.

At the very beginning of cardiac arrest (i.e., Q_h = 0 L/minute), P_a and P_v have not yet changed. Hence Q_r is still 5 L/min through a resistance of 20 mm Hg/L/min. Because of the disparity between Q_h and Q_r, P_a will begin to decrease rapidly and P_v will begin to rise rapidly.

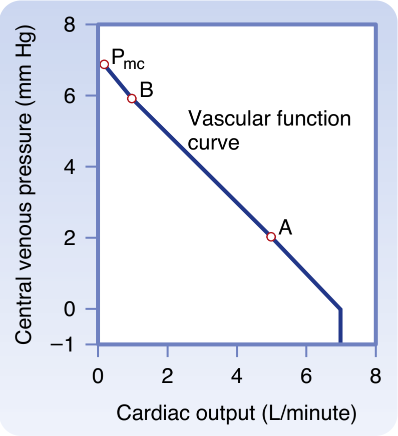
When the effects of cardiac arrest have attained the steady state, P_a will have fallen to 7 mm Hg and P_v will have risen to the same value. Because $P_a - P_v = 0$, flow across the resistance will cease (i.e., $Q_r = 0$).

The heart is resuscitated and it begins to pump at a constant value of Q_h = 1 L/minute. At the very beginning of resuscitation, P_a and P_v have not had time to change, and therefore Q_r is still 0 L/minute. Because Q_h exceeds Q_r by 1 L/minute, P_a will rise rapidly and P_v will fall rapidly. A new equilibrium will be attained when P_a increases to 26 mm Hg and P_v falls to 6 mm Hg. When $P_a - P_v$ = 20 mm Hg, the flow (Q_r) through the resistance will be 1 L/minute, which equals the cardiac output (Q_h).

• **Fig. 19.2 A** to **D,** Simplified model of the cardiovascular system, consisting of a pump, arterial compliance (C_a), peripheral resistance, and venous compliance (C_v).

The example of cardiac arrest aids in the understanding of the vascular function curve. The clinician can now begin to assemble a vascular function curve (Fig. 19.3). The independent variable (plotted along the x-axis) is cardiac output, and the dependent variable (plotted along the y-axis) is P_v. Two important points on this curve can be derived from the example in Fig. 19.2. One point (A in Fig. 19.3) represents the control state; that is, when cardiac output is 5 L/minute, P_v is 2 mm Hg. When the heart is arrested (cardiac output = 0), P_v becomes 7 mm Hg at equilibrium (see Fig. 19.2*C*); this pressure is the mean circulatory pressure.

The inverse relationship between P_v and cardiac output simply means that when cardiac output is suddenly decreased, the rate at which blood flows from arteries to veins through the capillaries is temporarily greater than the rate at which the heart pumps blood from the veins back into the arteries. During that transient period, a net volume of blood is transferred from arteries to veins; hence, P_a falls and P_v rises.



• **Fig. 19.3** Changes in central venous pressure produced by changes in cardiac output. The mean circulatory (or static) pressure (P_{mc}) is the equilibrium pressure throughout the cardiovascular system when cardiac output is 0. Points B and A represent the values of venous pressure at cardiac outputs of 1 and 5 L/minute, respectively.

Now suppose that cardiac output suddenly increases. This example illustrates how a third point (B in Fig. 19.3) on the vascular function curve is derived. Consider that the arrested heart is suddenly restarted and immediately begins pumping blood from the veins into the arteries at a rate of 1 L/minute (see Fig. 19.2*D*). When the heart first begins to beat, the arteriovenous pressure gradient is 0, and no blood is transferred from the arteries through the capillaries and into the veins. Thus when beating resumes, blood is depleted from the veins at the rate of 1 L/minute, and arterial blood volume is replenished from venous blood volume at that same absolute rate. Hence, P_v begins to fall and P_a begins to rise. Because of the difference in arterial and venous compliance, P_a rises at a rate 19 times faster than the rate at which P_v falls. The resultant arteriovenous pressure gradient causes blood to flow through the peripheral resistance vessels. If the heart maintains a constant output of 1 L/minute, P_a continues to rise and P_v continues to fall until the pressure gradient becomes 20 mm Hg. This gradient forces a rate of flow of 1 L/minute through a peripheral resistance of 20 mm Hg/L/minute. This gradient is achieved by a 19-mm Hg rise (to 26 mm Hg) in P_a and a 1-mm Hg fall (to 6 mm Hg) in P_v. This equilibrium value of P_v (6 mm Hg) for a cardiac output of 1 L/minute also appears on the vascular function curve of Fig. 19.3 (point B). The 1-mm Hg reduction in P_v reflects a net transfer of blood from the veins to the arteries of the circuit.

The reduction in P_v that can be evoked by a sudden increase in cardiac output is limited. At some critical maximal value of cardiac output, sufficient fluid is transferred from the veins to the arteries of the circuit for P_v to fall below ambient pressure. In a system of very distensible vessels, such as the venous system, the greater external pressure causes the vessels to collapse (see Chapter 17). This venous collapse impedes venous return to the heart. Hence, it limits the maximal value of cardiac output to 7 L/minute in this example (see Fig. 19.3), regardless of the capabilities of the pump.

Factors That Influence the Vascular Function Curve

Dependence of Venous Pressure on Cardiac Output

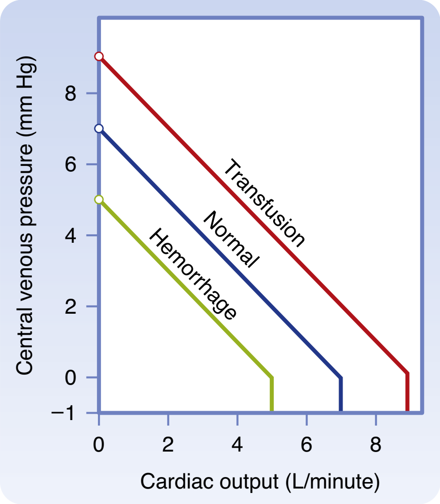
According to experimental and clinical observations, changes in cardiac output do indeed evoke the alterations in P_a and P_v that have been predicted by the simplified model in Fig. 19.2.

Blood Volume

The vascular function curve is affected by variations in total blood volume. During circulatory standstill (zero cardiac output), mean circulatory pressure depends only on total vascular compliance and blood volume. For a given vascular compliance, mean circulatory pressure is increased when blood volume is expanded **(hypervolemia)** and is decreased when blood volume is diminished **(hypovolemia)**. This relationship is illustrated by the y-axis intercepts in Fig. 19.4, in which mean circulatory pressure is 5 mm Hg after hemorrhage and 9 mm Hg after transfusion, in comparison with a value of 7 mm Hg at normal blood volume **(normovolemia or euvolemia)**.

IN THE CLINIC

Cardiac output may decrease abruptly when a major coronary artery suddenly becomes occluded. The **acute heart failure** that occurs as a result of **myocardial infarction** (death of myocardial tissue) is usually accompanied by a fall in arterial blood pressure and a rise in P_v. In Fig. 19.4 it is also apparent that the cardiac output at which $P_v = 0$ varies directly with blood volume. Therefore, the maximal value of cardiac output becomes progressively more limited as the total blood volume is reduced. However, the P_v at which the veins collapse (illustrated by the sharp change in slope of the vascular function curve) is not significantly altered by changes in blood volume. This pressure depends only on the ambient pressure surrounding the central veins. Ambient pressure is the pleural pressure in the thorax (see Chapter 21).



• **Fig. 19.4** Effects of increased blood volume *(transfusion curve)* and decreased blood volume *(hemorrhage curve)* on the vascular function curve. Similar shifts in the vascular function curve can be produced by increases and decreases, respectively, in venomotor tone.

Venomotor Tone

The effects of changes in venomotor tone on the vascular function curve closely resemble those of changes in blood volume. In Fig. 19.4, for example, the transfusion curve could also represent increased venomotor tone, whereas the hemorrhage curve could represent decreased tone. During circulatory standstill, for a given blood volume, the pressure within the vascular system rises as smooth muscle tension exerted within the vascular walls increases (these contractile changes in arteriolar and venous smooth muscle are under nervous and humoral control). The fraction of the blood volume located within the arterioles is very small, whereas the blood volume in the veins is large percentage of total blood volume (see Table 15.1). Thus changes in peripheral resistance (arteriolar tone) have no significant effect on mean circulatory pressure, but changes in venous tone can alter mean circulatory pressure appreciably. Hence, mean circulatory pressure rises with increased venomotor tone and falls with diminished venomotor tone.

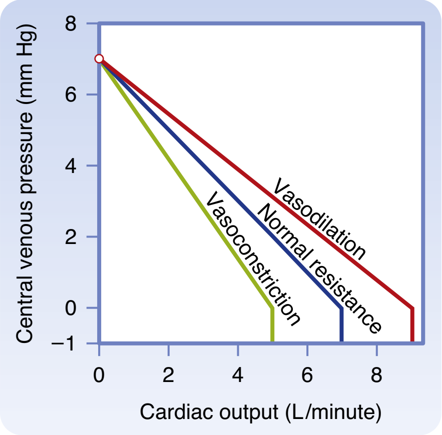
In experiments, the mean circulatory pressure attained approximately 1 minute after abrupt circulatory standstill is usually substantially above 7 mm Hg, even when blood volume is normal. The elevation to this pressure level is attributable to the generalized venoconstriction that is caused by cerebral ischemia, activation of chemoreceptors, and reduced excitation of baroreceptors. If resuscitation fails, this reflex response subsides as central nervous activity ceases, and mean circulatory pressure then usually falls to a value close to 7 mm Hg.

Blood Reservoirs

Venoconstriction is considerably greater in certain regions of the body than in others. In effect, vascular beds that undergo significant venoconstriction constitute blood reservoirs. The skin's vascular bed is one of the major blood reservoirs in humans. Blood loss evokes profound subcutaneous venoconstriction, which gives rise to the characteristically pale appearance of the skin in response to hemorrhage. Diversion of blood away from the skin frees several hundred milliliters of blood that can be perfused through more vital regions of the body. The vascular beds of the liver, lungs, and spleen are also important blood reservoirs. In humans, however, the volume changes in the spleen are considerably less extensive (see also the sections "Exercise" and "Hemorrhage").

Peripheral Resistance

The changes in the vascular function curve induced by alterations in arteriolar tone are depicted in Fig. 19.5. The amount of blood in the arterioles is small; these vessels contain only approximately 3% of total blood volume (see Chapter 15). Changes in the contractile state of arterioles do not significantly alter mean circulatory pressure. Thus vascular function curves that represent different peripheral resistances converge at a common point on the y-axis (see Fig. 19.5).



• **Fig. 19.5** Effects of arteriolar dilation and constriction on the vascular function curve.

P_v varies inversely with **total peripheral resistance (TPR)** when all other factors remain constant. Physiologically, the relationship between P_v and TPR can be explained as follows: If cardiac output is held constant, a sudden increase in TPR causes a progressively greater volume of blood to be retained in the arterial system. Blood volume in the arterial system continues to increase until P_a rises sufficiently to force a flow of blood equal to cardiac output through the resistance vessels. If total blood volume does not change, this increase in arterial blood volume is accompanied by an equivalent decrease in venous blood volume. Hence, an increase in TPR diminishes P_v proportionately. This relationship between TPR and P_v, together with the inability of peripheral resistance to affect mean circulatory pressure, accounts for the clockwise rotation of the vascular function curves in response to increased arteriolar constriction (see Fig. 19.5). Similarly, arteriolar dilation produces a counterclockwise rotation from the same vertical axis intercept. A higher maximal level of cardiac output is attainable when the arterioles are dilated than when they are constricted (see Fig. 19.5).

Interrelationships Between Cardiac Output and Venous Return

Cardiac output and venous return are tightly linked. Except for small, transient disparities, the heart cannot pump any more blood than is delivered to it through the venous system. Similarly, because the circulatory system is a closed circuit, venous return to the heart must equal cardiac output over any appreciable time interval. The flow around the entire closed circuit depends on the capability of the pump, the characteristics of the circuit, and the total fluid volume of the system.

Thus *cardiac output* and *venous return* are simply two terms for the flow around this closed circuit. Cardiac output is the volume of blood being pumped by the heart per unit time. Venous return is the volume of blood returning to the heart per unit time. At equilibrium, these two volumes are equal. In the following section, certain techniques of circuit analysis are discussed to provide some insight into the control of flow around the circuit.

