

7th edition

Cardiovascular Physiology

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Graw
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LANGUE

OBJECTIVES

The student understands the general mechanisms involved in local vascular control:

- ▶ *Identifies the major ways in which smooth muscle differs anatomically and functionally from striated muscle.*
- ▶ *Lists the steps leading to cross-bridge cycling in smooth muscle.*
- ▶ *Lists the major ion channels involved in the regulation of membrane potential in smooth muscle.*
- ▶ *Describes the processes of electromechanical and pharmacomechanical coupling in smooth muscle.*
- ▶ *Defines basal tone.*
- ▶ *Lists several substances potentially involved in local metabolic control.*
- ▶ *States the local metabolic vasodilator hypothesis.*
- ▶ *Describes how vascular tone is influenced by prostaglandins, histamine, and bradykinin.*
- ▶ *Describes the myogenic response of blood vessels.*
- ▶ *Defines active and reactive hyperemia and indicates a possible mechanism for each.*
- ▶ *Defines autoregulation of blood flow and briefly describes the metabolic, myogenic, and tissue pressure theories of autoregulation.*
- ▶ *Defines neurogenic tone and describes how sympathetic (and parasympathetic) neural influences can alter it.*
- ▶ *Describes how vascular tone is influenced by circulating catecholamines, vasopressin, and angiotensin II.*
- ▶ *Lists the major influences on venous diameters.*
- ▶ *Describes, in general, how control of flow differs between organs with strong local metabolic control of arteriolar tone and organs with strong neurogenic control of arteriolar tone.*

The student knows the dominant mechanisms of flow and blood volume control in the major body organs:

- ▶ *States the relative importance of local metabolic and neural control of coronary blood flow.*
- ▶ *Defines systolic compression and indicates its relative importance to blood flow in the endocardial and epicardial regions of the right and left ventricular walls.*

- ▶ *Describes the major mechanisms of flow and blood volume control in each of the following specific systemic organs: skeletal muscle, brain, splanchnic organs, skin, and kidney.*
- ▶ *States why mean pulmonary arterial pressure is lower than mean systemic arterial pressure.*
- ▶ *Describes how pulmonary vascular control differs from that in systemic organs.*



Because the body's metabolic needs are continually changing, the cardiovascular system must continually make adjustments in the diameter of its vessels. The purposes of these vascular changes are (1) to efficiently distribute the cardiac output among tissues with different current needs (the job of arterioles) and (2) to regulate the distribution of blood volume and cardiac filling (the job of veins). In this chapter we discuss our current understanding of how all this is accomplished.

VASCULAR SMOOTH MUSCLE



Vascular diameter adjustments are made by regulating the contractile activity of vascular smooth muscle cells, which are present in the walls of all vessels except capillaries. The task of the vascular smooth muscle is unique, because to maintain a certain vessel diameter in the face of the continual distending pressure of the blood within it, the vascular smooth muscle must be able to sustain active tension for prolonged periods.

There are many functional characteristics that distinguish smooth muscle from either skeletal or cardiac muscle. For example, when compared with these other muscle types, smooth muscle cells:

1. Contract and relax much more slowly.
2. Develop active tension over a greater range of muscle lengths.
3. Can change their contractile activity as a result of action potentials or changes in resting membrane potential.
4. May change their contractile activity in the absence of changes in membrane potential.
5. Maintain tension for prolonged periods at low energy cost.
6. Can be activated by stretch.

Contractile Machinery

Vascular smooth muscle cells are small (approximately $5\ \mu\text{m} \times 50\ \mu\text{m}$) spindle-shaped cells usually arranged circumferentially or at small helical angles in blood vessel walls. In many but not all vessels, adjacent smooth muscle cells are electrically connected by gap junctions similar to those found in the myocardium.

Just as in other muscle types, smooth muscle force development and shortening are the result of cross-bridge interaction between thick and thin contractile filaments composed of myosin and actin, respectively. In smooth muscle, however, these filaments are not arranged in regular, repeating sarcomere units. As a consequence, “smooth” muscle cells lack the microscopically visible striations, characteristic of skeletal and cardiac muscle cells. The actin filaments in smooth muscle are much longer than those in striated muscle. Many of these actin filaments attach to the inner surface of the cell at structures called *dense bands*. In the interior of the cell, actin filaments do not attach to Z-lines but rather anchor to small transverse structures called *dense bodies* that are themselves tethered to the surface membrane by cable-like *intermediate filaments*. Myosin filaments are interspersed between the smooth muscle actin filaments but in a more haphazard fashion than the regular interweaving pattern of striated muscle. In striated muscle, the contractile filaments are invariably aligned with the long axis of the cell whereas in smooth muscle, many contractile filaments travel obliquely or even transversely to the long axis of the cell. Despite the absence of organized sarcomeres, changes in smooth muscle length affect its ability to actively develop tension. Perhaps because of the long actin filaments and the lack of sarcomere arrangement, smooth muscle can develop tension over a greater range of length changes than either skeletal or cardiac muscle.

As in striated muscle, the strength of the cross-bridge interaction between thick and thin filaments in smooth muscle is controlled primarily by changes in the intracellular free Ca^{2+} level, which range from approximately 10^{-8} M in the relaxed muscle to 10^{-5} M during maximal contraction. However, the sequence of steps linking an increased free Ca^{2+} level to contractile filament interaction is different in smooth muscle than in striated muscle. In the smooth muscle:

1. Ca^{2+} first forms a complex with the calcium-binding protein *calmodulin*.
2. The Ca^{2+} –calmodulin complex then activates a phosphorylating enzyme called *myosin light-chain kinase*.
3. This enzyme causes phosphorylation by adenosine triphosphate (ATP) of the light-chain protein that is a portion of the cross-bridge head of myosin.
4. Myosin light-chain phosphorylation enables cross-bridge formation and cycling during which energy from ATP is utilized for tension development and shortening.



Smooth muscle is also unique in that once tension is developed, it can be maintained at very low energy costs, that is, without the need to continually split ATP in cross-bridge cycling. The mechanisms responsible are still somewhat unclear but presumably involve very slowly cycling or even non-cycling cross-bridges. This is often referred to as the *latch state* and may involve light-chain dephosphorylation of attached cross-bridges. Also by mechanisms that are yet incompletely understood, it is apparent that vascular smooth muscle contractile activity is regulated not only by changes in intracellular free Ca^{2+} levels but also by changes in the Ca^{2+} *sensitivity* of the contractile machinery. Thus, the

contractile state of vascular smooth muscle may sometimes change in the absence of changes in intracellular free Ca^{2+} levels.

Membrane Potentials

Smooth muscle cells have resting membrane potentials ranging from -40 to -65 mV and thus are generally lower than those in striated muscle. As in all cells, the resting membrane potential of the smooth muscle is determined largely by the cell permeability to potassium. Many types of K^+ channels have been identified in smooth muscle. The one that seems to be predominantly responsible for determining the resting membrane potential is termed an *inward rectifying-type* K^+ channel. (*Inward rectifying* implies that K^+ ions move into cells through this channel slightly more easily than they move out through it.) There are also *ATP-dependent* K^+ channels that are closed when cellular ATP levels are normal but open if ATP levels fall. Such channels have been proposed to be important in matching organ blood flow to the metabolic state of the tissue.

Smooth muscle cells regularly have action potentials only in certain vessels. When they do occur, smooth muscle action potentials are initiated primarily by inward Ca^{2+} current and are developed slowly like the “slow-type” cardiac action potentials (see Figure 2–2). As in the heart, this inward (depolarizing) Ca^{2+} current flows through a *voltage-operated calcium channel* (VOC); this type of channel is one of several types of calcium channels present in the smooth muscle. The repolarization phase of the action potential occurs primarily by an outward flux of potassium ions through both *delayed* K^+ channels and *calcium-activated* K^+ channels.

Many types of ion channels in addition to those mentioned have been identified in vascular smooth muscle, but in most cases their exact role in cardiovascular function remains obscure. For example, there appear to be nonselective, stretch-sensitive cation channels that may be involved in the response of smooth muscle to stretch. The reader should note, however, that many of the important ion channels in vascular smooth muscle are also important in heart muscle (see Table 2–1).

Electromechanical Versus Pharmacomechanical Coupling



In smooth muscle, changes in intracellular free Ca^{2+} levels can occur both with *and* without changes in membrane potential. The processes involved are called *electromechanical coupling* and *pharmacomechanical coupling*, respectively, and are illustrated in Figure 7–1.

Electromechanical coupling, shown in the left half of Figure 7–1, occurs because the smooth muscle surface membrane contains voltage-operated channels for calcium (the same VOCs that are involved in action potential generation). Membrane depolarization increases the open-state probability of these channels and thus leads to smooth muscle cell contraction and vessel constriction. Conversely, membrane hyperpolarization leads to smooth muscle relaxation and vessel dilation. Because the VOCs for Ca^{2+} are partially activated by the low resting membrane potential of the

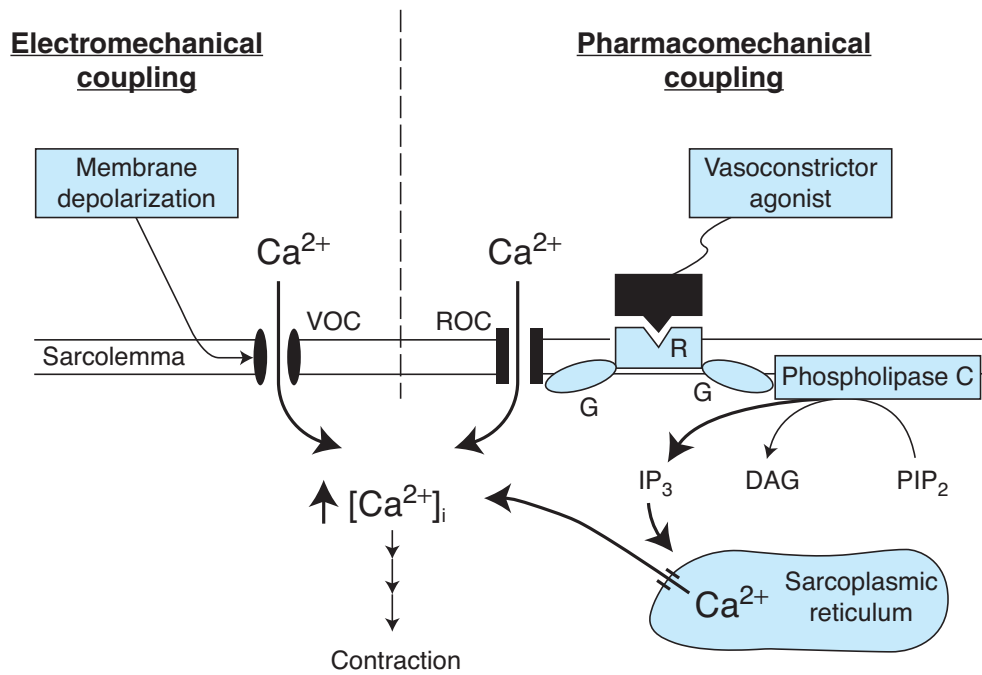


Figure 7-1. General mechanisms for activation of the vascular smooth muscle. VOC, voltage-operated Ca²⁺ channel; ROC, receptor-operated Ca²⁺ channel; R, agonist-specific receptor; G, GTP-binding protein; PIP₂, phosphatidylinositol biphosphate; IP₃, inositol triphosphate; DAG, diacylglycerol.

vascular smooth muscle, changes in resting potential can alter the resting calcium influx rate and therefore the basal contractile state.

With pharmacomechanical coupling, chemical agents (eg, released neurotransmitters) can induce smooth muscle contraction without the need for a change in membrane potential. As illustrated in the right side of Figure 7-1, the combination of a vasoconstrictor agonist (such as norepinephrine) with a specific membrane-bound receptor (such as an α_1 -adrenergic receptor) initiates events that cause intracellular free Ca²⁺ levels to increase for two reasons. One, the activated receptor may open surface membrane *receptor-operated channels* for Ca²⁺ that allow Ca²⁺ influx from the extracellular fluid. Two, the activated receptor may induce the formation of an intracellular “second messenger,” inositol trisphosphate (IP₃), that opens specific channels that release Ca²⁺ from the intracellular sarcoplasmic reticulum stores. In both processes, the activated receptor first stimulates specific guanosine triphosphate-binding proteins (GTP-binding proteins or *G proteins*). Such receptor-associated G proteins seem to represent a general first step through which most membrane receptors operate to initiate their particular cascade of events that ultimately lead to specific cellular responses.