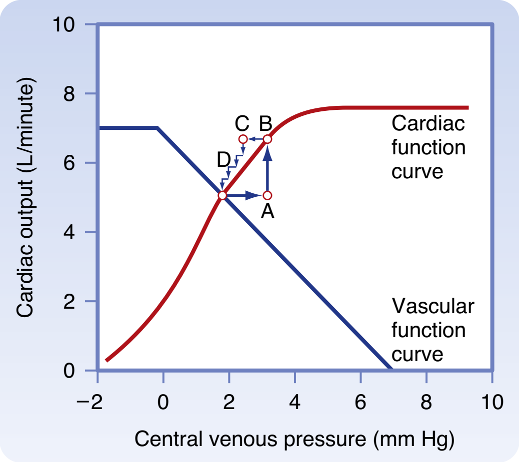
Relating the Cardiac Function Curve to the Vascular Function Curve

Coupling Between the Heart and the Vasculature

In accordance with the Frank-Starling law of the heart, cardiac output depends closely on right atrial (or central venous) pressure. Furthermore, right atrial pressure is approximately equal to right ventricular end-diastolic pressure because the normal tricuspid valve acts as a low-resistance junction between the right atrium and ventricle. Graphs of cardiac output as a function of P_v are called **cardiac function curves**; extrinsic regulatory influences may be expressed as shifts in such curves.

A typical cardiac function curve is plotted on the same coordinates as those for a normal vascular function curve in Fig. 19.6. The cardiac function curve is plotted according to the usual convention; that is, the independent variable (P_v) is plotted along the x-axis, and the dependent variable (cardiac output) is plotted along the y-axis. In accordance with the Frank-Starling mechanism, the cardiac function curve reveals that a rise in P_v increases cardiac output.

Conversely, the vascular function curve characterizes an inverse relationship between cardiac output and P_v; that is, a rise in cardiac output diminishes P_v. P_v is the dependent variable (or response) and cardiac output is the independent variable (or stimulus) for the vascular function curve. Therefore, to plot a vascular function curve in the conventional manner, P_v should be scaled along the y-axis and cardiac output along the x-axis.



• Fig. 19.6 Typical vascular and cardiac function curves plotted on the same coordinate axes. To plot both curves on the same graph, the x-axis and y-axis for the vascular function curves had to be switched; compare the assignment of axes with those in Figs. 19.3, 19.4, and 19.5. The coordinates of the equilibrium point, at the intersection of the cardiac and vascular function curves, represent the stable values of cardiac output and central venous pressure at which the system tends to operate. Any perturbation (e.g., a sudden increase in venous pressure to point A) institutes a sequence of changes in cardiac output and venous pressure that restore these variables to their equilibrium values.

To plot the cardiac and vascular function curves on the same set of axes requires a modification of the plotting convention for one of these curves. The convention for the vascular function curve is violated arbitrarily in this chapter. Note that the vascular function curve in Fig. 19.6 is intended to reflect how P_v (scaled along the x-axis) varies in response to a change in cardiac output (scaled along the y-axis).

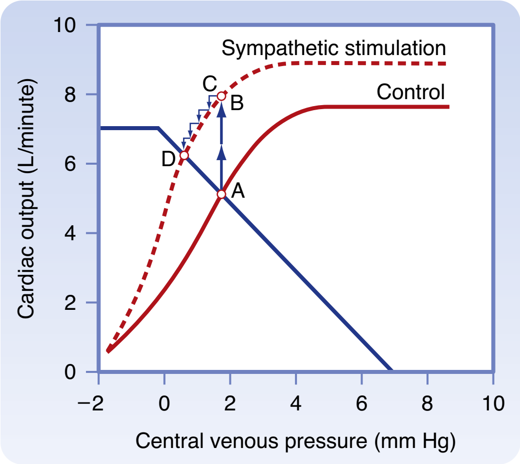
When the cardiovascular system is represented by a given pair of cardiac and vascular function curves, the intersection of these two curves defines the **equilibrium point** of that system. The coordinates of this equilibrium point represent the values of cardiac output and P_v at which the system tends to operate. Only transient deviations from such values of cardiac output and P_v are possible, as long as the given cardiac and vascular function curves characterize the system accurately.

The tendency to operate about this equilibrium point may best be illustrated by the response to a sudden change. Consider the changes caused by a sudden rise in P_v from the equilibrium point to point A in Fig. 19.6. This change in P_v might be caused by the rapid injection, during ventricular diastole, of a given volume of blood on the venous vessels of the circuit and simultaneous withdrawal of an equal volume from the arterial vessels of the circuit. Thus although P_v rises, total blood volume remains constant.

As defined by the cardiac function curve, this elevated P_v would increase cardiac output (from point A to point B in Fig. 19.6) during the next ventricular systole. The increased cardiac output would then cause the transfer of a net quantity of blood from the veins to the arteries of the circuit, with a consequent reduction in P_v. In one heartbeat, the reduction in P_v would be small (from point B to point C) because the heart would transfer only a fraction of the total venous blood volume to the arteries. As a result of this reduction in P_v, cardiac output during the very next beat diminishes (from point C to point D) by an amount dictated by the cardiac function curve. Because point C is still above the intersection point, the heart pumps blood from the veins to the arteries at a rate greater than that at which blood flows across the peripheral resistance from arteries to veins. Hence, P_v continues to fall. This process continues in diminishing steps until the point of intersection is reached. Only one specific combination of cardiac output and venous pressure—the equilibrium point, denoted by the coordinates of the point at which the curves intersect—satisfies the requirements of the cardiac and vascular function curves simultaneously. At the equilibrium point, cardiac output equals venous return, and the system is stable.

Myocardial Contractility

Combinations of cardiac and vascular function curves also help explain the effects of alterations in ventricular contractility on cardiac output and P_v. In Fig. 19.7, the lower cardiac function curve represents the control state,

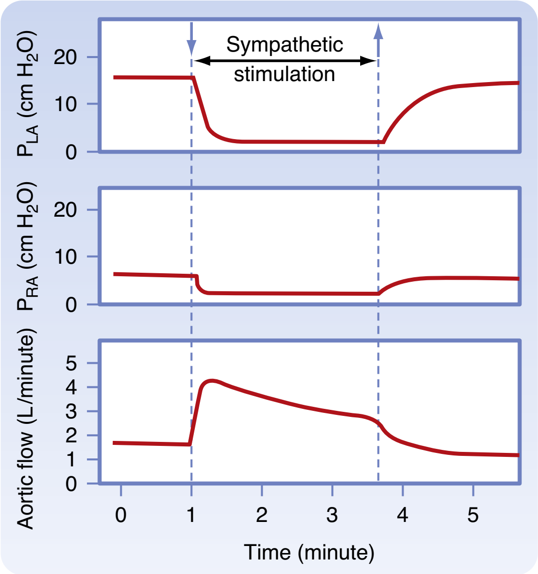


• **Fig. 19.7** Enhancement of myocardial contractility, as by stimulation of cardiac sympathetic nerves, causes the equilibrium values of cardiac output and central venous pressure (P_v) to shift from the intersection (point A) of the control vascular and cardiac function curves *(continuous curve)* to the intersection (point D) of the same vascular function curve with the cardiac function curve *(dashed curve)* that represents the response to sympathetic stimulation.

whereas the upper curve reflects the influence of increased myocardial contractility. This pair of curves is analogous to the ventricular function curves shown in Fig. 18.12. The enhanced ventricular contractility represented by the upper curve in Fig. 19.7 can be produced by electrical stimulation of the cardiac sympathetic nerves. When the effects of such neural stimulation are restricted to the heart, the vascular function curve is unaffected. Therefore, only one vascular function curve is needed for this hypothetical intervention (see Fig. 19.7).

During the control state of the model, the equilibrium values for cardiac output and P_v are designated by point A in Fig. 19.7. Cardiac sympathetic nerve stimulation abruptly raises cardiac output to point B because of the enhanced myocardial contractility. However, this high cardiac output causes an increase in the net transfer of blood from the veins to the arteries of the circuit, and as a consequence, P_v subsequently begins to fall (to point C). The reduction in P_v then leads to a small decrease in cardiac output. However, cardiac output is still sufficiently high to effect the net transfer of blood from the veins to the arteries of the circuit. Thus both P_v and cardiac output continue to fall gradually until a new equilibrium point (point D) is reached. This equilibrium point is located at the intersection of the vascular function curve and the new cardiac function curve. In Fig. 19.7, point D lies above and to the left of the control equilibrium point (point A) and indicates that sympathetic stimulation can evoke greater cardiac output despite the lower level of P_v.

The biological response to enhancement of myocardial contractility is mimicked by the hypothetical change predicted by the model in this chapter. As depicted in Fig. 19.8, sympathetic nerves innervating the heart are stimulated during the time denoted by the double-headed arrow.

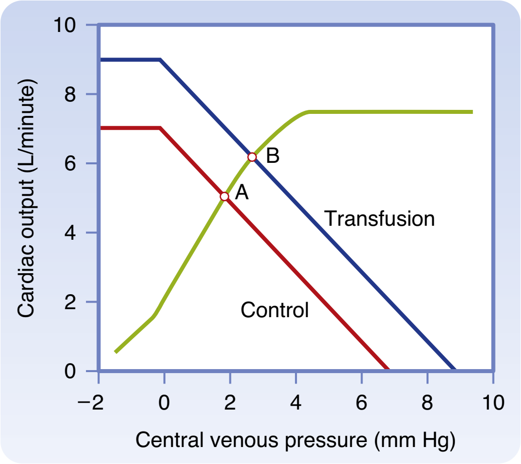


• **Fig. 19.8** During electrical stimulation of the cardiac sympathetic nerve fibers, aortic blood flow (cardiac output) increased, whereas pressures in the left atrium (P_{LA}) and right atrium (P_{RA}) diminished. These data conform to the conclusions derived from Fig. 19.7, in which the equilibrium values of cardiac output and venous pressure are observed to shift from point A to point D (i.e., cardiac output increased, but central venous pressure decreased) during cardiac sympathetic nerve stimulation. (Redrawn from Sarnoff SJ, et al. *Circ Res.* 1960;8:1108.)

During neural stimulation, cardiac output (aortic flow) rises quickly to a peak value and then falls gradually to a steady-state value significantly higher than the control level. The increase in aortic flow is accompanied by reductions in right and left atrial pressures.

Blood Volume

Changes in blood volume do not directly affect myocardial contractility, but they do influence the vascular function curve in the manner shown in Fig. 19.4. Thus to understand how changes in blood volume affect cardiac output and P_v, the appropriate cardiac function curve is plotted along with the vascular function curves that represent the control and experimental states (Fig. 19.9). When blood volume is increased by a blood transfusion, the equilibrium point (point B in Fig. 19.9), which denotes the values of cardiac output and P_v after transfusion, lies above and to the right of the control equilibrium point (point A). Thus transfusion increases both cardiac output and P_v. Hemorrhage causes the opposite effect. Mechanistically, the change in ventricular filling pressure (P_v) evoked by a given change in blood volume alters cardiac output by changing the sensitivity of the contractile proteins to the prevailing concentration of intracellular Ca^{++} (see Chapter 18). For reasons explained earlier, pure increases or decreases in venomotor tone elicit responses that are like those evoked by increases or decreases, respectively, in total blood volume.



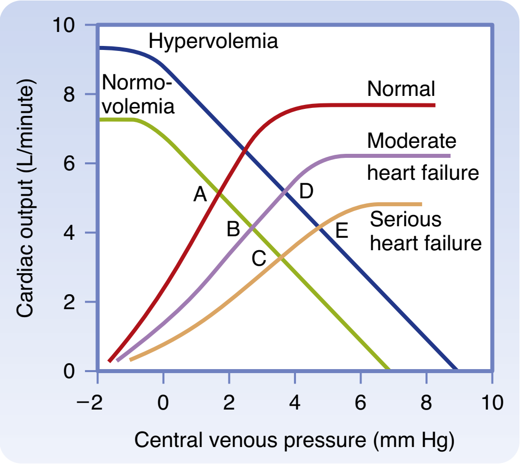
• **Fig. 19.9** After a blood transfusion, the vascular function curve is shifted to the right. Therefore, both cardiac output and venous pressure are increased, as denoted by translocation of the equilibrium point from point A to point B.

IN THE CLINIC

Heart failure is a general term that applies to conditions in which the pumping capability of the heart is impaired to the extent that the tissues of the body are not adequately perfused. In heart failure, myocardial contractility is impaired. Heart failure may be acute or chronic. Consequently, in a graph of cardiac and vascular function curves, the cardiac function curve is shifted downward and to the right, as depicted in Fig. 19.10.

Acute heart failure may be caused by toxic concentrations of drugs or by certain pathological conditions such as coronary artery occlusion. In acute heart failure, blood volume does not change immediately. In Fig. 19.10, therefore, the equilibrium point shifts from the intersection (point A) of the normal curves to the intersection (point B or point C) of the normal vascular function curve.

Chronic heart failure may occur in conditions such as essential hypertension or ischemic heart disease. In chronic heart failure, both the cardiac function and vascular function curves shift. The vascular function curve shifts because of an increase in blood volume caused in part by fluid retention by the kidneys. The fluid retention is related to the concomitant reduction in glomerular filtration rate and the decreased renal excretion of NaCl and water (see also Chapter 35). The resultant hypervolemia is reflected by a rightward shift of the vascular function curve, as shown in Fig. 19.10. Hence, with moderate degrees of heart failure, P_v is elevated, but cardiac output may be normal (point D). With more severe degrees of heart failure, P_v is still elevated, but cardiac output is subnormal (point E).

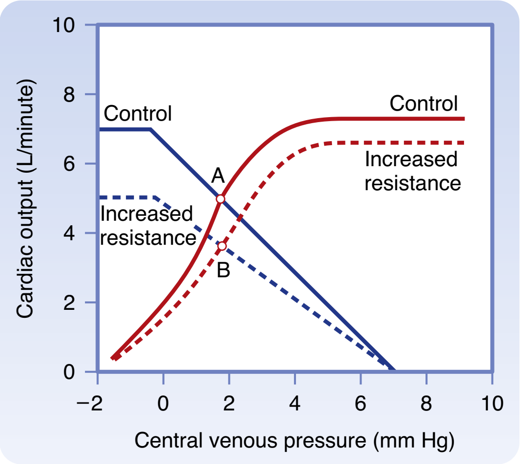


• **Fig. 19.10** Moderate or severe heart failure shifts the cardiac function curves downward and to the right. Before changes in blood volume, cardiac output decreases and central venous pressure rises (from control equilibrium point A to point B or point C). After the increase in blood volume that usually occurs in heart failure, the vascular function curve is shifted to the right. Hence, central venous pressure may be elevated with no reduction in cardiac output (point D) or, in severe heart failure, with some reduction in cardiac output (point E).

Peripheral Resistance

Analysis of the effects of changes in peripheral resistance on cardiac output and P_v is complex because both the cardiac and vascular function curves shift. When peripheral resistance increases (Fig. 19.11), the vascular function curve is rotated counterclockwise, but it converges on the same P_v axis intercept as the control curve does. Note that vasoconstriction causes a counterclockwise rotation of the vascular function curve in Fig. 19.11 but a clockwise rotation in Fig. 19.5. The direction of rotation differs because the axes for the vascular function curves were switched in these two figures, as explained earlier. The cardiac function curve in Fig. 19.11 is also shifted downward because at any given P_v, the heart is able to pump less blood against the greater cardiac afterload imposed by the increased peripheral resistance. Because both curves in Fig. 19.11 are displaced downward, the new equilibrium point (point B) is below the control point (point A); that is, an increase in peripheral resistance diminishes cardiac output.

Whether point B falls directly below point A or lies slightly to the right or left of it depends on the magnitude of the shift in each curve. For example, if a given increase in



• **Fig. 19.11** An increase in peripheral resistance shifts the cardiac and vascular function curves downward. At equilibrium, cardiac output is less (point B) when peripheral resistance is high than when peripheral resistance is normal (point A).

peripheral resistance shifts the vascular function curve more than it does the cardiac function curve, equilibrium point B is below and to the left of point A; that is, both cardiac output and P_v diminish. Conversely, if the cardiac function curve is displaced more than the vascular function curve, point B falls below and to the right of point A; that is, cardiac output decreases, but P_v rises.

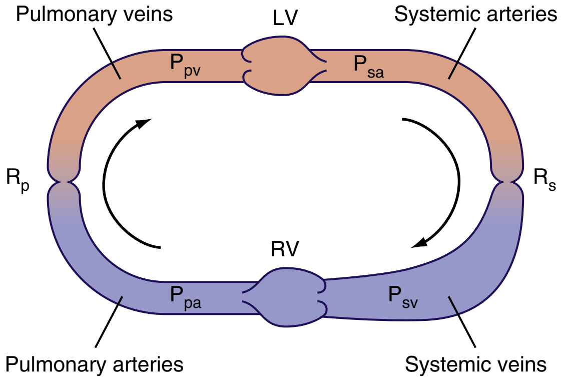
A More Complete Theoretical Model: The Two-Pump System

The preceding discussion shows that the interrelationships between cardiac output and P_v are complex, even in an oversimplified circulation model that includes only one pump and just the systemic circulation. In reality, the cardiovascular system includes the systemic and pulmonary circulations and two pumps: the left and right ventricles. Thus the interrelationships among ventricular output, arterial pressure, and atrial pressure are much more complex.

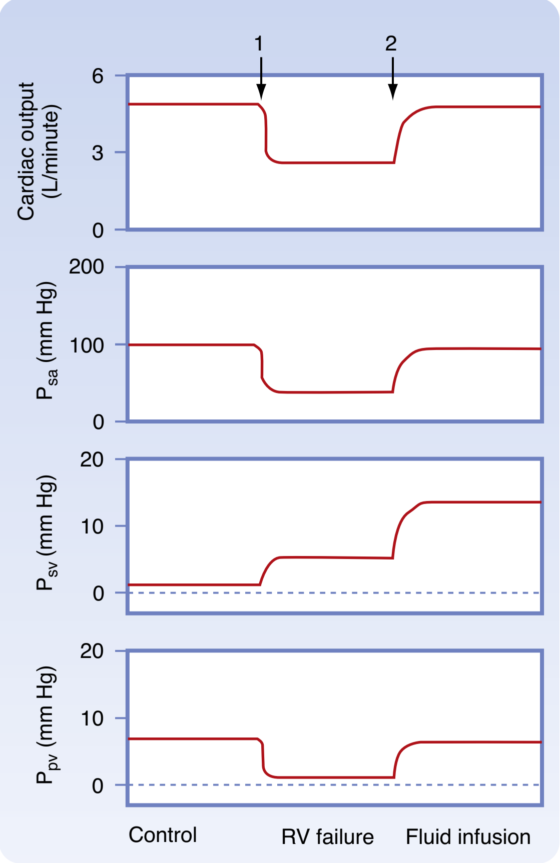
Fig. 19.12 depicts a more complete (but still oversimplified) cardiovascular system model that has two pumps in series (the left and right ventricles) and two vascular beds in series (the systemic and pulmonary vasculature). The series arrangement requires that the flow pumped by the two ventricles be virtually equal to each other over any substantial period; otherwise, all the blood would ultimately accumulate in one or the other of the vascular systems. Because the cardiac function curves for the two ventricles differ substantially, the filling (atrial) pressures for the two ventricles must differ appropriately to ensure equal stroke volumes (SVs) (see Fig. 18.13).

IN THE CLINIC

Any change in contractility that affects the two ventricles differently alters the distribution of blood volume in the two vascular systems. If a coronary artery to the left ventricle becomes occluded, left ventricular contractility is impaired, and **acute left ventricular failure** ensues. In the instant after occlusion, left atrial pressure does not change, and the left ventricle begins to pump at a diminished rate of flow. If the right ventricle is not affected by the acute coronary artery occlusion, the right ventricle initially continues to pump the normal flow. The disparate right and left ventricular outputs result in a progressive increase in left atrial pressure and a progressive decrease in right atrial pressure. Therefore, left ventricular output increases toward the normal value, and right ventricular output falls below the normal value. This process continues until the outputs of the two ventricles again become equal. At this new equilibrium, the output of the two ventricles is subnormal. The elevation in left atrial pressure is accompanied by an equal elevation in pulmonary venous pressure, which can have serious clinical consequences. The high pulmonary venous pressure can increase lung stiffness and lead to respiratory distress by increasing the mechanical work of pulmonary ventilation (see Chapter 22). Furthermore, the high pulmonary venous pressure causes an elevation in the hydrostatic pressure in the pulmonary capillaries and may lead to the transudation of fluid from the pulmonary capillaries to the pulmonary interstitium or into the alveoli **(pulmonary edema)**, which may be lethal.



• **Fig. 19.12** Simplified model of the cardiovascular system that consists of the left ventricle *(LV)* and right ventricle *(RV)*, systemic vascular resistance (R_s) and pulmonary vascular resistance (R_p), systemic arterial and venous compliance, and pulmonary arterial and venous compliance. P_{sa} and P_{sv} are the pressures in the systemic arteries and veins, respectively; P_{pa} and P_{pv} are the pressures in the pulmonary arteries and veins, respectively.



• **Fig. 19.13** Changes in cardiac output, systemic arterial pressure (P_{sa}), systemic venous pressure (P_{sv}), and pulmonary venous pressure (P_{pv}) evoked by simulated right ventricular *(RV)* failure and by simulated infusion of fluid in the circulatory model shown in Fig. 19.12. At *arrow 1,* the pumping action of the right ventricle was discontinued (simulated RV failure), and the right ventricle served only as a low-resistance conduit. At *arrow 2,* the fluid volume in the system was expanded, and the RV continued to serve only as a conduit. (Modified from Furey SA, et al. *Am Heart J.* 1984;107:404.)

Two basic principles to remember about ventricular function are that (1) the left ventricle pumps blood through the systemic vasculature and (2) the right ventricle pumps blood through the pulmonary vasculature. However, these principles do not necessarily imply that both ventricles are essential to perfuse the systemic and pulmonary vascular beds adequately. To better understand the relationships between the two ventricles and the two vascular beds, the right ventricular function is examined in more detail as follows.

In the circulatory system model shown in Fig. 19.12, consider the hemodynamic consequences that would occur if the right ventricle suddenly ceased its pump function but instead served merely as a passive, low-resistance conduit between the systemic veins and the pulmonary arteries. Under these conditions, the only functional pump would be the left ventricle, which would then be required to pump blood through both the systemic and pulmonary resistances (for the purposes of this discussion, consider the resistance to the flow of blood through the inactive right ventricle to be negligible).

Normally, pulmonary vascular resistance is approximately 10% as great as systemic vascular resistance. Because the two resistances are in series with one another, total resistance would be 10% greater than systemic resistance alone (see Chapter 17). In a normal cardiovascular system, a 10% increase in systemic vascular resistance would increase P_a (and hence left ventricular afterload) by approximately 10%. This increase would not drastically affect left ventricular function. Under certain conditions, however, this increase in P_a could significantly alter the function of the cardiovascular system. If the 10% increase in total resistance is achieved by adding a small degree of resistance (i.e., pulmonary vascular resistance) to that of the much larger systemic resistance, and if the pulmonary vascular resistance is separated from the systemic resistance by a large degree of compliance (the combined systemic venous and pulmonary arterial compliance), the 10% increase in total resistance could drastically impair operation of the cardiovascular system.

The simulated effects of inactivating the pumping action of the right ventricle in a hydraulic analog of the circulatory system are shown in Fig. 19.13. In the model, the right and left ventricles generate cardiac outputs that vary directly with their respective filling pressures. Under control conditions (when the right ventricle is functioning normally), the outputs of the left and right ventricles are equal (5 L/minute). The right ventricular pumping action causes the pressure in the pulmonary artery (not shown) to exceed the pressure in the pulmonary veins (P_{pv}) by an amount that forces fluid through the pulmonary vascular resistance at a rate of 5 L/minute. When the right ventricle ceases pumping (arrow 1 in Fig. 19.13), the systemic venous and pulmonary arterial systems, along with the right ventricle itself, become a common passive conduit with a large compliance. When the right ventricle ceases to transfer blood actively from the systemic veins to the pulmonary arteries, pulmonary arterial pressure (P_{pa}) decreases rapidly (not shown) and systemic venous pressure (P_{sv}) rises rapidly to a common value (≈5 mm Hg). At this low pressure, however, fluid flows from the pulmonary arteries to the pulmonary veins at a greatly reduced rate.

At the start of right ventricular arrest, the left ventricle is pumping fluid from the pulmonary veins to the systemic arteries at the control rate of 5 L/minute, which greatly exceeds the rate at which blood returns to the pulmonary veins once the right ventricle ceases to operate. Hence, pulmonary venous pressure (P_{pv}) drops sharply. Because pulmonary venous pressure is the preload for the left ventricle, left ventricular (cardiac) output drops abruptly as well and attains a steady-state value of approximately 2.5 L/minute. This effect in turn leads to a rapid reduction in systemic arterial pressure (P_{sa}). In short, stoppage of right ventricular pumping markedly curtails cardiac output, systemic arterial pressure, and pulmonary venous pressure and raises systemic venous pressure moderately (see Fig. 19.13).

Most of the hemodynamic problems induced by inactivation of the right ventricle can be reversed by an increase in the fluid (blood) volume of the system (arrow 2 in Fig. 19.13). If fluid is added until pulmonary venous pressure (left ventricular preload) is raised to its control value, cardiac output and systemic arterial pressure are restored almost to normal, but systemic venous pressure is abnormally elevated. If left ventricular function is normal, adding a normal left ventricular preload evokes normal left ventricular output. The 10% increase in peripheral resistance caused by adding the pulmonary vascular resistance to that of the systemic vascular resistance does not impose a serious burden on left ventricular pumping capacity.

When the right ventricle is inoperative, however, pulmonary blood flow is not normal unless the usual pulmonary arteriovenous pressure gradient (≈10–15 mm Hg) prevails. Hence, systemic venous pressure (P_{sv}) must exceed pulmonary venous pressure (P_{pv}) by this amount. Maintenance of high systemic venous pressure may lead to the accumulation of tissue fluid (edema) in dependent regions of the body, a characteristic finding in patients with right ventricular heart failure.