The reader should *not* conclude from Figure 7-1 that all vasoactive chemical agents (chemical agents that cause vascular effects) produce their actions on the smooth muscle without changing membrane potential. In fact, most vasoactive chemical agents do cause changes in membrane potential because their receptors can be linked, by G proteins or other means, to ion channels of many kinds.

Not shown in Figure 7–1 are the processes that remove Ca^{2+} from the cytoplasm of the vascular smooth muscle although they are important as well in determining the free cytosolic Ca^{2+} levels. As in cardiac cells (see Figure 2–7), smooth muscle cells actively pump calcium into the sarcoplasmic reticulum and outward across the sarcolemma. Calcium is also countertransported out of the cell in exchange for sodium.

Mechanisms for Relaxation

Hyperpolarization of the cell membrane is one mechanism for causing smooth muscle relaxation and vessel dilation. In addition, however, there are at least two general mechanisms by which certain chemical vasodilator agents can cause smooth muscle relaxation by pharmacomechanical means. In Figure 7–1, the specific receptor for a chemical vasoconstrictor agent is shown linked by a specific G protein to phospholipase C. In an analogous manner, other specific receptors may be linked by other specific G proteins to other enzymes that produce second messengers other than IP_3 . An example is the β_2 -adrenergic receptor¹ that is present in arterioles of the skeletal muscle and liver. β_2 -Receptors are not innervated but can sometimes be activated by abnormally elevated levels of circulating *epinephrine*. The β_2 -receptor is linked by a particular G protein (G_s) to adenylate cyclase. Adenylate cyclase catalyzes the conversion of ATP to cyclic adenosine monophosphate (cAMP). Increased intracellular levels of cAMP cause the activation of protein kinase A, a phosphorylating enzyme that in turn causes phosphorylation of proteins at many sites. The overall result is stimulation of Ca^{2+} efflux, membrane hyperpolarization, and decreased contractile machinery sensitivity to Ca^{2+} —all of which act synergistically to cause vasodilation. In addition to epinephrine, histamine and vasoactive intestinal peptide are vasodilator substances that act through the cAMP pathway.

In addition to cAMP, cyclic guanosine monophosphate (cGMP) is an important intracellular second messenger that causes vascular smooth muscle relaxation by mechanisms that are not yet clear. Nitric oxide is an important vasodilator substance that operates via the cGMP pathway. Nitric oxide can be produced by endothelial cells and also by nitrates, a clinically important class of vasodilator drugs. Nitric oxide is gaseous and easily diffuses into smooth muscle cells, where it activates the enzyme guanylyl cyclase that in turn causes cGMP formation from GTP.

Vascular Tone

Vascular tone is a term commonly used to characterize the general contractile state of a vessel or a vascular region. The “vascular tone” of a region can be taken as an indication of the “level of activation” of the individual smooth muscle cells in that region.

¹ Vascular β -receptors are designated β_2 -receptors and are pharmacologically distinct from the β_1 -receptors found on cardiac cells.

CONTROL OF ARTERIOLAR TONE

As described in Chapter 6, the blood flow through any organ is determined largely by its vascular resistance, which is dependent primarily on the diameter of its arterioles. Consequently, an organ's flow is controlled by factors that influence the arteriolar smooth muscle tone.

Basal Tone

Arterioles remain in a state of partial constriction even when all external influences on them are removed; hence, they are said to have a degree of *basal tone* (sometimes referred to as *intrinsic tone*). The understanding of the mechanism is incomplete, but basal arteriolar tone may be a reflection of the fact that smooth muscle cells inherently and actively resist being stretched as they continually are in pressurized arterioles. Another hypothesis is that the basal tone of arterioles is the result of a tonic production of local vasoconstrictor substances by the endothelial cells that line their inner surface. In any case, this basal tone establishes a baseline of partial arteriolar constriction from which the external influences on arterioles exert their dilating or constricting effects. These influences can be separated into three categories: local influences, neural influences, and hormonal influences.

Local Influences on Arterioles

LOCAL METABOLIC INFLUENCES



The arterioles that control flow through a given organ lie within the organ tissue itself. Thus, arterioles and the smooth muscle in their walls are exposed to the chemical composition of the interstitial fluid of the organ they serve. The interstitial concentrations of many substances reflect the balance between the metabolic activity of the tissue and its blood supply. Interstitial oxygen levels, for example, fall whenever the tissue cells are using oxygen faster than it is being supplied to the tissue by blood flow. Conversely, interstitial oxygen levels rise whenever excess oxygen is being delivered to a tissue from the blood. In nearly all vascular beds, exposure to low oxygen reduces arteriolar tone and causes vasodilation, whereas high oxygen levels cause arteriolar vasoconstriction.² Thus, a local feedback mechanism exists that automatically operates on arterioles to regulate a tissue's blood flow in accordance with its metabolic needs. Whenever blood flow and oxygen delivery fall below a tissue's oxygen demands, the oxygen levels around arterioles fall, the arterioles dilate, and the blood flow through the organ appropriately increases.

Many substances in addition to oxygen are present within tissues and can affect the tone of the vascular smooth muscle. When the metabolic rate of skeletal muscle is increased by exercise, for example, not only do tissue levels of oxygen decrease, but those of carbon dioxide, H^+ , and K^+ increase. Muscle tissue osmolarity also increases during exercise. All these chemical alterations cause arteriolar dilation. In

² An important exception to this rule occurs in the pulmonary circulation and is discussed later in this chapter.

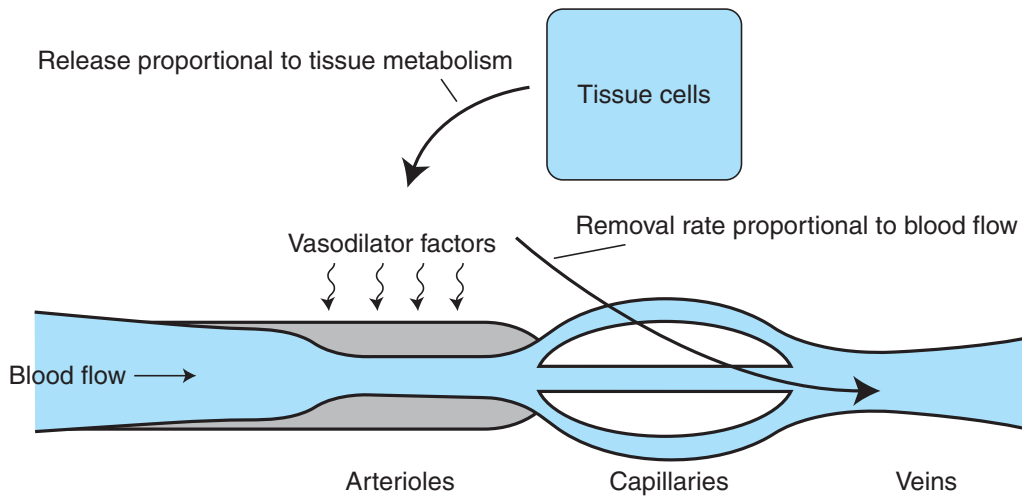


Figure 7–2. Local metabolic vasodilator hypothesis.

addition, with increased metabolic activity or oxygen deprivation, cells in many tissues may release *adenosine*, which is an extremely potent vasodilator agent.

At present, it is not known which of these (or possibly other) metabolically related chemical alterations within tissues are most important in the local metabolic control of blood flow. It appears likely that arteriolar tone depends on the combined action of many factors.

For conceptual purposes, Figure 7–2 summarizes current understanding of local metabolic control. Vasodilator factors enter the interstitial space from the tissue cells at a rate proportional to tissue metabolism. These vasodilator factors are removed from the tissue at a rate proportional to blood flow. Whenever tissue metabolism is proceeding at a rate for which the blood flow is inadequate, the interstitial vasodilator factor concentrations automatically build up and cause the arterioles to dilate. This, of course, causes blood flow to increase. The process continues until blood flow has risen sufficiently to appropriately match the tissue metabolic rate and prevent further accumulation of vasodilator factors. The same system also operates to reduce blood flow when it is higher than required by the tissue's metabolic activity, because this situation causes a reduction in the interstitial concentrations of metabolic vasodilator factors.

Local metabolic mechanisms represent by far the most important means of local flow control. By these mechanisms, individual organs are able to regulate their own flow in accordance with their metabolic needs. As indicated below, several other types of local influences on blood vessels have been identified. However, many of these represent fine-tuning mechanisms and many are important only in certain, usually pathological, situations.

LOCAL INFLUENCES FROM ENDOTHELIAL CELLS

Endothelial cells cover the entire inner surface of the cardiovascular system. A large number of studies have shown that blood vessels respond very differently to certain vascular influences when their endothelial lining is missing. Acetylcholine, for example, causes vasodilation of intact vessels but causes vasoconstriction of

vessels stripped of their endothelial lining. This and similar results led to the realization that endothelial cells can actively participate in the control of arteriolar diameter by producing local chemicals that affect the tone of the surrounding smooth muscle cells. In the case of the vasodilator effect of infusing acetylcholine through intact vessels, the vasodilator influence produced by endothelial cells has been identified as nitric oxide. Nitric oxide is produced within endothelial cells from the amino acid, L-arginine, by the action of an enzyme, nitric oxide synthase. Nitric oxide synthase is activated by a rise in the intracellular level of the Ca^{2+} . Nitric oxide is a small lipid-soluble molecule that, once formed, easily diffuses into adjacent smooth muscle cells where it causes relaxation by stimulating cGMP production as mentioned previously.

Acetylcholine and several other agents (including bradykinin, vasoactive intestinal peptide, and substance P) stimulate endothelial cell nitric oxide production because their receptors on endothelial cells are linked to receptor-operated Ca^{2+} channels. Probably more importantly from a physiological standpoint, flow-related shear stresses on endothelial cells stimulate their nitric oxide production presumably because stretch-sensitive channels for Ca^{2+} are activated. Such flow-related endothelial cell nitric oxide production may explain why, for example, exercise and increased blood flow through muscles of the lower leg can cause dilation of the blood-supplying femoral artery at points far upstream of the exercising muscle itself.

Agents that block nitric oxide production by inhibiting nitric oxide synthase cause significant increases in the vascular resistances of most organs. For this reason, it is believed that endothelial cells are normally always producing some nitric oxide that is importantly involved, along with other factors, in reducing the normal net resting tone of arterioles throughout the body.

Endothelial cells have also been shown to produce several other locally acting vasoactive agents including the vasodilators “endothelial-derived hyperpolarizing factor” and prostacyclin and the vasoconstrictor *endothelin*. The roles of these agents in the overall scheme of normal checks and balances on local flow control are speculative at present. With the possible exception of flow-dependent, shear stress-related influences on endothelial cells, it is difficult to imagine how endothelial factors could play much of a role in tissue-specific blood flow control. The endothelial cells of arterioles in any organ are exposed primarily to the conditions in the incoming arterial blood rather than those in the tissues being served. Therefore, endothelial factors seem more likely to be important in global than local blood flow control.

OTHER LOCAL CHEMICAL INFLUENCES



In addition to local metabolic influences on vascular tone, many specific locally produced and locally acting chemical substances have been identified that have vascular effects and therefore could be important in local vascular regulation in certain instances. In most cases, however, definite information about the relative importance of these substances in cardiovascular regulation is lacking.

Prostaglandins and *thromboxane* are a group of several chemically related products of the cyclooxygenase pathway of arachidonic acid metabolism. Certain prostaglandins are potent vasodilators, while others are potent vasoconstrictors. Despite the vasoactive potency of the prostaglandins and the fact that most tissues (including endothelial cells and vascular smooth muscle cells) are capable of

synthesizing prostaglandins, it has not been demonstrated convincingly that prostaglandins play a crucial role in *normal* vascular control. It is clear, however, that vasodilator prostaglandins are involved in inflammatory responses. Consequently, inhibitors of prostaglandin synthesis, such as aspirin, are effective anti-inflammatory drugs. Prostaglandins produced by platelets and endothelial cells are important in the hemostatic (flow stopping, antibleeding) vasoconstrictor and platelet-aggregating responses to vascular injury. Hence, aspirin is often prescribed to reduce the tendency for blood clotting—especially in patients with potential coronary flow limitations. Arachidonic acid metabolites produced via the lipoxygenase system (eg, *leukotrienes*) also have vasoactive properties and may influence blood flow and vascular permeability during inflammatory processes.