With this information, the principal function of the right ventricle may be characterized as follows. From the viewpoint of providing sufficient flow of blood to all tissues in the body, the left ventricle alone can carry out this function. Operation of the two ventricles in series is not essential

IN THE CLINIC

Clinically, **right ventricular heart failure** may be caused by occlusive disease predominantly of the coronary vessels to the right ventricle. These vessels are affected much less commonly than the vessels to the left ventricle. The major hemodynamic effects of acute right-sided heart failure are pronounced reductions in cardiac output and arterial blood pressure, and the principal treatment is infusion of blood or plasma. Bypass of the right ventricle (by anastomosis of the right atrium to the pulmonary artery) may be performed surgically in patients with certain **congenital cardiac defects,** such as severe narrowing of the tricuspid valve or maldevelopment of the right ventricle. The effects of acute right-sided heart failure or right ventricular bypass are directionally similar to those predicted previously from analysis of the model shown in Fig. 19.13.

to provide adequate blood flow to the tissues. The crucial function of the right ventricle is to prevent the rise in systemic venous (and pulmonary arterial) pressure that would be required to force the normal cardiac output through the pulmonary vascular resistance. A normal right ventricle, by preventing an abnormal rise in systemic venous pressure, prevents the development of extensive edema in dependent regions of the body.

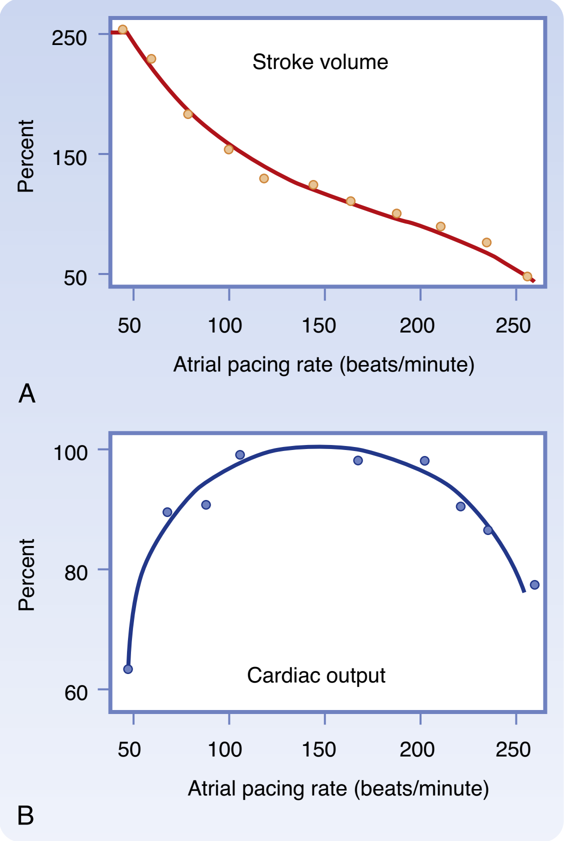
Role of the Heart Rate in Control of Cardiac Output

Cardiac output is the product of SV and HR. Analysis of the control of cardiac output has thus far been restricted to the control of SV, and the role of HR has not been considered. Analysis of the effect of a change in HR on cardiac output is complex because a change in HR alters the other three factors (preload, afterload, and myocardial contractility) that determine SV (see Fig. 19.1). An increase in HR, for example, shortens the duration of diastole. Hence, ventricular filling is diminished; that is, preload is reduced. If an increase in HR altered cardiac output, arterial pressure would change; that is, afterload would be altered. A rise in HR would increase the net influx of Ca^{++} per minute into myocardial cells (see also Chapter 18), and this influx would enhance myocardial contractility.

The effects of changes in HR on cardiac output have been studied extensively, and the results are similar to those shown in Fig. 19.14. As atrial pacing frequency is gradually increased, SV progressively diminishes (see Fig. 19.14*A*). The decrease in SV is caused by the reduced time for ventricular filling. The change in SV is not inversely proportional to the change in HR because the direction of the change in cardiac output (Q_h) is markedly influenced by the actual HR (see Fig. 19.14*B*). For example, as pacing frequency is increased from 50 to 100 beats/minute, the increase in HR augments Q_h. Because Q_h = SV × HR, the decrease in SV over this frequency range must be proportionately less than the increase in HR.

Over the frequency range from approximately 100 to 200 beats/minute, however, cardiac output is not affected significantly by changes in pacing frequency (see Fig. 19.14*B*). Hence, as pacing frequency is increased, the decrease in SV must be approximately equal to the increase in HR. In addition, generalized vascular autoregulation tends to keep tissue blood flow constant (see also Chapter 17). This adaptation leads to changes in preload and afterload that also keep cardiac output nearly constant.

Moreover, at excessively high pacing frequencies (above 200 beats/minute; see Fig. 19.14), further increases in HR decrease cardiac output. Therefore, the induced decrease in SV must have exceeded the increase in HR at this high range of pacing frequencies. At such high pacing frequencies, the ventricular filling time is so severely restricted that compensation is inadequate, and cardiac output decreases sharply. Although the relationship of cardiac output to HR is characteristically that of an inverted U in the general population, the relationship varies quantitatively among subjects and among physiological states.



• **Fig. 19.14** Changes in stroke volume **(A)** and cardiac output **(B)** induced by changes in the rate of atrial pacing. (Redrawn from Kumada M, et al. *Jpn J Physiol.* 1967;17:538.)

Strong correlations between HR and cardiac output must be interpreted cautiously. In people who are exercising, for example, cardiac output and HR usually increase proportionately, and SV may remain constant or increase only slightly (see the later section “Exercise”). It is tempting to conclude that the increase in cardiac output during exercise must be caused solely by the observed increase in HR. However, Fig. 19.14 shows that over a wide range of HRs, a change in HR may have little influence on cardiac output. The principal increase in cardiac output during exercise must therefore be attributed to other factors. Such ancillary factors include the pronounced reduction in peripheral vascular resistance because of the vasodilation in the active skeletal muscles and the increased contractility of cardiac muscle associated with the generalized increase in sympathetic neural activity. Nevertheless, the increase in HR is still an important factor. Abundant data show that if the HR cannot increase normally during exercise, the augmentation in cardiac output and the capacity for exercise are severely limited. Because SV changes only slightly during exercise, the increase in HR may play an important permissive role in augmenting cardiac output during physical exercise.

IN THE CLINIC

The characteristic relationship between cardiac output and heart rate explains the urgent need of treatment by patients who have excessively slow or excessively fast heart rates. Profound **bradycardia** (slow rate) may occur as a result of a very slow sinus rhythm in patients with **sick sinus syndrome** or as a result of a slow idioventricular rhythm in patients with **complete atrioventricular block.** In either rhythm disturbance, the capacity of the ventricles to fill during prolonged diastole is limited (often by the noncompliant pericardium). Hence, cardiac output usually decreases substantially because the very slow heart rate cannot be counterbalanced by a sufficiently large stroke volume. As a consequence, such bradycardia often necessitates the implantation of an artificial pacemaker. In patients with **supraventricular** or **ventricular tachycardia,** excessively high heart rates frequently necessitate emergency treatment because in such patients, cardiac output may be critically low, and the filling time is so restricted at very high heart rates that even small additional reductions in filling time cause disproportionately severe reductions in filling volume. Slowing the heart rate to a more normal rhythm can generally be accomplished pharmacologically, but electrical cardioversion may be required in emergencies (see Chapter 16).

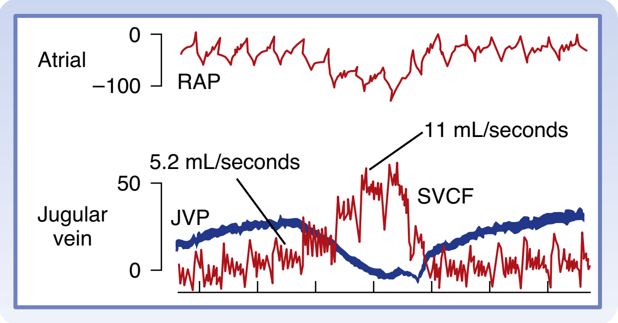
Ancillary Factors That Affect the Venous System and Cardiac Output

In earlier sections of this chapter, the descriptions of the interrelationships between P_v and cardiac output were simplified by restricting the discussion to the effects evoked by individual variables. However, because the cardiovascular system is regulated by so many feedback control loops, its responses are rarely simple. A change in blood volume, for example, not only affects cardiac output directly through the Frank-Starling mechanism but also triggers reflexes that alter other aspects of cardiac function (such as the HR, atrioventricular conduction, and myocardial contractility) and other characteristics of the vascular system (such as peripheral resistance and venomotor tone). Several other factors, especially gravity (see Chapter 17) and respiration, also regulate cardiac output.

Circulatory Effects of Respiratory Activity

The normal, periodic activity of the respiratory muscles causes rhythmic variations in vena caval flow (Fig. 19.15). During respiration, the reduction in intrathoracic pressure is transmitted to the lumens of the thoracic blood vessels. The reduction in P_v during inspiration increases the pressure gradient between extrathoracic and intrathoracic veins. The consequent acceleration in venous return to the right atrium is shown in Fig. 19.15 as an increase in superior vena caval blood flow from 5.2 mL/second during expiration to 11 mL/second during inspiration.

The exaggerated reduction in intrathoracic pressure achieved by a strong inspiratory effort against a closed glottis (called **Müller's maneuver**) does not increase venous return proportionately. The extrathoracic veins collapse near their entry into the chest when their internal pressures fall below the ambient level. As the veins collapse, flow into the chest momentarily stops. The cessation of flow causes pressure upstream to rise, which forces the collapsed segment to reopen.



• **Fig. 19.15** During a normal inspiration, intrathoracic pressure, right atrial pressure *(RAP)*, and jugular venous *(JVP)* pressure decrease, and flow in the superior vena cava *(SVCF)* increases (from 5.2 to 11 mL/second). All pressures are given in mm H_2O. Femoral arterial pressure (not shown) did not change substantially during the normal inspiration.

During normal expiration, flow into the central veins decelerates. However, the mean rate of venous return during normal respiration exceeds the flow during a brief period of **apnea** (cessation of respiration). Hence, normal inspiration apparently facilitates venous return more than normal expiration impedes it. In part, venous return is facilitated by the valves in the veins of the extremities. These valves prevent any reversal of flow during expiration. Thus the respiratory muscles and venous valves constitute an auxiliary pump for venous return.

IN THE CLINIC

The dramatic increase in intrathoracic pressure induced by coughing constitutes an auxiliary pumping mechanism for the blood despite its concurrent tendency to impede venous return. Certain diagnostic procedures, such as coronary angiography or electrophysiological testing of cardiac function, increase the risk for ventricular fibrillation; therefore, patients undergoing such procedures are trained to cough rhythmically on command during the study. If ventricular fibrillation does occur, each cough can generate substantial increases in arterial blood pressure, and enough cerebral blood flow may be promoted to sustain consciousness. The cough raises intravascular pressure equally in the intrathoracic arteries and veins. Blood is propelled through the extrathoracic tissues because the increased pressure is transmitted to the extrathoracic arteries but not to the extrathoracic veins because the venous valves prevent backward flow from the intrathoracic to the extrathoracic veins.

In most forms of artificial respiration (mouth-to-mouth resuscitation, mechanical respiration), endotracheal pressure above atmospheric pressure is used to inflate the lungs, and expiration occurs by passive recoil of the thoracic cage (see Chapter 21). Thus lung inflation is accompanied by an appreciable rise in intrathoracic pressure. Vena caval flow decreases sharply during the phase of positive-pressure lung inflation when the endotracheal pressure progressively rises. When negative endotracheal pressure is used to facilitate deflation, vena caval flow accelerates more than when the lungs are allowed to deflate passively.

Sustained expiratory efforts increase intrathoracic pressure and thus impede venous return. Straining against a closed glottis **(Valsalva's maneuver)** regularly occurs during coughing, defecation, and heavy lifting. Intrathoracic pressures in excess of 100 mm Hg have been recorded in trumpet players, and pressures higher than 400 mm Hg have been observed during paroxysms of coughing. Such increases in pressure are transmitted directly to the lumens of the intrathoracic arteries. After coughing stops, arterial blood pressure may fall precipitously because of the preceding impediment to venous return.

Interplay of Central and Peripheral Factors in Control of the Circulation

The primary function of the circulatory system is to deliver the nutrients needed for tissue metabolism and growth and to remove the products of metabolism. The contributions of the components of the cardiovascular system to maintain adequate tissue perfusion under different physiological conditions were discussed previously. In this section, the interrelationships among the various components of the circulatory system are explored. The autonomic nervous system and the baroreceptors and chemoreceptors play key roles in regulating the cardiovascular system. Control of fluid balance by the kidneys, with maintenance of a constant blood volume, is also very important.

In any well-regulated system, one way to evaluate the extent and sensitivity of its regulatory mechanisms is to disturb the system and to observe how it restores the preexisting steady state. Two such disturbances, physical exercise and hemorrhage, are discussed in the following sections to illustrate operation of the various regulatory factors.

Exercise

The cardiovascular adjustments that occur during exercise consist of a combination of neural and local (chemical) factors. Neural factors include (1) central command, (2) reflexes that originate in the contracting muscle, and (3) the baroreceptor reflex. Central command is the cerebrocortical activation of the sympathetic nervous system that produces cardiac acceleration, increased myocardial contractile force, and peripheral vasoconstriction. Reflexes are activated intramuscularly by stimulation of mechanoreceptors (by stretch, tension) and chemoreceptors (by metabolic products) in response to muscle contraction. Impulses from these receptors travel centrally via small myelinated (group III) and unmyelinated (group IV) afferent nerve fibers. Group IV unmyelinated fibers may represent the muscle chemoreceptors, inasmuch as no morphological chemoreceptor has been identified. The central connections of this reflex are unknown, but the efferent limb consists of sympathetic nerve fibers to the heart and peripheral blood vessels. The baroreceptor reflex is described in Chapter 18, and local factors that influence skeletal muscle blood flow (metabolic vasodilators) are described in Chapter 17. Vascular chemoreceptors are important in regulation of the cardiovascular system during exercise. Evidence for this assertion comes from the observations that the $Pa{CO_2}$, the $Pa{O_2}$, and the pH of arterial blood remain normal during exercise.

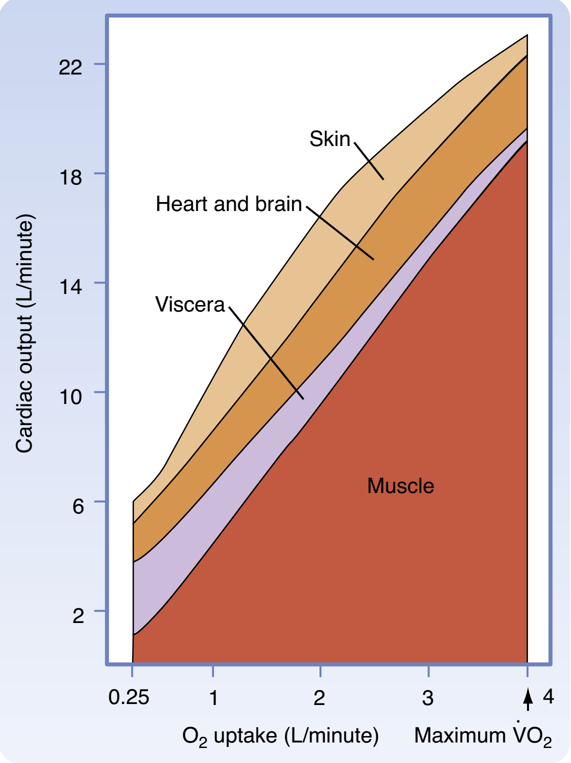
Mild to Moderate Exercise

In humans or trained animals, anticipation of physical activity inhibits vagal nerve impulses to the heart and increases sympathetic discharge. The result is an increase in HR and myocardial contractility. The tachycardia and enhanced contractility increase cardiac output.

Peripheral Resistance

When cardiac stimulation occurs, the sympathetic nervous system also changes vascular resistance in the periphery. Sympathetic nervous system–mediated vasoconstriction increases vascular resistance and thereby diverts blood away from the skin, kidneys, splanchnic regions, and inactive muscle (Fig. 19.16). This increase in vascular resistance persists throughout the period of exercise.

Cardiac output and blood flow to active muscles increase as the intensity of exercise increases. Blood flow to the myocardium increases, whereas flow to the brain is unchanged. Blood flow in the skin initially decreases during exercise, then increases as body temperature rises with increments in the duration and intensity of exercise, and finally decreases



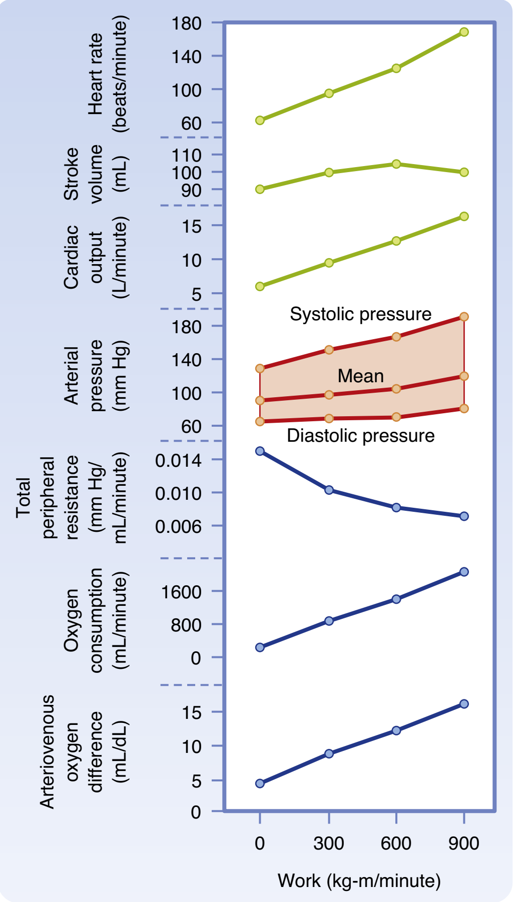
• **Fig. 19.16** Approximate distribution of cardiac output at rest and at different levels of exercise up to the maximal O_2 consumption ($\dot{V}O_2$) in a normal young man. (Redrawn from Ruch HP, Patton TC. *Physiology and Biophysics.* 12th ed. Philadelphia: Saunders; 1974.)

when the skin vessels constrict as total body O_2 consumption nears its maximal value (see Fig. 19.16).

The major circulatory adjustment to prolonged exercise occurs in the vasculature of the active muscles. Local formation of vasoactive metabolites causes marked dilation of the resistance vessels. This dilation progresses with increases in the intensity of exercise. Potassium is one of the vasodilator substances released by the contracting muscle, and this ion may be partly responsible for the initial decrease in vascular resistance in the active muscles. Other contributing factors may be the release of adenosine and a decrease in tissue pH during sustained exercise. The local accumulation of metabolites causes the terminal arterioles to relax, and blood flow through the muscle may increase 15- to 20-fold above the resting level. This metabolic vasodilation of the precapillary vessels in active muscles occurs very soon after the onset of exercise. The decrease in TPR enables the heart to pump more blood at a lesser load, and it pumps more efficiently than if TPR were unchanged (see Chapter 17 and 18).

Marked changes in the capillary circulation also occur during exercise. At rest, only a small percentage of the capillaries are perfused, whereas in actively contracting muscle, all or nearly all of the capillaries contain flowing blood **(capillary recruitment).** The surface area available for exchange of gases, water, and solutes is increased many times. Furthermore, hydrostatic pressure in the capillaries is increased because of relaxation of the resistance vessels. Hence, water and solutes move into the muscle tissue. Tissue pressure rises and remains elevated during exercise as fluid continues to move out of the capillaries; this tissue fluid is carried away by the lymphatic vessels. Lymph flow is increased as a result of the rise in capillary hydrostatic pressure and the massaging effect of the contracting muscles on the valve-containing lymphatic vessels (see Chapter 17).

Contracting muscle avidly extracts O_2 from the perfusing blood and thereby increases the arteriovenous O_2 difference (Fig. 19.17). This release of O_2 from blood is facilitated by the shift in the oxyhemoglobin dissociation curve during exercise. During exercise, the high concentration of CO_2 and the formation of lactic acid cause a reduction in tissue pH. This decrease in pH, in addition to the increase in temperature in the contracting muscle, shifts the oxyhemoglobin dissociation curve to the right (see Chapter 24). Therefore, at any given Po_2, less O_2 is held by the hemoglobin in the red blood cells, and consequently more O_2 is available for the tissues. Oxygen consumption may increase as much as 60-fold, with only a 15-fold increase in muscle blood flow. Muscle myoglobin may serve as a limited O_2 store during exercise, and it can release the attached O_2 at very low partial pressures. However, myoglobin can also facilitate O_2 transport from capillaries to mitochondria by serving as an O_2 carrier.



• **Fig. 19.17** Effects of different levels of exercise (i.e., work) on several cardiovascular variables. (Data from Carlsten A, Grimby G. *The Circulatory Response to Muscular Exercise in Man.* Springfield, IL: Charles C Thomas; 1966.)

Cardiac Output

Because the enhanced sympathetic drive and the reduced parasympathetic inhibition of the sinoatrial node continue during exercise, tachycardia persists. If the workload is moderate and constant, the HR reaches a certain level and remains there throughout the period of exercise. However, if the workload increases, the HR increases concomitantly until a plateau of approximately 180 beats per minute is reached during strenuous exercise. In contrast to the large increase in HR, the increase in SV is only approximately 10% to 35%, the larger values occurring in trained individuals (see Fig. 19.17). In well-trained distance runners, whose cardiac output can reach six to seven times the resting level, SV attains approximately twice the resting value.

Thus the increase in cardiac output observed during exercise is correlated principally with an increase in HR. If the baroreceptors are denervated, the cardiac output and HR responses to exercise are small in comparison with those in individuals with normally innervated baroreceptors. However, with total cardiac denervation, exercise still increases cardiac output as much as it does in normal individuals. This increase in cardiac output is achieved chiefly by means of an elevated SV. However, if a β-adrenergic receptor antagonist is given to dogs with denervated hearts, exercise performance is impaired. The β-adrenergic receptor antagonist prevents the cardiac acceleration and enhanced contractility caused by increased amounts of circulating catecholamines. Therefore, the increase in cardiac output necessary for maximal exercise performance is limited.

IN THE CLINIC

Cardiac muscle size (growth) is directly related to the amount of work that is imposed upon it. During development and in endurance exercise, cardiac growth is achieved at a constant relation between systolic blood pressure and the ratio of wall thickness to ventricular chamber radius. An echocardiographic measurement used to distinguish physiological from pathological hypertrophy is relative wall thickness (ratio of left ventricular wall thickness to chamber radius). In physiological hypertrophy, left ventricular mass and radius increase proportionately so that relative wall thickness does not change significantly. Examples of physiological hypertrophy occur in endurance athletes and in pregnant women, in whom left ventricular enlargement occurs with volume overload at constant relative wall thickness. Physiological hypertrophy is associated with an increased arteriolar diameter in experimental animals. Also, capillary density increases in proportion to the degree of hypertrophy. This is in contrast to the situation in pathological hypertrophy, in which a reduction of capillary density (rarefaction) can occur. Neither myocardial fibrosis nor derangement of muscle fiber orientation is detected in physiological hypertrophy, in contrast to the findings in pathological hypertrophy.

Venous Return

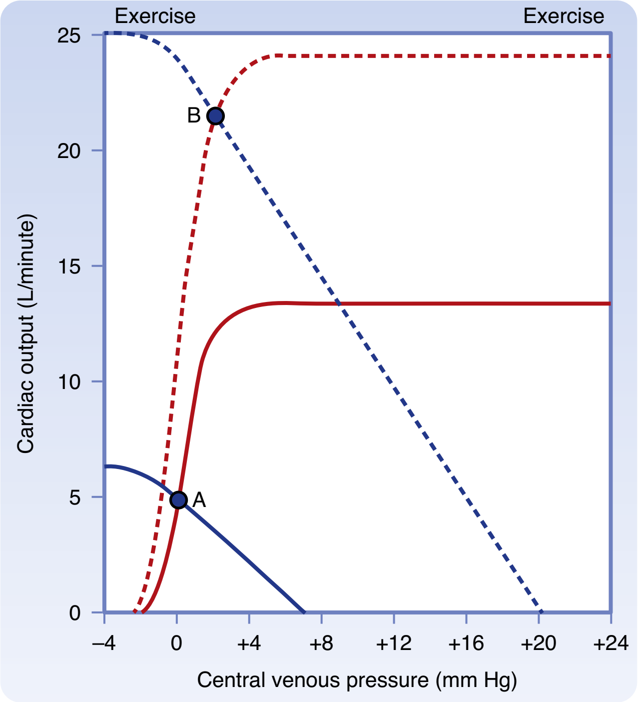
In addition to the contribution made by sympathetically mediated constriction of the capacitance vessels in both exercising and nonexercising parts of the body, venous return is aided by the auxiliary pumping action of the working skeletal muscles and the muscles of respiration (see also Chapter 17 and 21). The intermittently contracting muscles compress the veins that course through them. Because the venous valves are oriented toward the heart, the contracting muscle pumps blood back toward the right atrium (see Chapter 17). In exercise, the flow of venous blood to the heart is also aided by the deeper and more frequent respirations that increase the pressure gradient between the abdominal and thoracic veins (intrathoracic pressure becomes more negative during exercise).