Histamine is synthesized and stored in high concentrations in secretory granules of tissue mast cells and circulating basophils. When released, histamine produces arteriolar vasodilation (via the cAMP pathway) and increases vascular permeability, which leads to edema formation and local tissue swelling. Histamine increases vascular permeability by causing separations in the junctions between the endothelial cells that line the vascular system. Histamine release is classically associated with *antigen–antibody reactions* in various allergic and immune responses. Many drugs and physical or chemical insults that damage tissue also cause histamine release. Histamine can stimulate sensory nerve endings to cause itching and pain sensations. While clearly important in many pathological situations, it seems unlikely that histamine participates in normal cardiovascular regulation.

Bradykinin is a small polypeptide that has about 10 times the vasodilator potency of histamine on a molar basis. It also acts to increase capillary permeability by opening the junctions between endothelial cells. Bradykinin is formed from certain plasma globulin substrates by the action of an enzyme, *kallikrein*, and is subsequently rapidly degraded into inactive fragments by various tissue kinases. Like histamine, bradykinin is thought to be involved in the vascular responses associated with tissue injury and immune reactions. It also stimulates nociceptive nerves and may thus be involved in the pain associated with tissue injury.

TRANSMURAL PRESSURE

The passive elastic mechanical properties of arteries and veins and how changes in transmural pressure affect their diameters were discussed in Chapter 6. The effect of transmural pressure on arteriolar diameter is more complex because arterioles respond both *passively* and *actively* to changes in transmural pressure. For example, a sudden increase in the internal pressure within an arteriole produces (1) first an initial slight passive mechanical distention (slight because arterioles are relatively thick-walled and muscular), and (2) then an active constriction that, within seconds, may completely reverse the initial distention. A sudden decrease in transmural pressure elicits essentially the opposite response, that is, an immediate passive decrease in diameter followed shortly by a decrease in active tone, which returns the arteriolar diameter to near that which existed before the pressure change. The active phase of such behavior is referred to as a *myogenic response*, because it seems to originate within the smooth muscle itself. The mechanism of the myogenic response is not

known for certain, but stretch-sensitive ion channels on arteriolar vascular smooth muscle cells are likely candidates for involvement.

All arterioles have some normal distending pressure to which they are probably actively responding. Therefore, the myogenic mechanism is likely to be a fundamentally important factor in determining the basal tone of arterioles everywhere. Also, for obvious reasons and as soon discussed, the myogenic response is potentially involved in the vascular reaction to any cardiovascular disturbance that involves a change in arteriolar transmural pressure.

FLOW RESPONSES CAUSED BY LOCAL MECHANISMS

In organs with a highly variable metabolic rate, such as skeletal and cardiac muscles, the blood flow closely follows the tissue's metabolic rate. For example, skeletal muscle blood flow increases within seconds of the onset of muscle exercise and returns to control values shortly after exercise ceases. This phenomenon, which is illustrated in Figure 7–3A, is known as *exercise* or *active hyperemia* (*hyperemia* means high flow). It should be clear how active hyperemia could result from the local metabolic

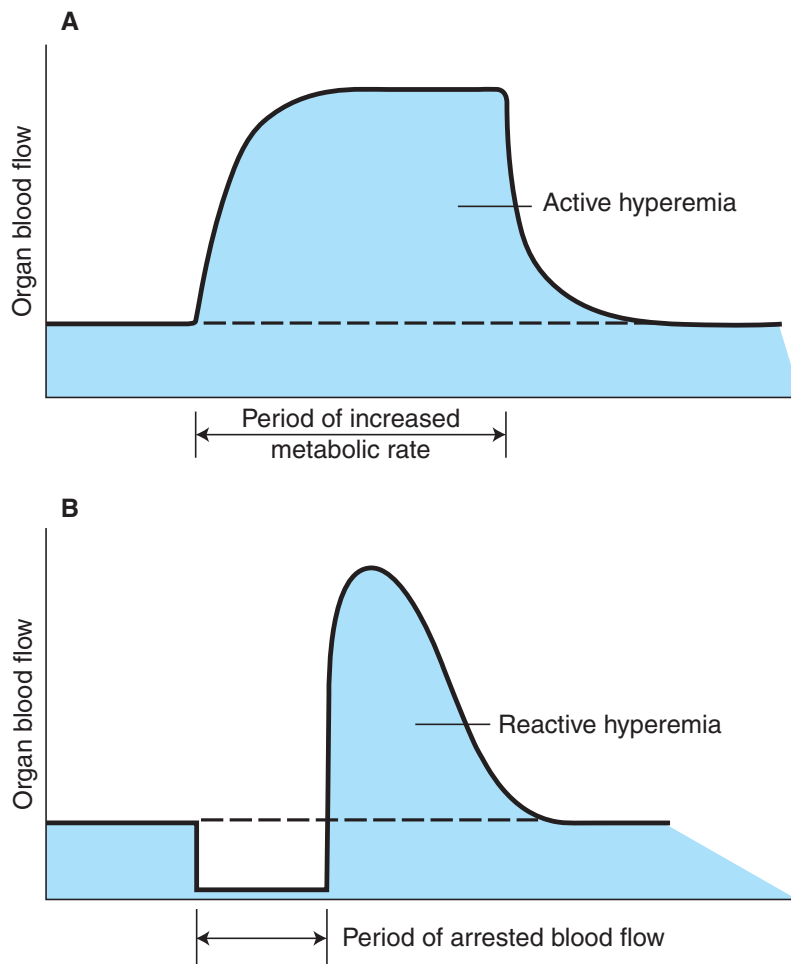


Figure 7–3. Organ blood flow responses caused by local mechanisms: active and reactive hyperemias.

vasodilator feedback on the arteriolar smooth muscle. As alluded to previously, once initiated by local metabolic influences on small resistance vessels, endothelial flow-dependent mechanisms may assist in propagating the vasodilation to larger vessels upstream, which helps promote the delivery of blood to the exercising muscle.

Reactive or postocclusion hyperemia is a higher than normal blood flow that occurs transiently after the removal of any restriction that has caused a period of lower than normal blood flow. The phenomenon is illustrated in Figure 7–3B. For example, flow through an extremity is higher than normal for a period after a tourniquet is removed from the extremity. Both local metabolic and myogenic mechanisms may be involved in producing reactive hyperemia. The magnitude and duration of reactive hyperemia depend on the duration and severity of the occlusion as well as the metabolic rate of the tissue. These findings are best explained by an interstitial accumulation of metabolic vasodilator substances during the period of flow restriction. However, unexpectedly large flow increases can follow arterial occlusions lasting only 1 or 2 seconds. These may be explained best by a myogenic dilation response to the reduced intravascular pressure and decreased stretch of the arteriolar walls that exists during the period of occlusion.

Except when displaying active and reactive hyperemia, nearly all organs tend to keep their blood flow constant despite variations in arterial pressure—that is, they *autoregulate* blood flow. As shown in Figure 7–4A, an abrupt increase in arterial pressure is normally accompanied by an initial abrupt increase in organ blood flow that then gradually returns toward normal despite the sustained elevation in arterial pressure. The initial rise in flow with increased pressure is expected from the basic flow equation ($\dot{Q} = \Delta P/R$). The subsequent return of flow toward the normal level is caused by a gradual increase in active arteriolar tone and resistance to blood flow. Ultimately, a new steady state is reached with only slightly elevated blood flow because the increased driving pressure is counteracted by a higher than normal vascular resistance. As with the phenomenon of reactive hyperemia, blood flow autoregulation may be caused by both local metabolic feedback mechanisms and myogenic mechanisms. The arteriolar vasoconstriction responsible for the autoregulatory response shown in Figure 7–4A, for example, may be partially due to (1) a “washout” of metabolic vasodilator factors from the interstitium by the excessive initial blood flow and (2) a myogenic increase in arteriolar tone stimulated by the increase in stretching forces that the increase in pressure imposes on the vessel walls. There is also a *tissue pressure hypothesis* of blood flow autoregulation for which it is assumed that an abrupt increase in arterial pressure causes transcapillary fluid filtration and thus leads to a gradual increase in interstitial fluid volume and pressure. Presumably the increase in extravascular pressure would cause a decrease in vessel diameter by simple compression. This mechanism might be especially important in organs such as the kidney and brain whose volumes are constrained by external structures.

Although not illustrated in Figure 7–4A, autoregulatory mechanisms operate in the opposite direction in response to a decrease in arterial pressure below the normal value. One important general consequence of local autoregulatory mechanisms is that the steady-state blood flow in many organs tends to remain near the normal value over quite a wide range of arterial pressure. This is illustrated in the graph in Figure 7–4B. As discussed later, the inherent ability of certain organs to maintain

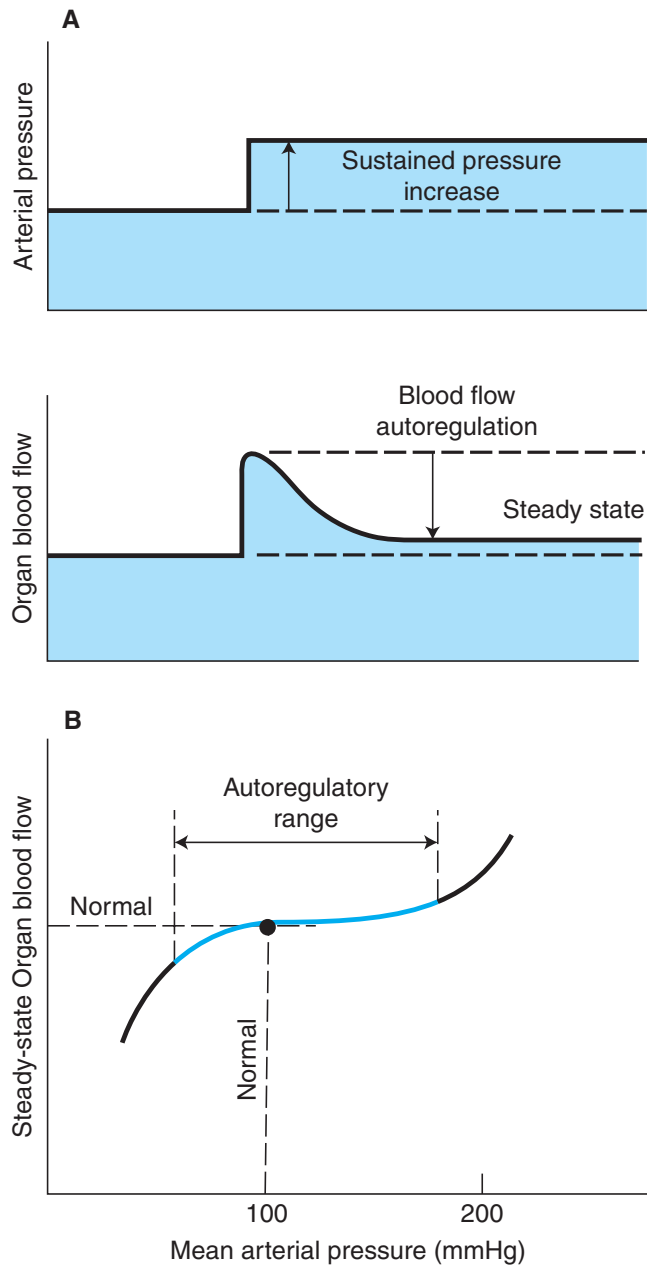


Figure 7-4. Autoregulation of organ blood flow.

adequate blood flow despite lower than normal arterial pressure is of considerable importance in situations such as shock from blood loss.

Neural Influences on Arterioles

SYMPATHETIC VASOCONSTRICTOR NERVES



These neural fibers innervate arterioles in all systemic organs and provide by far the most important means of *reflex* control of the vasculature. Sympathetic vasoconstrictor nerves are the backbone of the system for controlling total

peripheral resistance and thus are essential participants in global cardiovascular tasks such as regulating arterial blood pressure.



Sympathetic vasoconstrictor nerves release norepinephrine from their terminal structures in amounts generally proportional to their electrical activity. Norepinephrine causes an increase in the tone of arterioles after combining with an α_1 -adrenergic receptor on smooth muscle cells. Norepinephrine appears to increase vascular tone primarily by pharmacomechanical means. The mechanism involves G-protein linkage of α -adrenergic receptors to phospholipase C and subsequent Ca^{2+} release from intracellular stores by the action of the second messenger IP_3 , as illustrated in the right side of Figure 7-1.