In humans, blood reservoirs do not contribute much to the circulating blood volume. In fact, blood volume is usually reduced slightly during exercise, as evidenced by a rise in the hematocrit ratio. This decrease in blood volume is caused by water loss externally through sweating and enhanced ventilation and by fluid movement into the contracting muscle. However, fluid loss is counteracted in several ways. Fluid loss from the vascular compartment into the contracting muscles eventually reaches a plateau as interstitial fluid pressure rises and opposes the increased hydrostatic pressure in capillaries of the active muscle. Fluid loss is partially offset by movement of fluid from the splanchnic regions and inactive muscle into the bloodstream. This influx of fluid results from (1) a decrease in hydrostatic pressure in the capillaries of these tissues and (2) an increase in plasma osmolarity because of movement of osmotically active molecules into blood from the contracting muscle. Reduction in urine formation by the kidneys also helps conserve body water.

The large volume of venous blood returning to the heart is so effectively pumped through the lungs and out into the aorta that P_v remains essentially constant. Thus the Frank-Starling mechanism of a greater initial fiber length does not account for the greater SV in moderate exercise. Radiographs of individuals at rest and during exercise reveal a decrease in heart size during exercise. However, during maximal or near-maximal exercise, right atrial pressure and end-diastolic ventricular volume do increase, and the Frank-Starling mechanism contributes to the enhanced SV in very vigorous exercise.

Coupling Between Heart and Vasculature During Exercise

In an active, healthy (untrained) individual, the mechanisms previously described typically lead to a fourfold to fivefold increase in cardiac output during vigorous exercise (Fig. 19.18). Increased cardiac output is the fundamental means by which more O_2 is delivered to exercising muscles (see Fig. 19.17). The cardiac function curve during exercise reflects increased SV (up to ~1.5-fold) and heart rate (up to ~3-fold). The vascular function curve during dynamic exercise reflects a marked decrease in peripheral resistance (changed slope) and an increase in mean circulatory filling pressure (changed intercept), which result from increased venous constriction (tone) in the skeletal muscle "pump,"



• **Fig. 19.18** Cardiac and vascular function curves are greatly altered during strenuous exercise, which allows cardiac output to increase fourfold to fivefold. The operating point of the cardiovascular system moves from point A to point B. The cardiac function curve during strenuous exercise is the result of increased HR, stroke volume, and contractility. The vascular function curve reflects greatly decreased total peripheral resistance and increased mean circulatory pressure. At the new operating point (point B), cardiac output is increased more than fourfold, but filling pressure is increased only slightly.

and the respiratory "pump." In these conditions, the cardiovascular system is able to operate at a new point (point B in Fig. 19.18), in which cardiac output is increased while filling pressure is little changed. The graphical analysis (see Fig. 19.18) shows that without the systemic changes in vascular function, even a heart beating strongly and fast would be able to produce only a small increase in cardiac output.

Arterial Pressure

If exercise involves a large proportion of the body musculature, as in running or swimming, the reduction in total vascular resistance can be considerable. Nevertheless, arterial pressure starts to rise with the onset of exercise, and the increase in blood pressure approximately parallels the severity of the exercise performed (see Fig. 19.17). Therefore, the increase in cardiac output is proportionally greater than the decrease in TPR. The vasoconstriction produced in the inactive tissues by the sympathetic nervous system (and to some extent by the release of catecholamines from the adrenal medulla) is important for maintenance of normal or increased blood pressure. Sympathectomy or drug-induced blockade of the adrenergic sympathetic nerve fibers decreases arterial pressure (hypotension) during exercise.

Sympathetic neural activity also elicits vasoconstriction in active skeletal muscle when additional muscles are recruited. In experiments in which one leg is working at maximal levels and then the other leg starts to work, blood flow decreases in the first working leg. Furthermore, blood levels of norepinephrine rise significantly during exercise, and most of the norepinephrine is released from sympathetic nerves to the active muscles.

As body temperature rises during exercise, the skin vessels dilate in response to thermal stimulation of the heat-regulating center in the hypothalamus, and TPR decreases further. This reduction in TPR would reduce blood pressure were it not for the increased cardiac output and the constriction of arterioles in the renal, splanchnic, and other tissues.

In general, P_a rises during exercise as a result of the increase in cardiac output. However, the effect of enhanced cardiac output is offset by an overall decrease in TPR, and therefore mean blood pressure increases only slightly. Vasoconstriction in the inactive vascular beds helps maintain normal arterial blood pressure for adequate perfusion of the active tissues. The actual P_a attained during exercise thus represents a balance between cardiac output and TPR (see Chapter 17). Systolic pressure usually increases more than diastolic pressure, which results in an increase in pulse pressure (see Fig. 19.17). The larger pulse pressure is primarily attributable to a greater SV, but also to more rapid ejection of blood by the left ventricle and diminished peripheral runoff during the brief ventricular ejection period (see also Chapter 17).

Severe Exercise

During exhaustive exercise, the compensatory mechanisms begin to fail. The HR attains a maximal level of approximately 180 beats per minute, and SV reaches a plateau. The HR may then decrease, which results in a fall in blood pressure. The exercising individual also frequently becomes dehydrated. Sympathetic vasoconstrictor activity supersedes the vasodilator influence on vessels of the skin so that the rate of heat loss is decreased. Body temperature is normally elevated during exercise. A reduction in heat loss through cutaneous vasoconstriction can lead to very high body temperatures and to acute distress during severe exercise. Tissue pH and blood pH decrease as a result of increased production of lactic acid and CO_2. The reduced pH may be a key factor that determines the maximal amount of exercise that a given individual can tolerate. Muscle pain, a subjective feeling of exhaustion, and loss of the will to continue determine exercise tolerance. A summary of the neural and local effects of exercise on the cardiovascular system is diagrammed in Fig. 19.19.

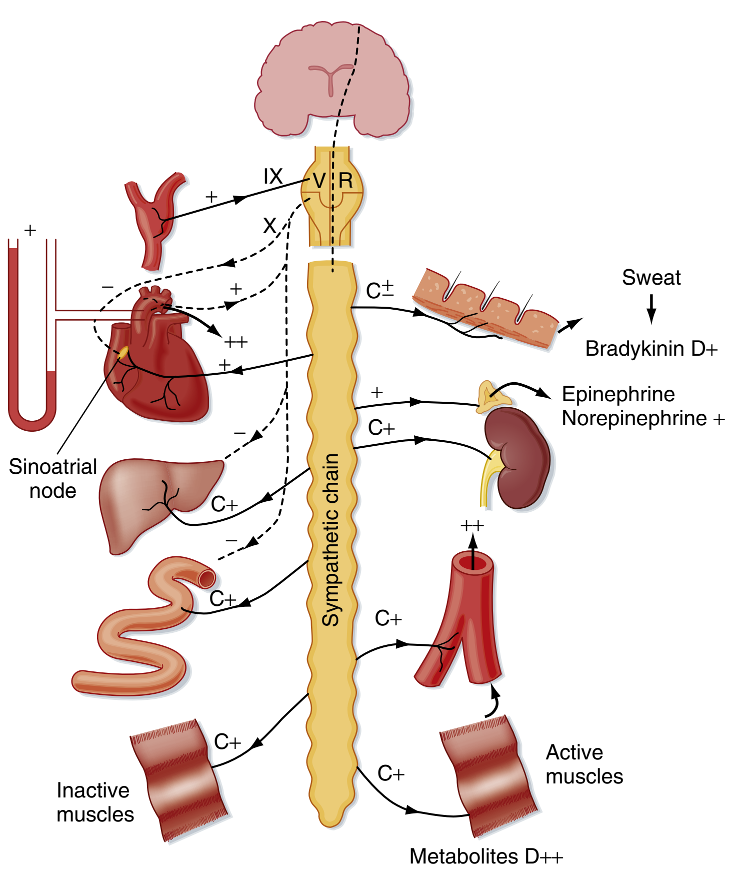
Postexercise Recovery

When exercise stops, the HR and cardiac output quickly decrease: The sympathetic drive to the heart is essentially removed. In contrast, TPR remains low for some time after the exercise is stopped, presumably because vasodilator metabolites have accumulated in the muscles during the exercise period. As a result of the reduced cardiac output and persistence of vasodilation in the muscles, arterial pressure falls, often below pre-exercise levels, for brief periods. Blood pressure is then stabilized at normal levels by the baroreceptor reflexes.

Limits of Exercise Performance

The two main factors that limit skeletal muscle performance in humans are the rate of O_2 use by the muscles and the O_2 supply to the muscles. However, O_2 use by muscle is probably not a critical factor. During exercise, maximal O_2 consumption (maximal $\dot{V}O_2$) by a large percentage of the body's muscle mass is unchanged or increases only slightly when additional muscles are activated. In fact, during exercise of a large muscle mass, as in vigorous bicycling, the addition of bilateral arm exercise without change in the cycling effort produces only a small increase in cardiac output and maximal $\dot{V}O_2$. However, the additional arm exercise decreases blood flow to the legs. This centrally mediated (baroreceptor reflex) vasoconstriction during maximal cardiac output prevents the fall in blood pressure that would otherwise be caused by metabolically induced vasodilation in the active muscle. If use of O_2 by muscles were a significant limiting factor, recruitment of more contracting muscles would entail the use of much more O_2 to meet the enhanced O_2 requirements.

Limitation of the O_2 supply could be caused by inadequate oxygenation of blood in the lungs or limitation of the supply of O_2-laden blood to the muscles. Failure by the lungs to oxygenate blood fully can be ruled out because even with the most strenuous exercise at sea level, arterial blood is fully saturated with O_2. Therefore, O_2 delivery to the active muscles (or blood flow because the arterial blood O_2 content is normal) appears to be the limiting factor in muscle performance. This limitation could be caused by the inability to increase cardiac output beyond a critical level. In turn,



• Fig. 19.19 Cardiovascular adjustments in exercise. *Plus signs* indicate increased activity, and *minus signs* indicate decreased activity. *C,* Vasoconstrictor activity; *D,* vasodilator activity; *IX,* glossopharyngeal nerve; *VR,* vasomotor region; *X,* vagus nerve.

this inability is caused by a limitation in SV because the HR reaches maximal levels before maximal $\dot{V}O_2$ is reached. Hence, the major factor that limits muscle performance is the pumping capacity of the heart.

Physical Training and Conditioning

The response of the cardiovascular system to regular exercise is to increase its capacity to deliver O_2 to the active muscles and improve the ability of the muscle to use O_2. Maximal $\dot{V}O_2$ varies with the level of physical conditioning. Training progressively increases maximal $\dot{V}O_2$, which reaches a plateau at the highest level of conditioning. Highly trained athletes have a lower resting HR, a greater SV, and lower peripheral resistance than they had before training or after deconditioning. The low resting HR is caused by a higher vagal tone and a lower sympathetic tone. During exercise, the maximal HR of a trained individual is the same as that in an untrained person, but it is attained at a higher level of exercise. A trained person also exhibits low vascular resistance in the muscles. If an individual exercises one leg regularly over an extended period and does not exercise the other leg, vascular resistance is lower and maximal $\dot{V}O_2$ is higher in the “trained” leg than in the “untrained” leg.

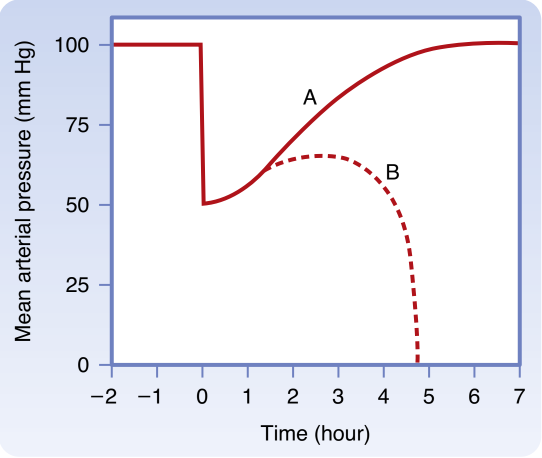
Physical conditioning is also associated with greater extraction of O_2 from the blood (greater arteriovenous O_2 difference) by the muscles. With long-term training, capillary density in skeletal muscle increases. Also, an increase in the number of arterioles may account for the decrease in muscle vascular resistance. The number of mitochondria increases, as does the number of oxidative enzymes in mitochondria. In addition, levels of adenosine triphosphatase (ATPase) activity, myoglobin, and enzymes involved in lipid metabolism increase in response to physical conditioning.

IN THE CLINIC

Endurance training, such as running or swimming, increases left ventricular volume without increasing left ventricular wall thickness. In contrast, strength exercises, such as weightlifting, increase left ventricular wall thickness (hypertrophy) with little effect on ventricular volume. However, this increase in wall thickness is small in relation to that observed in chronic hypertension, in which afterload is persistently elevated because of high peripheral resistance.

Hemorrhage

The cardiovascular system is significantly affected, in multiple ways, in an individual who has lost a significant quantity of blood. Major hemorrhage can lead to the life-threatening condition, shock, in which the cardiovascular system is



• Fig. 19.20 Changes in mean arterial pressure after rapid hemorrhage. At time 0, rapid loss of blood causes a reduction in the mean arterial pressure to 50 mm Hg. After a period in which the pressure returns toward the control level, some individuals continue to improve (curve A) until the control pressure is attained. However, in other individuals, the pressure begins to decline (curve B) until death ensues.

unable to perform its primary function, adequate perfusion of tissues and delivery of the required oxygen. Arterial systolic, diastolic, and pulse pressures decrease, and the arterial pulse is rapid and feeble. The cutaneous veins collapse, and they fill slowly when compressed centrally. The skin is pale, moist, and slightly cyanotic.