Sympathetic vasoconstrictor nerves normally have a continual or *tonic firing activity*. This tonic activity of sympathetic vasoconstrictor nerves makes the normal contractile tone of arterioles considerably greater than their basal tone. The additional component of vascular tone is called *neurogenic tone*. When the firing rate of sympathetic vasoconstrictor nerves is increased above normal, arterioles constrict and cause organ blood flow to fall below normal. Conversely, vasodilation and increased organ blood flow can be caused by sympathetic vasoconstrictor nerves if their normal tonic activity level is reduced. Thus, an organ's blood flow can either be reduced below normal or be increased above normal by changes in the sympathetic vasoconstrictor fiber firing rate.

OTHER NEURAL INFLUENCES

Blood vessels, as a general rule, do not receive innervation from the parasympathetic division of the autonomic nervous system. However, *parasympathetic vasodilator nerves*, which release *acetylcholine*, are present in the vessels of the brain and the heart, but their influence on arteriolar tone in these organs appears to be inconsequential. Parasympathetic vasodilator nerves are also present in the vessels of the salivary glands, pancreas, gastric mucosa, and external genitalia. In the latter, they are responsible for the vasodilation of inflow vessels responsible for erection.

Hormonal Influences on Arterioles



Under normal circumstances, hormonal influences on blood vessels are generally thought to be of minor consequence in comparison to the local metabolic and neural influences. However, it should be emphasized that the understanding of how the cardiovascular system operates in many situations is incomplete. Thus, the hormones discussed in the following sections may play more important roles in cardiovascular regulation than is now appreciated.

CIRCULATING CATECHOLAMINES

During activation of the sympathetic nervous system, the adrenal glands release the catecholamines *epinephrine* and *norepinephrine* into the bloodstream. Under normal circumstances, the blood levels of these agents are probably not high enough to cause significant cardiovascular effects. However, circulating catecholamines may have cardiovascular effects in situations (such as vigorous exercise or hemorrhagic shock) that

involve high activity of the sympathetic nervous system. In general, the cardiovascular effects of high levels of circulating catecholamines parallel the direct effects of sympathetic activation, which have already been discussed; both epinephrine and norepinephrine can activate cardiac β_1 -adrenergic receptors to increase the heart rate and myocardial contractility and can activate vascular α -receptors to cause vasoconstriction. Recall that in addition to the α_1 -receptors that mediate vasoconstriction, arterioles in a few organs also possess β_2 -adrenergic receptors that mediate vasodilation. Because vascular β_2 -receptors are more sensitive to epinephrine than are vascular α_1 -receptors, moderately elevated levels of circulating epinephrine can cause vasodilation, whereas higher levels cause α_1 -receptor-mediated vasoconstriction. Vascular β_2 -receptors are not innervated and therefore are *not* activated by norepinephrine, released from sympathetic vasoconstrictor nerves. The physiological importance of these vascular β_2 -receptors is unclear because adrenal epinephrine release occurs during periods of increased sympathetic activity when arterioles would simultaneously be undergoing direct neurogenic vasoconstriction. Again, under normal circumstances, circulating catecholamines are not an important factor in cardiovascular regulation.

VASOPRESSIN



This polypeptide hormone, also known as antidiuretic hormone, plays an important role in extracellular fluid homeostasis and is released into the bloodstream from the posterior pituitary gland in response to low blood volume and/or high extracellular fluid osmolarity. Vasopressin acts on collecting ducts in the kidneys to decrease renal excretion of water. Its role in body fluid balance has some very important indirect influences on cardiovascular function, which is discussed in more detail in Chapter 9. Vasopressin, however, is also a potent arteriolar vasoconstrictor. Although it is not thought to be significantly involved in normal vascular control, direct vascular constriction from abnormally high levels of vasopressin may be important in the response to certain disturbances such as severe blood loss through hemorrhage.

ANGIOTENSIN II



Angiotensin II is a circulating polypeptide that regulates aldosterone release from the adrenal cortex as part of the system for controlling body's sodium balance. This system, discussed in greater detail in Chapter 9, is very important in blood volume regulation. Angiotensin II is also a very potent vasoconstrictor agent. Although it should not be viewed as a normal regulator of arteriolar tone, direct vasoconstriction from angiotensin II seems to be an important component of the general cardiovascular response to severe blood loss. There is also strong evidence suggesting that direct vascular actions of angiotensin II may be involved in intrarenal mechanisms for controlling kidney function. In addition, angiotensin II may be partially responsible for the abnormal vasoconstriction that accompanies many forms of hypertension. Again, it should be emphasized that knowledge of many pathological situations—including hypertension—is incomplete. These situations may well involve vascular influences that are not yet recognized.

CONTROL OF VENOUS TONE

Before considering the details of the control of venous tone, recall that venules and veins play a much different role in the cardiovascular system than do arterioles. Arterioles are the inflow valves that control the rate of nutritive blood flow through organs and individual regions within them. Appropriately, arterioles are usually strongly influenced by the current local metabolic needs of the region in which they reside, whereas veins are not. Veins do, however, collectively regulate the distribution of available blood volume between the peripheral and central venous compartments. Recall that central blood volume (and therefore pressure) has a marked influence on stroke volume and cardiac output. Consequently, when one considers what *peripheral* veins are doing, one should be thinking primarily about what the effects will be on *central* venous pressure and cardiac output.



Veins contain the vascular smooth muscle that is influenced by many things that influence the vascular smooth muscle of arterioles. Constriction of the veins (venoconstriction) is largely mediated through activity of the sympathetic nerves that innervate them. As in arterioles, these sympathetic nerves release norepinephrine, which interacts with α_1 -receptors and produces an increase in venous tone and a decrease in vessel diameter. There are, however, several functionally important differences between veins and arterioles. Compared with arterioles, veins normally have little basal tone. Thus, veins are normally in a dilated state. One important consequence of the lack of basal venous tone is that vasodilator metabolites that may accumulate in the tissue have little effect on veins.

Because of their thin walls, veins are much more susceptible to physical influences than are arterioles. The large effect of internal venous pressure on venous diameter is discussed in Chapter 6 and is evident in the pooling of blood in the veins of the lower extremities that occurs during prolonged standing (as discussed further in Chapter 10).

Often external compressional forces are an important determinant of venous volume. This is especially true of veins in the skeletal muscle. Very high pressures are developed inside skeletal muscle tissue during contraction and cause venous vessels to collapse. Because veins and venules have one-way valves, the blood displaced from veins during skeletal muscle contraction is forced in the forward direction toward the right side of the heart. In fact, rhythmic skeletal muscle contractions can produce a considerable pumping action, often called the *skeletal muscle pump*, which helps return blood to the heart during exercise.

SUMMARY OF PRIMARY VASCULAR CONTROL MECHANISMS

As is apparent from the previous discussion, vessels are subject to a wide variety of influences, and special influences and/or situations often apply to particular organs. Certain general factors, however, dominate the primary control of the peripheral vasculature when it is viewed from the standpoint of overall cardiovascular system function; these influences are summarized in Figure 7–5. Basal tone, local

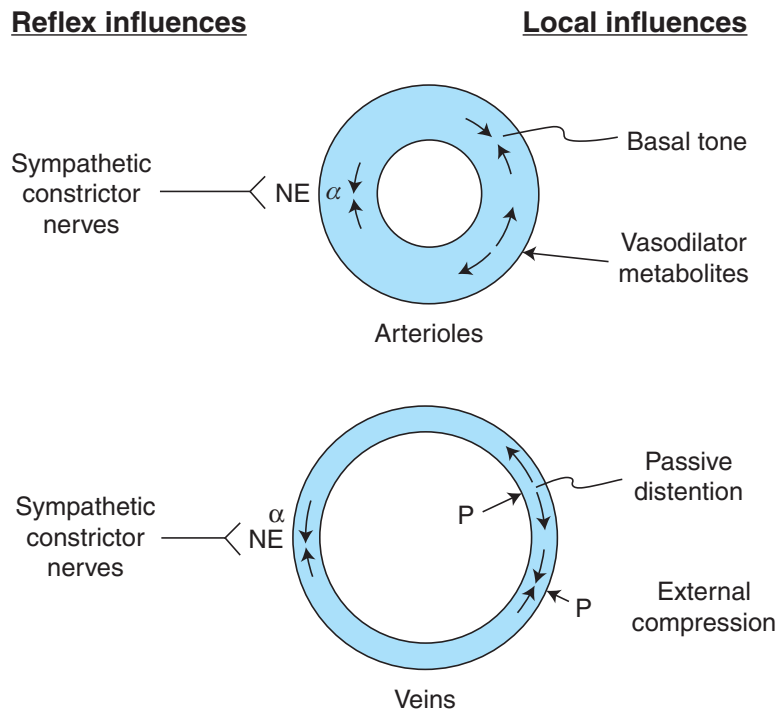


Figure 7-5. Primary influences on arterioles and veins. NE, norepinephrine; α , alpha-adrenergic receptor; P, pressure.

metabolic vasodilator factors, and sympathetic vasoconstrictor nerves acting through α_1 -receptors are the major factors controlling arteriolar tone and therefore the blood flow rate through peripheral organs. Sympathetic vasoconstrictor nerves, internal pressure, and external compressional forces are the most important influences on venous diameter and therefore on peripheral–central distribution of blood volume.



As evident in the remaining sections of this chapter, many details of vascular control vary from organs to organs. However, with regard to flow control, most organs can be placed somewhere in a spectrum that ranges from almost total dominance by local metabolic mechanisms to almost total dominance by sympathetic vasoconstrictor nerves.

The flow in organs such as the brain, heart muscle, and skeletal muscle is very strongly controlled by local metabolic control, whereas the flow in the kidneys, skin, and splanchnic organs is very strongly controlled by sympathetic nerve activity. Consequently, some organs are automatically forced to participate in overall cardiovascular reflex responses to a greater extent than are other organs. The overall plan seems to be that, in cardiovascular emergency, flow to the brain and heart will be preserved at the expense of everything else if need be.

VASCULAR CONTROL OF CORONARY BLOOD FLOW

The major right and left coronary arteries that serve the heart tissue are the first vessels to branch off the aorta. Thus, the driving force for myocardial blood flow

is the systemic arterial pressure, just as it is for other systemic organs. Most of the blood that flows through the myocardial tissue returns to the right atrium by way of a large cardiac vein called the *coronary sinus*.

Local Metabolic Control



As emphasized before, coronary blood flow is controlled primarily by local metabolic mechanisms and thus it responds rapidly and accurately to changes in myocardial oxygen consumption. In a resting individual, the myocardium extracts 70 to 75% of the oxygen in the blood that passes through it. Coronary sinus blood normally has a lower oxygen content than blood at any other place in the cardiovascular system. Myocardial oxygen extraction cannot increase significantly from its resting value. Consequently, increases in myocardial oxygen consumption must be accompanied by appropriate increases in coronary blood flow.

The issue of *which* metabolic vasodilator factors play the dominant role in modulating the tone of coronary arterioles is unresolved at present. Many believe that adenosine, released from myocardial muscle cells in response to increased metabolic rate, may be an important local coronary metabolic vasodilator influence. Regardless of the specific details, myocardial oxygen consumption is the most important influence on coronary blood flow.

Systolic Compression

Large forces and/or pressures are generated *within* the myocardial tissue during cardiac muscle contraction. Such intramyocardial forces press on the outside of coronary vessels and cause them to collapse during systole. Because of this *systolic compression* and the associated collapse of coronary vessels, coronary vascular resistance is greatly increased during systole. The result, at least for much of the left ventricular myocardium, is that coronary flow is lower during systole than during diastole, even though systemic arterial pressure (ie, coronary perfusion pressure) is highest during systole. This is illustrated in the left coronary artery flow trace shown in Figure 7–6. Systolic compression has much less effect on flow through the right ventricular myocardium, as is evident from the right coronary artery flow trace in Figure 7–6. This is because the peak systolic intraventricular pressure is much lower for the right heart than for the left heart, and the systolic compressional forces in the right ventricular wall are correspondingly less than those in the left ventricular wall.

Systolic compressional forces on coronary vessels are greater in the endocardial (inside) layers of the left ventricular wall than in the epicardial layers.³ Thus, the flow to the endocardial layers of the left ventricle is impeded more than the flow to epicardial layers by systolic compression. Normally, the endocardial region of the myocardium can make up for the lack of flow during systole by a high flow in the diastolic interval. However, when coronary blood flow is limited—for example, by

³ Consider that the endocardial surface of the left ventricle is exposed to intraventricular pressure (≈ 120 mmHg during systole), while the epicardial surface is exposed only to intrathoracic pressure (≈ 0 mmHg).

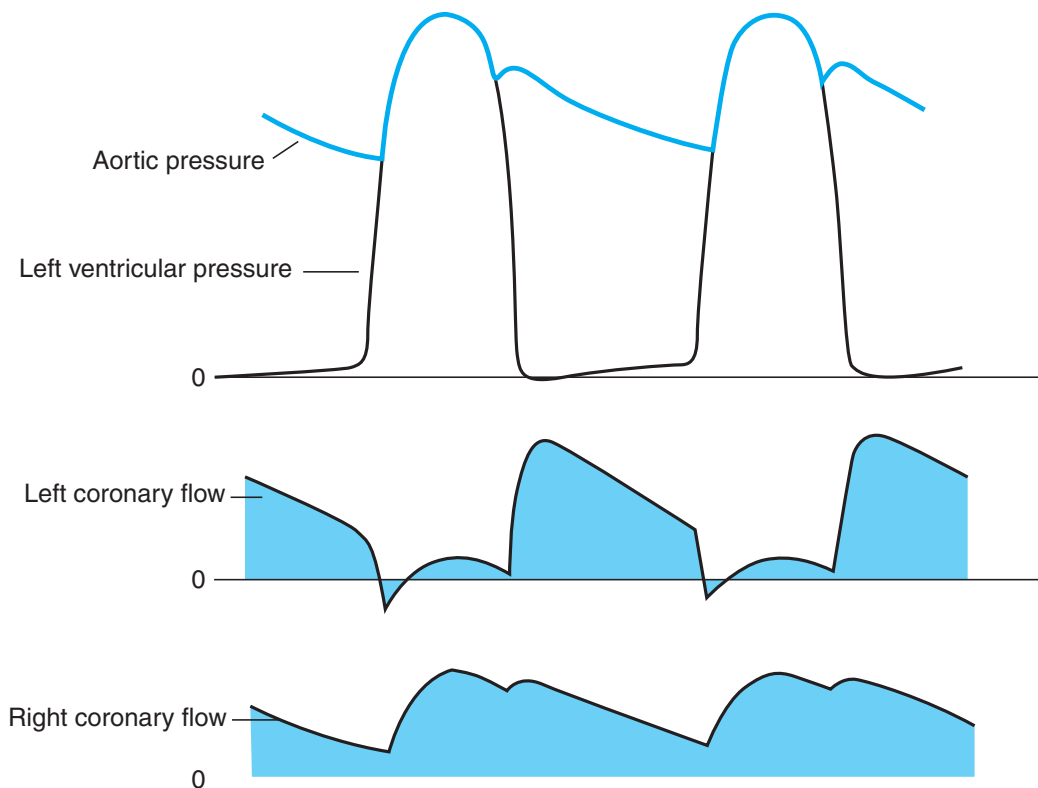


Figure 7-6. Phasic flows in the left and right coronary arteries in relation to aortic and left ventricular pressures.

coronary disease and stenosis—the endocardial layers of the left ventricle are often the first regions of the heart to have difficulty maintaining a flow sufficient for their metabolic needs. *Myocardial infarcts* (areas of tissue killed by lack of blood flow) occur most frequently in the endocardial layers of the left ventricle.

Neural Influences on Coronary Flow



Coronary arterioles are densely innervated with sympathetic vasoconstrictor fibers, yet when the activity of the sympathetic nervous system increases, the coronary arterioles normally vasodilate rather than vasoconstrict. This is because an increase in sympathetic tone increases myocardial oxygen consumption by increasing the heart rate and contractility. The increased local metabolic vasodilator influence apparently outweighs the concurrent vasoconstrictor influence due to an increase in the activity of sympathetic vasoconstrictor fibers that terminate on coronary arterioles. It has been experimentally demonstrated that a given increase in cardiac sympathetic nerve activity causes a greater increase in coronary blood flow after the direct vasoconstrictor influence of sympathetic nerves on coronary vessels has been eliminated with α -receptor blocking agents. However, sympathetic vasoconstrictor nerves do not appear to influence coronary flow enough to affect the mechanical performance of normal hearts. Whether these coronary vasoconstrictor

fibers might be functionally important in certain pathological situations is an open question.

VASCULAR CONTROL IN SPECIFIC ORGANS

The material presented in the rest of this chapter is perhaps most useful when considering the overall physiological characteristics of the specific organ or organ system. However, to give an overview of some of the vascular adaptations that can exist, the most important and/or unique circulatory characteristics for some major organs or organ systems are itemized in the following sections.

Skeletal Muscle Blood Flow

1. *Because of the large mass of the skeletal muscle, blood flow through it is an important factor in overall cardiovascular hemodynamics.* Collectively, the skeletal muscles constitute 40 to 45% of body weight—more than any other single body organ. Even at rest, approximately 15% of the cardiac output goes to skeletal muscle, and during strenuous exercise the skeletal muscle may receive more than 80% of the cardiac output.
2. *Resting skeletal muscle has a high level of intrinsic vascular tone.* Because of this high tone of the smooth muscle in resistance vessels of resting skeletal muscles, the blood flow per gram of tissue is quite low when compared with that of other organs such as the kidneys. However, resting skeletal muscle blood flow is still substantially above that required to sustain its metabolic needs. Resting skeletal muscles normally extract only 25 to 30% of the oxygen delivered to them in arterial blood. Thus, changes in the activity of sympathetic vasoconstrictor fibers can reduce resting muscle blood flow without compromising resting tissue metabolic processes.
3.  *Local metabolic control of arteriolar tone is the most important influence on blood flow through exercising muscle.* A particularly important characteristic of skeletal muscle is its very wide range of metabolic rates. During heavy exercise, the oxygen consumption rate of and oxygen extraction by skeletal muscle tissue can reach the high values typical of the myocardium. In most respects, the factors that control blood flow to exercising muscle are similar to those that control coronary blood flow. Local metabolic control of arteriolar tone is very strong in exercising skeletal muscle, and muscle oxygen consumption is the most important determinant of its blood flow. Blood flow in the skeletal muscle can increase 20-fold during a bout of strenuous exercise.
4.  *Alterations in sympathetic neural activity can alter non exercising skeletal muscle blood flow.* For example, maximum sympathetic discharge rates can decrease blood flow in a resting muscle to less than one-fourth its normal value, and conversely, if all neurogenic tone is removed, resting skeletal muscle blood flow may double. This is a modest increase in flow compared

what can occur in an exercising skeletal muscle. Nonetheless, because of the large mass of tissue involved, changes in the vascular resistance of resting skeletal muscle brought about by changes in sympathetic activity are very important in the overall reflex regulation of arterial pressure.

5. *Alterations in sympathetic neural activity can influence exercising skeletal muscle blood flow.* As discussed in Chapter 10, the cardiovascular response to muscle exercise involves a general increase in sympathetic activity. This of course reduces flow to susceptible organs, which include non exercising muscles. In exercising muscles, the increased sympathetic vasoconstrictor nerve activity is not evident as outright vasoconstriction but does limit the degree of metabolic vasodilation. One important function that this seemingly counterproductive process may serve is that of preventing an excessive reduction in total peripheral resistance during exercise. Indeed, if arterioles in most of the skeletal muscles in the body were allowed to dilate to their maximum capacity simultaneously, total peripheral resistance would be so low that the heart could not possibly supply enough cardiac output to maintain arterial pressure.
6. *Rhythmic contractions can increase venous return from exercising skeletal muscle.* As in the heart, muscle contraction produces large compressional forces within the tissue, which can collapse vessels and impede blood flow. Strong, sustained (tetanic) skeletal muscle contractions may actually stop muscle blood flow. Approximately 10% of the total blood volume is normally contained within the veins of the skeletal muscle, and during rhythmic exercise the “skeletal muscle pump” is very effective in displacing blood from skeletal muscle veins. Valves in the veins prevent reverse flow back into the muscles. Blood displaced from the skeletal muscle into the central venous pool is an important factor in the hemodynamics of strenuous whole body exercise.
7. *Veins in skeletal muscle can constrict in response to increased sympathetic activity.* However, veins in the skeletal muscle are rather sparsely innervated with sympathetic vasoconstrictor fibers, and the rather small volume of blood that can be mobilized from the skeletal muscle by sympathetic nerve activation is probably not of much significance to total body hemodynamics. This is in sharp contrast to the large displacement of blood from exercising muscle by the muscle pump mechanism. (This is discussed in more detail when postural reflexes are considered in Chapter 10.)

Cerebral Blood Flow

1. *Interruption of cerebral blood flow for more than a few seconds leads to unconsciousness and to brain damage within a very short period.* One rule of overall cardiovascular system function is that, in *all* situations, measures are taken that are appropriate to preserve adequate blood flow to the brain.
2. *Cerebral blood flow is regulated almost entirely by local mechanisms.* The brain as a whole has a nearly constant rate of metabolism that, on a per gram basis, is nearly as high as that of myocardial tissue. Flow through the cerebrum is

autoregulated very strongly and is little affected by changes in arterial pressure unless it falls below approximately 60 mmHg. When arterial pressure decreases below 60 mmHg, brain blood flow decreases proportionately. It is presently unresolved whether metabolic mechanisms or myogenic mechanisms or both are involved in the phenomenon of cerebral autoregulation.



3. *Local changes in cerebral blood flow may be influenced by local metabolic conditions.* Presumably because the overall average metabolic rate of brain tissue shows little variation, total brain blood flow is remarkably constant over nearly all situations. The cerebral activity in discrete locations within the brain, however, changes from situation to situation. As a result, blood flow to discrete regions is not constant but closely follows the local neuronal activity. The mechanisms responsible for this strong local control of cerebral blood flow are as yet undefined, but H^+ , K^+ , oxygen, and adenosine seem most likely to be involved.
4. *Cerebral blood flow decreases whenever arterial blood PCO_2 falls below normal.* Conversely, cerebral blood flow increases whenever the partial pressure of carbon dioxide (PCO_2) is raised above normal in the arterial blood. This is the normal state of affairs in most tissues, but it plays out importantly when it happens in the brain. For example, the dizziness, confusion, and even fainting that can occur when a person hyperventilates (and “blows off” CO_2) are a direct result of cerebral vasoconstriction. It appears that cerebral arterioles respond not to changes in PCO_2 but to changes in the extracellular H^+ concentration (ie, pH) caused by changes in PCO_2 . Cerebral arterioles also vasodilate whenever the partial pressure of oxygen (PO_2) in arterial blood falls significantly below normal values. However, higher than normal arterial blood PO_2 , such as that caused by pure oxygen inhalation, produces little decrease in cerebral blood flow.
5. *Sympathetic and parasympathetic neural influences on cerebral blood flow are minimal.* Although cerebral vessels receive both sympathetic vasoconstrictor and parasympathetic vasodilator fiber innervation, cerebral blood flow is influenced very little by changes in the activity of either under normal circumstances. Sympathetic vasoconstrictor responses may, however, be important in protecting cerebral vessels from excessive passive distention following large, abrupt increases in arterial pressure.
6. *The “blood–brain barrier” refers to the tightly connected vascular endothelial cells that severely restrict transcapillary movement of all polar and many other substances.*⁴ Because of this blood–brain barrier, the extracellular space of the brain represents a special fluid compartment in which the chemical composition is regulated separately from that in the plasma and general body extracellular fluid compartment. The extracellular compartment of the brain encompasses both interstitial fluid and *cerebrospinal fluid* (CSF), which surrounds the brain and spinal cord and fills the brain ventricles. The CSF is formed from plasma by selective

⁴ Brain capillaries have a special carrier system for glucose and present no barrier to oxygen and carbon dioxide diffusion. Thus, the blood–brain barrier does not restrict nutrient supply to the brain tissue.

secretion (not simple filtration) by specialized tissues, the *choroid plexes*, located within the ventricles. These processes regulate the chemical composition of the CSF. The interstitial fluid of the brain takes on the chemical composition of CSF through free diffusional exchange.


The blood–brain barrier serves to protect the cerebral cells from ionic disturbances in the plasma. Also, by exclusion and/or endothelial cell metabolism, it prevents many circulating hormones (and drugs) from influencing the parenchymal cells of the brain and the vascular smooth muscle cells in brain vessels.