Course of Arterial Blood Pressure Changes

Cardiac output decreases as a result of blood loss. The amount of blood removed when it is donated is approximately 10% of total blood volume; its removal is well tolerated, and mean arterial blood pressure changes little. This is not the case when greater amounts are lost from the circulation. The changes in P_a evoked by acute hemorrhage are illustrated in Fig. 19.19. If sufficient blood is rapidly withdrawn to decrease P_a to 50 mm Hg, the pressure then tends to rise spontaneously toward the control level over the next 20 or 30 minutes. In some individuals (curve A in Fig. 19.20), this trend continues, and normal pressure is regained within a few hours. In others (curve B in Fig. 19.20), the pressure rises initially after the cessation of hemorrhage. The pressure then begins to decline, and it continues to fall at an accelerating rate until death ensues. This progressive deterioration in cardiovascular function is termed *hemorrhagic shock.* At some time after the hemorrhage, the deterioration in the cardiovascular system becomes irreversible. A lethal outcome in patients with hemorrhagic shock can be prevented only temporarily by any known therapy, including massive transfusions of donor blood.

Compensatory Mechanisms

The changes in arterial pressure immediately after acute blood loss (see Fig. 19.20) indicate that certain compensatory mechanisms must be operative. Any mechanism that raises arterial blood pressure toward normal in response to a reduction in pressure is designated a negative feedback mechanism. This mechanism is termed *negative* because the direction of the secondary change in pressure is opposite to the direction of the initiating change after the acute blood loss. The following negative feedback responses are evoked: (1) baroreceptor reflexes, (2) chemoreceptor reflexes, (3) cerebral ischemia responses, (4) reabsorption of tissue fluids, (5) release of endogenous vasoconstrictor substances, and (6) renal conservation of salt and water.

Baroreceptor Reflexes

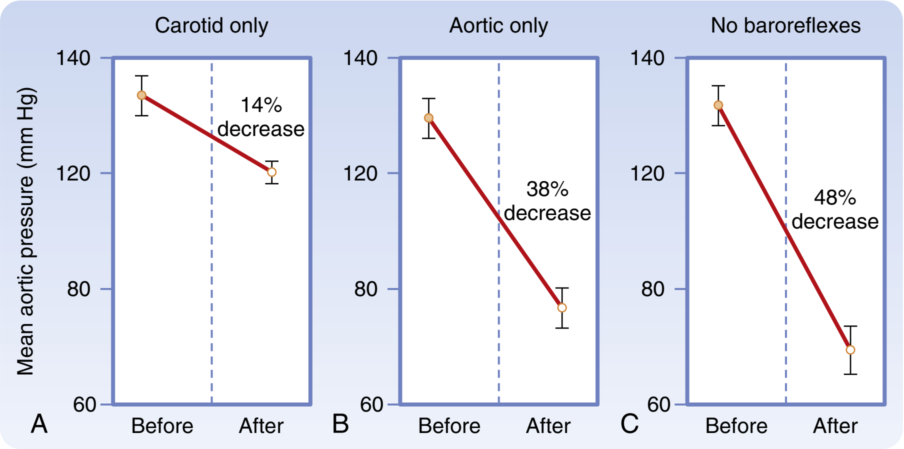
The reductions in P_a and pulse pressure during hemorrhage decrease stimulation of the baroreceptors in the carotid sinuses and aortic arch (see Chapter 18). Several cardiovascular responses are thus evoked, all of which tend to restore arterial pressure to the normal level. Such responses include reduction of vagal tone and enhancement of sympathetic tone, increased HR, and enhanced myocardial contractility.

The increased sympathetic tone also produces generalized venoconstriction, which has the same hemodynamic consequences as transfusion of blood (see Fig. 19.9). Sympathetic activation constricts certain blood reservoirs. This vasoconstriction acts as an autotransfusion of blood into the circulation. In humans, the cutaneous, pulmonary, and hepatic branches of the vasculature constitute the principal blood reservoirs.

Generalized arteriolar constriction is a prominent response to the reduced baroreceptor stimulation during hemorrhage. The reflex increase in peripheral resistance minimizes the fall in arterial pressure caused by the reduction in cardiac output. Fig. 19.21 shows the effect of an 8% blood loss on mean aortic pressure. When both vagus nerves were cut to eliminate the influence of the aortic arch baroreceptors and only the carotid sinus baroreceptors were operative (see Fig. 19.21*A*), this hemorrhage decreased mean aortic pressure by 14%. This pressure change did not differ significantly from the decline in pressure (12%) evoked by the same hemorrhage before vagotomy (not shown). When the carotid sinuses were denervated and the aortic baroreceptor reflexes were intact, the 8% blood loss decreased mean aortic pressure by 38% (see Fig. 19.21*B*). Hence, the carotid sinus baroreceptors were more effective than the aortic baroreceptors in attenuating the fall in pressure. However, when both sets of afferent baroreceptor pathways were interrupted (see Fig. 19.21*C*), an 8% blood loss reduced arterial pressure by 48%.

Arteriolar constriction is widespread during hemorrhage but it is by no means uniform. Vasoconstriction is most pronounced in the cutaneous, skeletal muscle, and splanchnic vascular beds, and it is slight or absent in the cerebral and coronary circulations in response to hemorrhage. In many instances, cerebral and coronary vascular resistance is diminished. The reduced cardiac output is redistributed to favor flow through the brain and the heart.

In the early stages of mild to moderate hemorrhage, renal resistance changes only slightly. The tendency for increased sympathetic activity to constrict the renal vessels is counteracted by autoregulatory mechanisms (see Chapters 18 and 35).



• **Fig. 19.21** Changes in mean aortic pressure in response to an 8% blood loss in three conditions. **A,** The carotid sinus baroreceptors were intact and the aortic reflexes were interrupted. **B,** The aortic reflexes were intact and the carotid sinus reflexes were interrupted. **C,** All sinoaortic reflexes were abrogated. (Data from Shepherd JT. *Circulation.* 1974;50:418. Derived from the data of Edis AJ. *Am J Physiol.* 1971;221:1352.)

With more prolonged and severe hemorrhage, however, renal vasoconstriction becomes intense.

The renal and splanchnic vasoconstriction during hemorrhage is least severe in the heart and brain. However, if such constriction persists too long, it may be detrimental. Frequently, patients survive the acute hypotensive period of a prolonged, severe hemorrhage, only to die several days later from the kidney failure that results from renal ischemia. Intestinal ischemia may also have dire effects. For example, intestinal bleeding and extensive sloughing of the mucosa can occur after only a few hours of hemorrhagic hypotension. Furthermore, the diminished splanchnic flow swells the centrilobular cells in the liver. The resulting obstruction of the hepatic sinusoids causes portal venous pressure to rise, and this response intensifies intestinal blood loss.

Chemoreceptor Reflexes

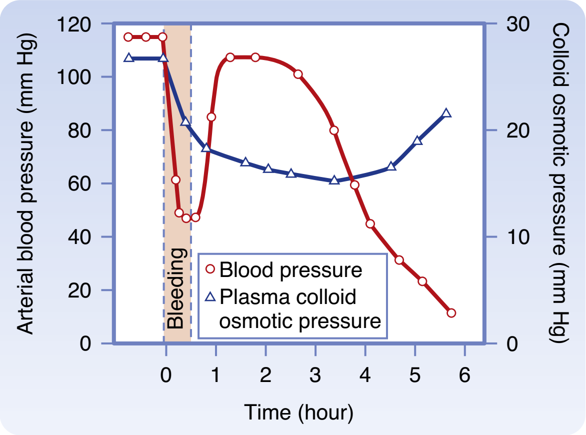
Reductions in arterial pressure below approximately 60 mm Hg do not evoke any additional responses through the baroreceptor reflexes because this pressure level constitutes the threshold for stimulation (see Chapters 18). However, low arterial pressure may stimulate peripheral chemoreceptors because inadequacy of local blood flow leads to hypoxia in the chemoreceptor tissue. Chemoreceptor excitation may then enhance the already existent peripheral vasoconstriction evoked by the baroreceptor reflexes. In addition, respiratory stimulation assists venous return by the auxiliary pumping mechanism described earlier (see also Chapter 21).

Cerebral Ischemia

When arterial pressure falls below approximately 40 mm Hg as a consequence of blood loss, the resulting cerebral ischemia activates the sympathoadrenal system. The discharge by sympathetic nerves is several times greater than the maximal neural activity that occurs when the baroreceptors cease to be stimulated. The vasoconstriction and increase in myocardial contractility may be pronounced. With more severe degrees of cerebral ischemia, however, the vagal centers also become activated. The resulting bradycardia aggravates the hypotension that initiated the cerebral ischemia

Reabsorption of Tissue Fluids

The arterial hypotension, arteriolar constriction, and reduced venous pressure during hemorrhagic hypotension cause the hydrostatic pressure in the capillaries to drop. The balance of these forces promotes the net reabsorption of interstitial fluid into the vascular compartment (see Chapter 17). The rapidity of this response is displayed in Fig. 19.22. When 45% of the estimated blood volume is removed over a 30-minute period, mean arterial blood pressure declines rapidly and then is largely restored to nearly the control level. Plasma colloid osmotic pressure declines markedly during the bleeding and continues to decrease more gradually for several hours. The reduction in colloid osmotic pressure reflects dilution of the blood by tissue fluids that contain little protein.



• **Fig. 19.22** Changes in arterial blood pressure and plasma colloid osmotic pressure in response to withdrawal of 45% of the estimated blood volume over a 30-minute period, beginning at time 0. (Redrawn from Zweifach BW. *Anesthesiology.* 1974;41:157.)

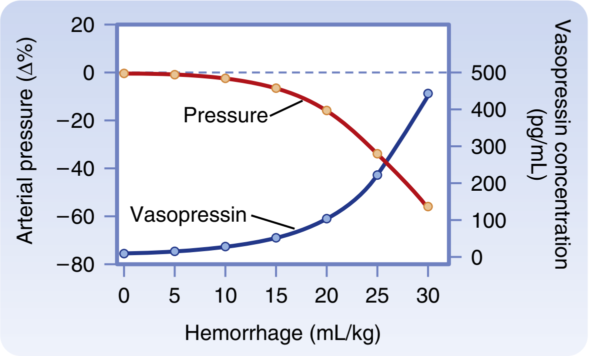
Considerable quantities of fluid may thus be drawn into the circulation during hemorrhage. Approximately 0.25 mL of fluid per minute per kilogram of body weight may be reabsorbed by the capillaries. Thus approximately 1 L of fluid per hour might be autoinfused from the interstitial spaces into the circulatory system of an average individual after acute blood loss. Substantial quantities of fluid may shift slowly from the intracellular space to the extracellular space. This fluid exchange is probably mediated by secretion of cortisol from the adrenal cortex in response to hemorrhage. Cortisol is essential for the full restoration of plasma volume after hemorrhage.

Endogenous Vasoconstrictors

The catecholamines epinephrine and norepinephrine are released from the adrenal medulla in response to the same stimuli that evoke widespread sympathetic nervous discharge (see Chapter 43). Blood levels of catecholamines are high during and after hemorrhage. When blood loss is such that arterial pressure is reduced to 40 mm Hg, the level of catecholamines increases as much as 50-fold. Epinephrine comes almost exclusively from the adrenal medulla, whereas norepinephrine is derived from both the adrenal medulla and peripheral sympathetic nerve endings. These humoral substances reinforce the effects of the sympathetic nervous activity listed previously.

Vasopressin (antidiuretic hormone), a potent vasoconstrictor, is secreted by the posterior pituitary gland in response to hemorrhage (see Chapters 35 and 41). The plasma concentration of vasopressin rises progressively as arterial blood pressure diminishes (Fig. 19.23). The receptors responsible for the augmented release of vasopressin are the aortic arch and carotid sinus baroreceptors (high pressure) and stretch receptors in the left atrium (low pressure).

The diminished renal perfusion during hemorrhagic hypotension leads to the secretion of renin from the juxtaglomerular apparatus (see Chapters 35). This enzyme acts on a plasma protein, angiotensinogen, to form the decapeptide angiotensin I, which in turn is cleaved to the active octapeptide angiotensin II by angiotensin-converting enzyme; angiotensin II is a very powerful vasoconstrictor.



• Fig. 19.23 Mean percentage changes in arterial blood pressure and plasma vasopressin concentration in response to blood loss. (Redrawn from Shen YT, et al. *Circ Res.* 1991;68:1422.)