Splanchnic Blood Flow

1. *Because of the high blood flow through and the high blood volume in the splanchnic bed, vascular control importantly influences overall cardiovascular hemodynamics.* A number of abdominal organs, including the gastrointestinal tract, spleen, pancreas, and liver, are collectively supplied with what is called the *splanchnic blood flow*. Splanchnic blood flow is supplied to these abdominal organs through many arteries, but it all ultimately passes through the liver and returns to the inferior vena cava through the hepatic veins. The organs of the splanchnic region receive approximately 25% of the resting cardiac output and moreover contain more than 20% of the circulating blood volume. Thus, adjustments in either the blood flow or the blood volume of this region have extremely important effects on the cardiovascular system.
2.  *Sympathetic neural activity plays an important role in vascular control of the splanchnic circulation.* Collectively, the splanchnic organs have a relatively high blood flow and extract only 15 to 20% of the oxygen delivered to them in the arterial blood. The arteries and veins of all the organs involved in the splanchnic circulation are richly innervated with sympathetic vasoconstrictor nerves. Maximal activation of sympathetic vasoconstrictor nerves can produce an 80% reduction in flow to the splanchnic region and also cause a large shift of blood from the splanchnic organs to the central venous pool. In humans, a large fraction of the blood mobilized from the splanchnic circulation during periods of sympathetic activation comes from the constriction of veins in the liver. In many other species, the spleen acts as a major reservoir from which blood is mobilized by sympathetically mediated contraction of the smooth muscle located in the outer capsule of the organ.
3.  *Local metabolic activity associated with motility, secretion, and absorption is associated with local increases in splanchnic blood flow.* There is a great diversity of function among individual organs and even regions within organs in the splanchnic region. The mechanisms of vascular control in specific areas of the splanchnic region are not well understood but are likely to be quite varied. Nonetheless, because most of the splanchnic organs are involved in the digestion and absorption of food from the gastrointestinal tract, splanchnic blood flow increases after food ingestion. A large meal can elicit a 30 to 100% increase

in splanchnic flow, but individual organs in the splanchnic region probably have higher percentage increases in flow at certain times because they are involved sequentially in the digestion–absorption process.

Renal Blood Flow


1. *Acute adjustments in renal blood flow have important hemodynamic consequences.* The kidneys normally receive approximately 20% of the cardiac output of a resting individual. This flow can be reduced to practically zero during strong sympathetic activation. Thus, the control of renal blood *flow* is important to overall cardiovascular function. However, because the kidneys are such small organs, changes in renal blood *volume* are inconsequential to overall cardiovascular hemodynamics.
2.  *Renal blood flow is strongly influenced by sympathetic neural stimulation.* Alterations in sympathetic neural activity can have marked effects on total renal blood flow by altering the neurogenic tone of renal resistance vessels. In fact, extreme situations involving intense and prolonged sympathetic vasoconstrictor activity (as may accompany severe blood loss) can lead to dramatic reduction in renal blood flow, permanent kidney damage, and renal failure.
3. *Local mechanism may influence local vascular tone, but physiological roles are not clear.* It has long been known that experimentally *isolated* kidneys (ie, kidneys deprived of their normal sympathetic input) autoregulate their flow quite strongly. The mechanism responsible for this phenomenon has not been definitely established, but myogenic, tissue pressure, and metabolic hypotheses have been advanced. The real question is what purpose such a strong local mechanism plays in the intact organism where it seems to be largely overridden by reflex mechanisms. In an intact individual, renal blood flow is not constant but is highly variable, depending on the prevailing level of sympathetic vasoconstrictor nerve activity.

The mechanisms responsible for the intrinsic regulation of renal blood flow and kidney function have not been established. Although studies suggest that prostaglandins and some intrarenal renin–angiotensin system may be involved, the whole issue of local renal vascular control remains quite obscure. Renal function is itself of paramount importance to overall cardiovascular function, as described in Chapter 9.

Cutaneous Blood Flow

1. *The physiological role of skin blood flow is to help regulate body temperature.* The metabolic activity of body cells produces heat, which must be lost in order for the body temperature to remain constant. The skin is the primary site of exchange of body heat with the external environment. Alterations in cutaneous blood flow in response to various metabolic states and environmental conditions

provide the primary mechanism responsible for temperature homeostasis. (Other mechanisms such as shivering, sweating, and panting also participate in body temperature regulation under more extreme conditions.)

2. *Decreases in body temperature decrease skin blood flow and vice versa.* Cutaneous blood flow, which is about 6% of the resting cardiac output, can decrease to about one-twentieth of its normal value when heat is to be retained (eg, in a cold environment, during the development stages of a fever). In contrast, cutaneous blood flow can increase up to seven times its normal value when heat is to be lost (eg, in a hot environment, accompanying a high metabolic rate, after a fever “breaks”).
3. *Structural adaptations of the cutaneous vascular beds promote heat loss or heat conservation.* The anatomic interconnections between microvessels in the skin are highly specialized and extremely complex. An extensive system of interconnected veins called the *venous plexus* normally contains the largest fraction of cutaneous blood volume, which, in individuals with lightly pigmented skin, gives the skin a reddish hue. To a large extent, heat transfer from the blood takes place across the large surface area of the venous plexus. The venous plexus is richly innervated with sympathetic vasoconstrictor nerves. When these fibers are activated, blood is displaced from the venous plexus, and this helps reduce heat loss and also lightens the skin color. Because the skin is one of the largest body organs, venous constriction can shift a considerable amount of blood into the central venous pool.
4.  *Reflex sympathetic neural activity has important but complex influences on skin blood flow.* Cutaneous resistance vessels are richly innervated with sympathetic vasoconstrictor nerves, and because these fibers have a normal tonic activity, cutaneous resistance vessels normally have a high degree of neurogenic tone. When body temperature rises above normal, skin blood flow is increased by reflex mechanisms. In certain areas (such as the hands, ears, and nose), vasodilation appears to result entirely from the withdrawal of sympathetic vasoconstrictor tone. In other areas (such as the forearm, forehead, chin, neck, and chest), the cutaneous vasodilation that occurs with body heating greatly exceeds that which occurs with just the removal of sympathetic vasoconstrictor tone. This “active” vasodilation is closely linked to the onset of sweating in these areas. The sweat glands in human cutaneous tissue are innervated by *cholinergic sympathetic fibers* that release acetylcholine. Activation of these nerves elicits sweating *and* an associated marked cutaneous vasodilation. The exact mechanism for this sweating-related cutaneous vasodilation remains unclear because it is not abolished by agents that block acetylcholine’s vascular effects. It has long been thought that it was caused by local bradykinin formation secondary to the process of sweat gland activation. Newer evidence suggests that the cholinergic sympathetic nerves to sweat glands may release not only acetylcholine but also other vasodilator cotransmitters. Although these special sympathetic nerves are very important to temperature regulation, they do not participate in the normal, moment-to-moment, regulation of the cardiovascular system.

5. *Cutaneous vessels respond to changes in local skin temperature.* In general, local cooling leads to local vasoconstriction and local heating causes local vasodilation. The mechanisms for this are unknown. If the hand is placed in ice water, there is initially a nearly complete cessation of hand blood flow accompanied by intense pain. After some minutes, hand blood flow begins to rise to reach values greatly in excess of the normal value, hand temperature increases, and the pain disappears. This phenomenon is referred to as *cold-induced vasodilation*. With continued immersion, hand blood flow cycles every few minutes between periods of essentially no flow and periods of hyperemia. The mechanism responsible for cold vasodilation is unknown, but it has been suggested that norepinephrine may lose its ability to constrict vessels when their temperature approaches 0°C. Whatever the mechanism, cold-induced vasodilation apparently serves to protect exposed tissues from cold damage.
6. *Cutaneous vessels respond to local damage with observable responses.* Tissue damage from burns, ultraviolet radiation, cold injury, caustic chemicals, and mechanical trauma produces reactions in skin blood flow. A classical reaction called the *triple response* is evoked after vigorously stroking the skin with a blunt point. The first component of the triple response is a *red line* that develops along the direct path of the abrasion in about 15 seconds. Shortly thereafter, an irregular *red flare* appears that extends about 2 cm on either side of the red line. Finally, after a minute or two, a *wheel* appears along the line of the injury. The mechanisms involved in the triple response are not well understood, but it seems likely that histamine release from damaged cells is at least partially responsible for the dilation evidenced by the red line and the subsequent edema formation of the wheal. The red flare seems to involve nerves in some sort of a local *axon reflex* because it can be evoked immediately after cutaneous nerves are sectioned but not after the peripheral portions of the sectioned nerves degenerate.

Pulmonary Blood Flow

1. *Pulmonary blood flow equals cardiac output.* The rate of blood flow through the lungs is necessarily equal to cardiac output in all circumstances. When cardiac output increases threefold during exercise, for example, pulmonary blood flow must also increase threefold. Although the flow through a systemic organ is determined by its vascular resistance ($\dot{Q} = \Delta P/R$), the blood flow rate through the lungs is determined simply by the cardiac output ($\dot{Q} = \text{CO}$).
2. *Pulmonary vascular resistance is about one-seventh of total systemic vascular resistance.* Pulmonary vessels do offer some vascular resistance. Although the level of pulmonary vascular resistance does not usually influence the pulmonary flow rate, it is important because it is one of the determinants of pulmonary arterial pressure ($\Delta P = \dot{Q} \times R$). Recall that mean *pulmonary* arterial pressure is approximately 13 mmHg, whereas mean *systemic* arterial pressure is approximately 100 mmHg. The reason for the difference in pulmonary and systemic arterial

pressures is not that the right side of the heart is weaker than the left side of the heart but rather that pulmonary vascular resistance is inherently much lower than systemic total peripheral resistance. The pulmonary bed has a low resistance because it has relatively large vessels throughout.

3. *Pulmonary arteries and arterioles are less muscular and more compliant than are systemic arteries and arterioles.* When pulmonary arterial pressure increases, the pulmonary arteries and arterioles become larger in diameter. Thus, an increase in pulmonary arterial pressure *decreases* pulmonary vascular resistance. This phenomenon is important because it tends to limit the increase in pulmonary arterial pressure that occurs with increases in cardiac output.
4. *Pulmonary arterioles constrict in response to local alveolar hypoxia.* One of the most important active responses in the pulmonary vasculature is the *hypoxic vasoconstriction* of pulmonary arterioles in response to low oxygen levels within the alveoli. This is exactly opposite to the vasodilation that occurs in systemic arterioles in response to low tissue P_{O_2} . The mechanisms that cause this unusual response in pulmonary vessels are unclear. Current evidence suggests that local prostaglandin synthesis may be involved in pulmonary hypoxic vasoconstriction. Whatever the mechanism, hypoxic vasoconstriction is essential to efficient lung gas exchange because it diverts blood flow away from areas of the lung that are underventilated. Consequently, the best-ventilated areas of the lung also receive the most blood flow. Presumably as a consequence of hypoxic arteriolar vasoconstriction, general hypoxia (such as that encountered at high altitude) causes an increase in pulmonary vascular resistance and pulmonary arterial hypertension.
5. *Autonomic nerves play no major role in control of pulmonary vascular activity.* Both pulmonary arteries and veins receive sympathetic vasoconstrictor fiber innervation, but reflex influences on pulmonary vessels appear to be much less important than the physical and local hypoxic influences. Pulmonary veins serve a blood reservoir function for the cardiovascular system, and sympathetic vasoconstriction of pulmonary veins may be important in mobilizing this blood during periods of general cardiovascular stress.
6. *Low capillary hydrostatic pressure promotes fluid reabsorption and prevents fluid accumulation in pulmonary airways.* A consequence of the low mean pulmonary arterial pressure is the low pulmonary capillary hydrostatic pressure of approximately 8 mmHg (compared with approximately 25 mmHg in systemic capillaries). Because the plasma oncotic pressure in lung capillaries is near 25 mmHg, as it is in all capillaries, it is likely that the transcapillary forces in the lungs strongly favor continual fluid reabsorption. This cannot be the complete story, however, because the lungs, like other tissues, continually produce some lymph and some net capillary filtration is required to produce lymphatic fluid. This filtration is possible despite the unusually low pulmonary capillary hydrostatic pressure because pulmonary interstitial fluid has an unusually high protein concentration and thus oncotic pressure.

KEY CONCEPTS



Continual adjustments of vascular diameter are required to properly distribute the cardiac output to the various systemic tissues (the role of arterioles) and maintain adequate cardiac filling (the role of veins).



Vascular adjustments are made by changes in the tone of the vascular smooth muscle.



The vascular smooth muscle has many unique properties that make it sensitive to a wide array of local and reflex stimuli and capable of maintaining tone for long periods.



The tone of arterioles, but not veins, can be strongly influenced by local vasodilator factors produced by local tissue metabolism.



In abnormal situations (such as tissue injury or severe blood volume depletion), certain local factors such as histamine and bradykinin, and hormonal factors such as vasopressin and angiotensin have significant vascular influences.



Sympathetic vasoconstrictor nerves provide the primary reflex mechanisms for regulating both arteriolar and venous tones.



Sympathetic vasoconstrictor nerves release norepinephrine, which interacts with α_1 -adrenergic receptors on the vascular smooth muscle to induce vasoconstriction.



The relative importance of local metabolic versus reflex sympathetic control of arteriolar tone (and therefore blood flow) varies from organs to organs.



In some organs (such as the brain, heart muscle, and exercising skeletal muscle), blood flow normally closely follows metabolic rate because of local metabolic influences on arterioles.




In other organs (such as skin and kidneys), blood flow is normally regulated more by sympathetic nerves than by local metabolic conditions.



STUDY QUESTIONS

- 7-1. Which of the following would increase blood flow through a skeletal muscle?
- an increase in tissue P_{CO_2}
 - an increase in tissue adenosine
 - the presence of α -receptor-blocking drugs
 - sympathetic activation

- 7-2. Autoregulation of blood flow implies that arterial pressure is adjusted by local mechanisms to ensure constant flow through an organ. True or false?
- 7-3. Coronary blood flow will normally increase when
- arterial pressure increases
 - the heart rate increases
 - sympathetic activity increases
 - the heart is dilated
- 7-4. The arterioles of skeletal muscle would have little or no tone in the absence of normal sympathetic vasoconstrictor fiber activity. True or false?
- 7-5. A person who hyperventilates (breathes rapidly and deeply) gets dizzy. Why?
- 7-6. A patient complains of severe leg pains after walking a short distance. The pains disappear after the patient rests. (This symptom is called intermittent claudication.) What might be the problem?
- 7-7. How would a stenotic aortic valve influence coronary blood flow?
- 7-8. Vascular smooth muscle differs from cardiac muscle in that it
- contains no actin molecules
 - can be directly activated in the absence of action potentials
 - is unresponsive to changes in intracellular calcium levels
 - is unresponsive to changes in membrane potentials
 - is unresponsive to changes in muscle length
- 7-9. Arteriolar constriction tends to do which of the following?
- decrease total peripheral resistance
 - decrease mean arterial pressure
 - decrease capillary hydrostatic pressure
 - increase transcapillary fluid filtration
 - increase blood flow through the capillary bed
- 7-10. When an organ responds to an increase in metabolic activity with a decrease in arteriolar resistance, this is known as
- active hyperemia
 - reactive hyperemia
 - autoregulation of blood flow
 - flow-dependent vasodilation
 - metabolic vasoconstriction
- 

Central Venous Pressure: An Indicator of Circulatory Hemodynamics

8

OBJECTIVES

The student understands how central venous pressure can be used to assess circulatory states and how venous return, cardiac output, and central venous pressure are interrelated:

- ▶ *Describes the overall arrangement of the systemic circulation and identifies the primary functional properties of each of its major components.*
- ▶ *Defines mean circulatory filling pressure and states the primary factors that determine it.*
- ▶ *Defines venous return and explains how it is distinguished from cardiac output.*
- ▶ *States the reason why cardiac output and venous return must be equal in the steady state.*
- ▶ *Lists the factors that control venous return.*
- ▶ *Describes the relationship between central venous pressure and venous return and draws the normal venous return curve.*
- ▶ *Defines peripheral venous pressure.*
- ▶ *Lists the factors that determine peripheral venous pressure.*
- ▶ *Predicts the shifts in the venous return curve that occur with altered blood volume and altered venous tone.*
- ▶ *Describes how the output of the left heart pump is matched to that of the right heart pump.*
- ▶ *Draws the normal venous return and cardiac output curves on a graph and describes the significance of the point of curve intersection.*
- ▶ *Predicts how normal venous return, cardiac output, and central venous pressure will be altered with any given combination of changes in cardiac sympathetic tone, peripheral venous sympathetic tone, or circulating blood volume.*
- ▶ *Identifies possible conditions that result in abnormally high or low central venous pressure.*

INTERACTION OF SYSTEM COMPONENTS

Once one has learned the basic facts concerning the individual pieces of the cardiovascular system, it is important to step back, take a broad view, and see how those pieces interact in the operation of the intact system.

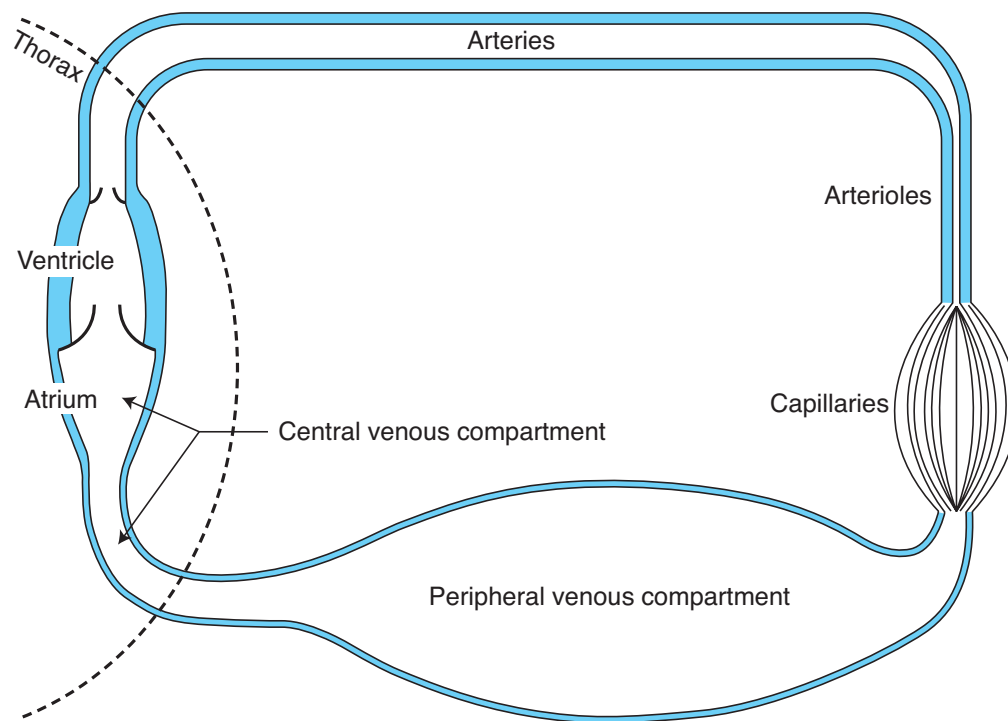


Figure 8–1. Major functionally distinct components of the systemic cardiovascular circuit.

As illustrated in Figure 8–1, the cardiovascular system is a closed hydraulic circuit that includes the heart, arteries, arterioles, capillaries, and veins.¹ The venous side of this system is often conceptually separated into two different compartments: (1) a large and diverse peripheral section (the peripheral venous compartment) and (2) a smaller intrathoracic section that includes the vena cavae and the right atrium (the central venous compartment). Each of the segments of this circuit has a distinctly different role to play in the overall operation of the system because of inherent differences in anatomical volume, resistance to flow, and compliance that are summarized in Table 8–1.

Note especially the surprisingly high ventricular diastolic compliance of 24 mL/mmHg in Table 8–1. This value indicates how exquisitely sensitive the ventricular end-diastolic volume (and therefore stroke volume and cardiac output) is to small changes in cardiac filling pressure (ie, central venous pressure). In all physiological and pathological situations, cardiac filling pressure is a crucial factor that determines how well the cardiovascular system will be operating.

¹ The pulmonary circuit is not included in Figure 8–1 because it does not influence the major points to be made in this chapter. The primary leap of faith in this omission is that, because of Starling's law of the heart, changes in the end-diastolic volume of the *right* ventricle cause equal changes in the end-diastolic volume of the *left* ventricle.

Table 8–1. Typical Properties of the Major Components of the Systemic Cardiovascular Circuit*

Compartment	V_0 (mL)	C (mL/mmHg)	R (mmHg/L per minute)
Ventricle in diastole	30	24	0
Arteries	600	2	1
Arterioles	100	0	13
Capillaries	250	0	5
Peripheral venous compartment	2500	110	1
Central venous compartment	80	4	0
Entire circuit	3560	140	20

*Values are for a normal, young, resting 70-kg adult.

V_0 , anatomical volume of compartment at zero pressure; C , compliance of compartment; R , resistance to flow through compartment.

Mean Circulatory Filling Pressure

Imagine the heart arrested in diastole with no flow around the circuit shown in Figure 8–1. It will take a certain amount of blood just to fill the anatomical space contained by the systemic system without stretching any of its walls or developing any internal pressure. This amount is 3.56 L, as indicated by the total systemic circuit volume (V_0) in Table 8–1. Normally, however, the systemic circuit contains approximately 4.5 L of blood and thus is somewhat inflated. From the total systemic circuit compliance (C) given in Table 8–1, one can see that an extra 1000 mL of blood would result in an internal pressure of approximately 7 mmHg (ie, 1000 mL/140 mL per mmHg). This theoretical pressure is called the *mean circulatory filling pressure* and is the actual pressure that would exist throughout the system in the absence of flow.



The two major variables that affect mean circulatory filling pressure are the circulating blood volume and the state of the peripheral venous vessel tone. In the latter case, look at Figure 8–1 and imagine how constriction of the vessels of the large venous compartment (increasing venous tone) will significantly increase pressure throughout the system. In contrast, squeezing on arterioles (increasing arteriolar tone) will have a negligible effect on mean circulatory filling pressure because arterioles contain so little blood in any state. The other major components of the system (arteries and capillaries) essentially do not actively change their volume.

Flow-Induced Distribution of Blood Volume and Pressure

The presence of flow around the circuit does not change the total volume of blood in the system or the mean circulatory filling pressure. The flow caused by cardiac pumping action does, however, tend to shift some of the blood volume from the venous side of the circuit to the arterial side. This causes pressures on the arterial side to rise above the mean circulatory pressure while pressures on the venous side

fall below it. Because veins are about 50 times more compliant than arteries (Table 8–1), the flow-induced decrease in venous pressure is only about 1/50th as large as the accompanying increase in arterial pressure. Thus, flow or no flow, pressure in the peripheral venous compartment is normally quite close to the mean circulatory filling pressure.

CENTRAL VENOUS PRESSURE: AN INDICATOR OF CIRCULATORY STATUS

The cardiovascular system must adjust its operation continually to meet changing metabolic demands of the body. Because the cardiovascular system is a closed hydraulic loop, adjustments in any one part of the circuit will have pressure, flow, and volume effects throughout the circuit. Because of the critical influence of cardiac filling on cardiovascular function, the remainder of this chapter focuses on the factors that determine the pressure in the central venous compartment. In addition, the way in which measures of central venous pressure can provide clinically useful information about the state of the circulatory system is discussed.

The central venous compartment corresponds roughly to the volume enclosed by the right atrium and the great veins in the thorax. Blood *leaves* the central venous compartment by entering the right ventricle at a rate that is equal to the cardiac output. *Venous return*, in contrast, is by definition the rate at which blood returns to the thorax from the peripheral vascular beds and thus is the rate at which blood *enters* the central venous compartment. The important distinction between venous return *to* the central venous compartment and cardiac output *from* the central venous compartment is illustrated in Figure 8–2.