Renal Conservation of Salt and Water

Fluid and electrolytes are conserved by the kidneys during hemorrhage in response to various stimuli, including increased secretion of vasopressin, as noted previously (see Fig. 19.23), and increased renal sympathetic nerve activity, which enhances NaCl reabsorption by the nephron (decreased excretion). The lower arterial pressure decreases the glomerular filtration rate, which also curtails the excretion of water and electrolytes. In addition, the elevated levels of angiotensin II, as described earlier, stimulate the release of aldosterone from the adrenal cortex. Aldosterone, in turn, stimulates reabsorption of NaCl by the nephrons. Thus NaCl and water excretion is decreased (see also Chapter 35).

Decompensatory Mechanisms

In contrast to negative feedback mechanisms, hemorrhage also evokes latent positive feedback mechanisms. These mechanisms exaggerate any primary change initiated by the blood loss. Specifically, positive feedback mechanisms aggravate the hypotension induced by blood loss and tend to initiate vicious cycles, which may lead to death.

Whether a positive feedback mechanism will lead to a vicious cycle depends on the gain of that mechanism. Gain is the ratio of the secondary change evoked by a given mechanism to the initiating change itself. A gain greater than 1 induces a vicious cycle; a gain of less than 1 does not. Consider a positive feedback mechanism with a gain of 2. If P_a were to decrease by 10 mm Hg, a positive feedback mechanism with a gain of 2 would then evoke a secondary reduction in pressure of 20 mm Hg, which in turn would cause a further decrease of 40 mm Hg. Thus each change would induce a subsequent one that is twice as great. Hence, P_a would decline at an ever-increasing rate until death occurred. This process is depicted in curve B in Fig. 19.20.

Conversely, a positive feedback mechanism with a gain of 0.5 also exaggerates any change in P_a, but the change would not necessarily lead to death. If arterial pressure suddenly decreased by 10 mm Hg, a positive feedback mechanism would initiate a secondary, additional fall of 5 mm Hg. This decrease, in turn, would provoke a further decrease of 2.5 mm Hg. The process would continue in ever-diminishing steps until arterial pressure approached an equilibrium value.

Some of the more important positive feedback mechanisms that are evident during hemorrhage include (1) cardiac failure, (2) acidosis, (3) central nervous system depression, (4) aberrations in blood clotting, and (5) depression of the mononuclear phagocytic system (MPS).[b] These mechanisms are discussed next.

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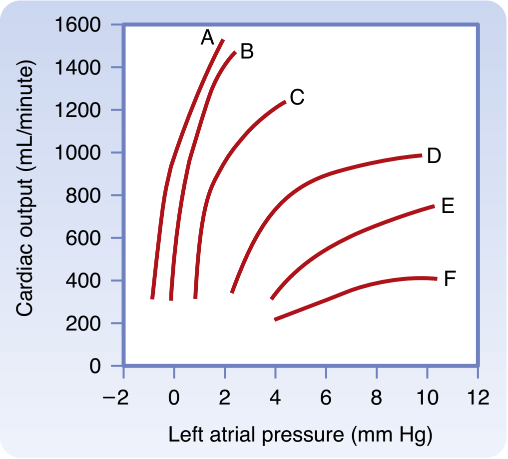
[b] The MPS (previously called the *reticuloendothelial system*) consists of macrophages that are distributed throughout the body. They are derived from bone marrow and exist for a short period in circulating blood as monocytes. They then migrate into tissues, where they phagocytose foreign material and present antigens to lymphocytes to initiate the adaptive immune response. Cells of the MPS include the Kupffer cells of the liver, alveolar macrophages, microglia, and Langerhans cells.



• **Fig. 19.24** Ventricular function curves for the left ventricle during the course of hemorrhagic shock. *Curve A* represents the control function curve; *curves B* to *F* represent time after the hemorrhage: 117 minutes *(curve B),* 247 minutes *(curve C),* 280 minutes *(curve D),* 295 minutes *(curve E),* and 310 minutes *(curve F).* (Redrawn from Crowell JW, Guyton AC. *Am J Physiol.* 1962;203:248.)

Cardiac Failure

Shifts to the right in ventricular function curves, particularly in the later stages of hemorrhagic shock (Fig. 19.24), provide evidence of a progressive depression in myocardial contractility during hemorrhage.

The hypotension induced by hemorrhage reduces coronary blood flow and therefore depresses ventricular function. The consequent reduction in cardiac output further reduces arterial pressure, a classic example of a positive feedback mechanism. Furthermore, reduced blood flow to peripheral tissues leads to an accumulation of vasodilator metabolites that decrease peripheral resistance and therefore aggravate the fall in arterial pressure.

Acidosis

The inadequate blood flow during hemorrhage affects the metabolism of all cells. The decreased O_2 delivery to cells accelerates tissue production of lactic acid and other acid metabolites. Moreover, impaired kidney function prevents adequate excretion of the excess H^+, and generalized metabolic acidosis ensues. The resulting depressant effect of acidosis on the heart is a further reduction in tissue perfusion, which aggravates the metabolic acidosis. Acidosis also reduces the reactivity of the heart and resistance vessels to neurally released and circulating catecholamines and thereby intensifies the hypotension.

Central Nervous System Depression

The hypotension in shock reduces cerebral blood flow. Moderate degrees of cerebral ischemia induce pronounced sympathetic nervous stimulation of the heart, arterioles, and veins, as noted earlier. In severe hypotension, however, the cardiovascular centers in the brainstem eventually become depressed because of inadequate cerebral blood flow. The resulting loss of sympathetic tone then reduces cardiac output and peripheral resistance. The consequent reduction in P_a intensifies the inadequate cerebral perfusion.

Endogenous opioids, such as enkephalins and β-endorphin, may be released into the brain substance and into the circulation in response to the same stresses that provoke circulatory shock. Opioids are stored, along with catecholamines, in secretory granules in the adrenal medulla and in sympathetic nerve terminals, and they are released together in response to stress. Similar stimuli cause the release of β-endorphin and adrenocorticotropic hormone from the anterior pituitary gland. Opioids depress the brainstem centers that mediate some of the compensatory autonomic adaptations to blood loss, endotoxemia, and other shock-provoking stress. Conversely, the opioid antagonist naloxone improves cardiovascular function and rates of survival in various forms of shock.

Aberrations in Blood Clotting

The alterations in blood clotting after hemorrhage are typically biphasic. An initial phase of hypercoagulability is followed by a secondary phase of hypocoagulability and fibrinolysis. In the initial phase, platelets and leukocytes adhere to the vascular endothelium, and intravascular clots, or thrombi, develop within a few minutes of the onset of severe hemorrhage. This phenomenon, called *disseminated intravascular coagulation* (DIC), occurs when thrombin is activated and causes widespread deposition of fibrin within narrow and medium-diameter vessels.

The initial phase is further enhanced by the release of thromboxane A_2 from various ischemic tissues. Thromboxane A_2 aggregates platelets. As more platelets aggregate, more thromboxane A_2 is released and more platelets are trapped. This form of positive feedback intensifies and prolongs the clotting tendency. Inflammatory cytokines (interleukin-6, tumor necrosis factor) also contribute to DIC. The rate of mortality from certain standard shock-provoking procedures has been reduced considerably by the administration of anticoagulants such as heparin.

In the later stages of hemorrhagic hypotension, the clotting time is prolonged, and fibrinolysis is prominent. Fibrinolysis occurs when clotting factors and platelets are depleted.

Depression of the Mononuclear Phagocytic System

During the course of hemorrhagic hypotension, MPS function becomes depressed. The phagocytic activity of the MPS is modulated by an opsonic protein. The opsonic activity in plasma diminishes during shock, and this change may account in part for the depression in MPS function. As a result, antibacterial and antitoxin defense mechanisms are impaired. Hypoperfusion also suppresses the barrier function of the adherens junctions and tight junctions in the intestinal epithelium. Endotoxins from the normal bacterial flora of the intestine constantly enter the circulation. Ordinarily, they are inactivated by the MPS, principally in the liver. Disruption of the intestinal epithelial barrier, together with depression of the MPS, allows these endotoxins to invade the general circulation. Endotoxins produce profound, generalized vasodilation, mainly by inducing the synthesis of an isoform of nitric oxide synthase in the smooth muscle of blood vessels throughout the body. The profound vasodilation aggravates the hemodynamic changes caused by blood loss.

In addition to their role in inactivating endotoxin, macrophages release many of the mediators associated with shock. These mediators include acid hydrolases, neutral proteases, oxygen free radicals, certain coagulation factors, and the following arachidonic acid derivatives: prostaglandins, thromboxanes, and leukotrienes. Macrophages also release certain monokines that modulate temperature regulation, intermediary metabolism, hormone secretion, and the immune system.

Interactions of Positive and Negative Feedback Mechanisms

Hemorrhage provokes a multitude of circulatory and metabolic derangements. Some of these changes are compensatory, and others are decompensatory. Some of these feedback mechanisms possess high gain and others possess low gain. Furthermore, the gain of any specific mechanism varies with the severity of the hemorrhage. For example, with only a slight loss of blood, P_a is maintained within the normal range and the gain of the baroreceptor reflexes is high. With greater losses of blood, when P_a is below 60 mm Hg (i.e., below the threshold for the baroreceptors), further reductions in pressure have no additional influence through the baroreceptor reflexes. Hence, below this critical pressure, the baroreceptor reflex gain is zero or near zero.

In general, with minor degrees of blood loss, the gains of negative feedback mechanisms are high, whereas those of positive feedback mechanisms are low. The opposite is true with more severe hemorrhage. The gains of the various mechanisms add algebraically. Therefore, whether a vicious cycle develops depends on whether the sum of the positive and negative gains exceeds 1. Total gains in excess of 1 are, of course, more likely to occur with severe losses of blood. Therefore, to avert a vicious cycle, serious hemorrhages must be treated quickly and intensively, preferably by whole blood transfusion, before the process becomes irreversible.

Key Points

1. Two important relationships between cardiac output (Q_h) and central venous pressure (P_v) prevail in the cardiovascular system. With regard to the heart, Q_h varies directly with P_v (or preload) over a very wide range of P_v. This relationship is represented by the cardiac function curve, and it expresses the Frank-Starling mechanism. In the vascular system, P_v varies inversely with Q_h. This relationship is represented by the vascular function curve, and it reflects the fact that as Q_h increases, a greater fraction of the total blood volume resides in the arteries and a smaller volume resides in the veins.
2. The principal cardiac mechanisms that govern cardiac output are the changes in numbers of myocardial crossbridges that interact and in the affinity of the contractile proteins for Ca^{++}. The principal factors that govern the vascular function curve are arterial and venous compliance, peripheral vascular resistance, and total blood volume.
3. The equilibrium values of Q_h and P_v that prevail under a given set of conditions are determined by the intersection of the cardiac and vascular function curves. At very low and very high HRs, the heart is unable to produce adequate Q_h. At very low HRs, the increase in filling during diastole cannot compensate for the small number of cardiac contractions per minute. At very high HRs, the large number of contractions per minute cannot compensate for the inadequate filling time.
4. Gravity influences Q_h because the veins are so compliant, and substantial quantities of blood tend to pool in the veins of dependent portions of the body. Respiration changes the pressure gradient between the intrathoracic and extrathoracic veins. Hence, respiration serves as an auxiliary pump, which may affect the mean level of Q_h and induce rhythmic changes in SV during the various phases of the respiratory cycle.
5. In anticipation of exercise, vagus nerve impulses to the heart are inhibited and the sympathetic nervous system is activated by central command. The result is an increase in HR, myocardial contractile force, and regional vascular resistance. In addition, vascular resistance increases in the skin, kidneys, splanchnic regions, and inactive muscles and decreases markedly in the active muscles. The overall effect is a pronounced reduction in TPR, which, along with the auxiliary pumping action of the contracting skeletal muscles, greatly increases venous return. The increases in HR and myocardial contractility, both induced by the activation of cardiac sympathetic nerves, enables the heart to transfer blood to the pulmonary and systemic circulations, thereby increasing cardiac output. SV increases only slightly. O_2 consumption and blood O_2 extraction increase, and systolic pressure and mean blood pressure increase slightly. As body temperature rises during exercise, the skin blood vessels dilate. However, when the HR becomes maximal during severe exercise, the skin vessels constrict. This increases the effective blood volume but causes greater increases in body temperature and a feeling of exhaustion. The limiting factor in exercise performance is delivery of blood to the active muscles.
6. Acute blood loss induces tachycardia, hypotension, generalized arteriolar constriction, and generalized venoconstriction. Acute blood loss invokes a number of negative feedback (compensatory) mechanisms, such as baroreceptor and chemoreceptor reflexes, responses to moderate cerebral ischemia, reabsorption of tissue fluids, release of endogenous vasoconstrictors, and renal conservation

of water and electrolytes. Acute blood loss also invokes a number of positive feedback (decompensatory) mechanisms, such as cardiac failure, acidosis, central nervous system depression, aberrations in blood coagulation, and depression of the MPS. The outcome of acute blood loss depends on the sum of gains of the positive and negative feedback mechanisms and on the interactions between these mechanisms.