In any stable situation, venous return must equal cardiac output or blood would gradually accumulate in either the central venous compartment or the peripheral vasculature. However, there are often temporary differences between cardiac output and venous return. Whenever such differences exist, the volume of the central venous compartment must be changing. Because the central venous compartment is

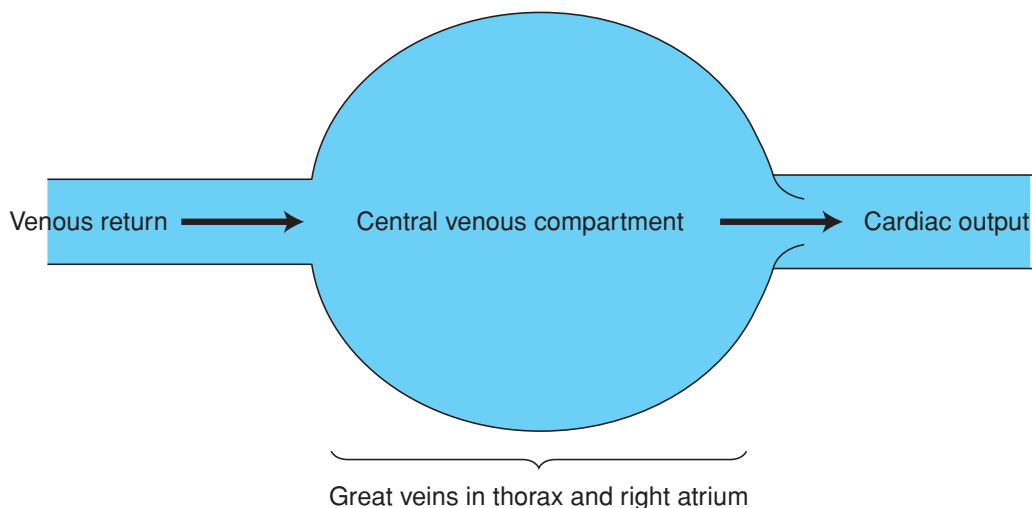


Figure 8–2. Distinction between cardiac output and venous return.

enclosed by elastic tissues, any change in central venous volume produces a corresponding change in central venous pressure.

As discussed in Chapter 3, the central venous pressure (ie, cardiac filling pressure) has an extremely important *positive* influence on stroke volume, and therefore, cardiac output (Starling's law of the heart). As argued later, central venous pressure has an equally important *negative* effect on venous return. Thus, central venous pressure is always automatically driven to a value that makes cardiac output equal to venous return. The factors that determine central venous pressure in any given situation are discussed in the following section.

INFLUENCE OF CENTRAL VENOUS PRESSURE ON VENOUS RETURN

The important factors involved in the process of venous return can be summarized as shown in Figure 8–3A. Basically, venous return is blood flow from the peripheral venous compartment to the central venous compartment through converging vessels. Anatomically the peripheral venous compartment is scattered throughout the systemic organs, but functionally it can be viewed as a single vascular space that has a particular pressure (P_{PV}) at any instant of time. The normal operating pressure in the peripheral venous compartment is usually very close to mean circulatory filling pressure. Moreover, the same factors that influence mean circulatory filling pressure have essentially equal influences on peripheral venous pressure. Thus “peripheral venous pressure” can be viewed as essentially equivalent to “mean circulatory filling pressure.” The blood flow rate between the peripheral venous compartment and the central venous compartment is governed by the basic flow equation ($\dot{Q} = \Delta P/R$), where ΔP is the pressure drop between the peripheral and central venous compartments and R is the small resistance associated with the peripheral veins. In the example in Figure 8–3, peripheral venous pressure is assumed to be 7 mmHg. Thus, there will be no venous return when the central venous pressure (P_{CV}) is also 7 mmHg as shown in Figure 8–3B.



If the peripheral venous pressure remains at 7 mmHg, decreasing central venous pressure will increase the pressure drop across the venous resistance and consequently cause an elevation in venous return. This relationship is summarized by the *venous function curve*, which shows how venous return increases as central venous pressure drops.² If central venous pressure reaches very low values and falls below the intrathoracic pressure, the veins in the thorax are compressed which therefore tends to limit venous return. In the example in Figure 8–3, intrathoracic pressure is taken to be 0 mmHg and the flat portion of the venous function curve indicates that lowering central venous pressure below 0 mmHg produces no additional increase in venous return.

² The slope of the venous function curve is determined by the value of the venous vascular resistance. Lowering the venous vascular resistance would tend to raise the venous function curve and make it steeper because more venous return would result for a given difference between P_{PV} and P_{CV} . However, if P_{PV} is 7 mmHg, venous return will be 0 L/min when $P_{CV} = 7$ mmHg at any level of venous vascular resistance ($\dot{Q} = \Delta P/R$). We have chosen to ignore the complicating issue of changes in venous vascular resistance because they do not affect the general conclusions to be drawn from the discussion of venous function curves.

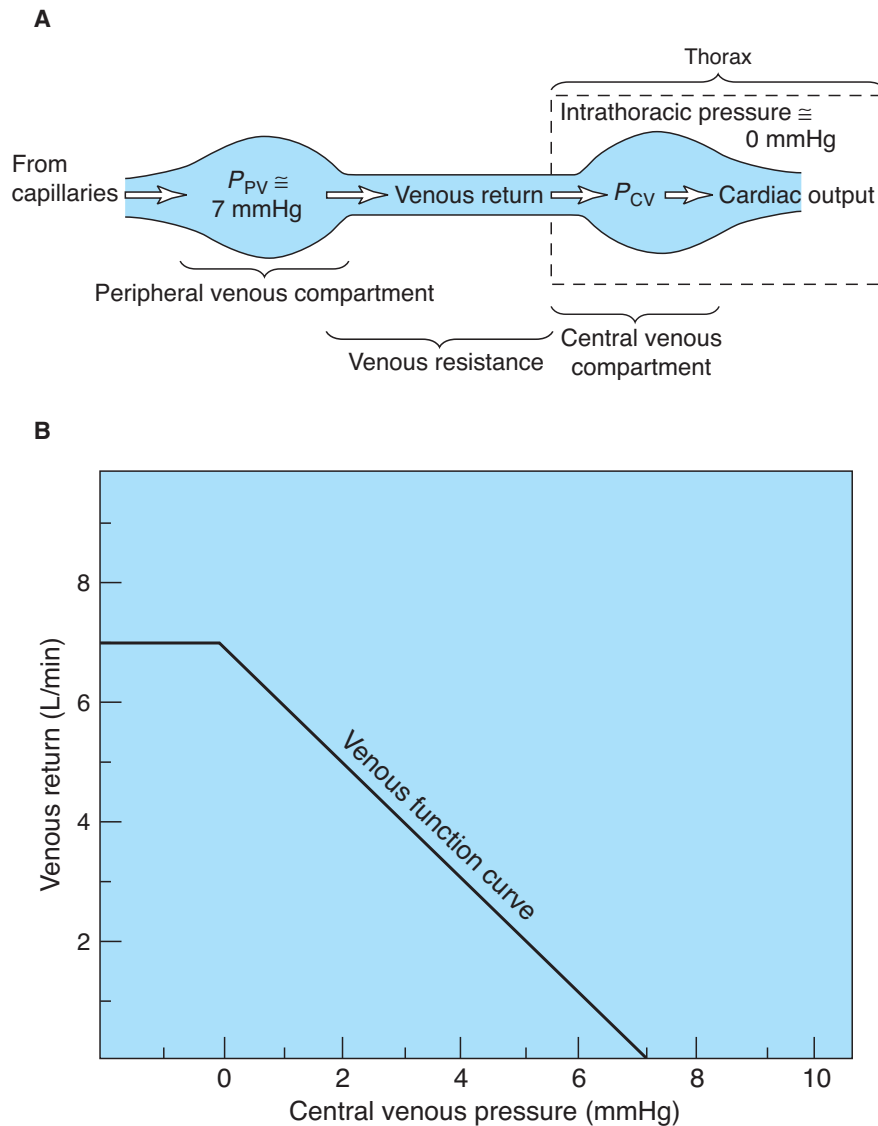


Figure 8–3. (A) Factors influencing venous return and (B) the venous function curve.

Just as a cardiac function curve shows how central venous pressure influences cardiac output, a *venous function curve* shows how central venous pressure influences venous return.³

INFLUENCE OF PERIPHERAL VENOUS PRESSURE ON VENOUS RETURN

As can be deduced from Figure 8–3A, it is the pressure difference between the peripheral and central venous compartments that determines venous return.

³ Graphic relationships are almost invariably plotted with the *independent* variable on the horizontal axis (abscissa) and the *dependent* variable on the vertical axis (ordinate) and they *must* be read in that sense. For example, Figure 8–3B says that increasing central venous pressure tends to cause decreased venous return. Figure 8–3B *does not* imply that increasing venous return will tend to lower central venous pressure.

Therefore, an increase in peripheral venous pressure can be just as effective in increasing venous return as a drop in central venous pressure.



The two ways in which peripheral venous pressure can change were discussed in Chapter 6. First, because veins are elastic vessels, changes in the *volume* of blood contained within the peripheral veins alter the peripheral venous pressure. Moreover, because the veins are much more compliant than any other vascular segment, changes in circulating blood volume produce larger changes in the volume of blood in the veins than in any other vascular segment. For example, blood loss by hemorrhage or loss of body fluids through severe sweating, vomiting, or diarrhea will decrease circulating blood volume and significantly reduce the volume of blood contained in the veins and thus decrease the peripheral venous pressure. Conversely, transfusion, fluid retention by the kidney, or transcapillary fluid reabsorption will increase circulating blood volume and venous blood volume. Whenever circulating blood volume increases, so does peripheral venous pressure.



Recall from Chapter 7 that the second way that peripheral venous pressure can be altered is through changes in venous tone produced by increasing or decreasing the activity of sympathetic vasoconstrictor nerves supplying the venous smooth muscle. Peripheral venous pressure increases whenever the activity of sympathetic vasoconstrictor fibers to veins increases. In addition, an increase in any force compressing veins from the outside has the same effect on the pressure inside veins as an increase in venous tone. Thus, such things as muscle exercise and wearing elastic stockings tend to elevate peripheral venous pressure.



Whenever peripheral venous pressure is altered, the relationship between central venous pressure and venous return is also altered. For example, whenever peripheral venous pressure is elevated by increases in blood volume or by sympathetic stimulation, the venous function curve shifts upward and to the right (Figure 8–4). This phenomenon can be most easily understood by focusing first on the central venous pressure at which there will be no venous return. If peripheral venous pressure is 7 mmHg, then venous return will be 0 L/min when central venous pressure is 7 mmHg. If peripheral venous pressure is increased to 10 mmHg, then considerable venous return will occur when central venous pressure is 7 mmHg, and venous return will stop only when central venous pressure is raised to 10 mmHg. Thus, increasing peripheral venous pressure shifts the whole venous function curve upward and to the right. By similar logic, decreased peripheral venous pressure caused by blood loss or decreased sympathetic vasoconstriction of peripheral veins shifts the venous function curve downward and to the left (Figure 8–4).

DETERMINATION OF CARDIAC OUTPUT AND VENOUS RETURN BY CENTRAL VENOUS PRESSURE

The significance of the fact that central venous pressure simultaneously affects both cardiac output and venous return can be best seen by plotting the cardiac function curve (the Starling curve) and the venous function curve on the same graph, as shown in Figure 8–5.

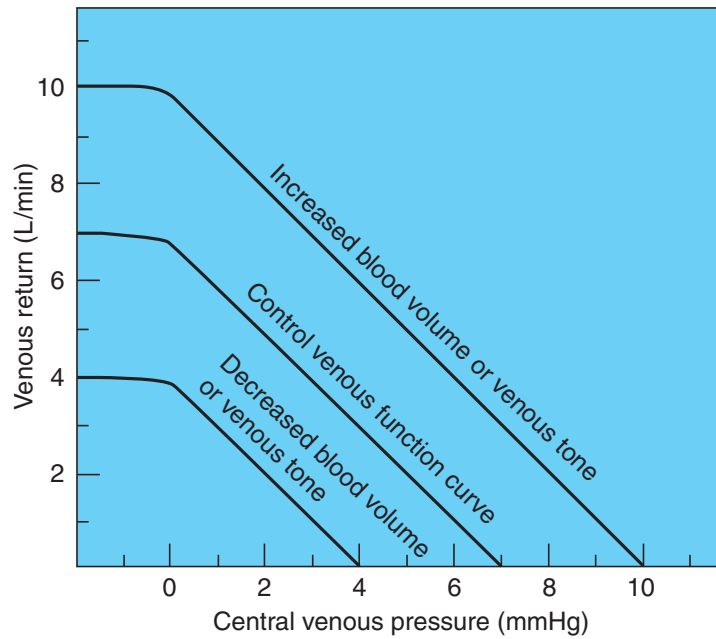


Figure 8-4. Effect of changes in blood volume and venous tone on venous function curves.

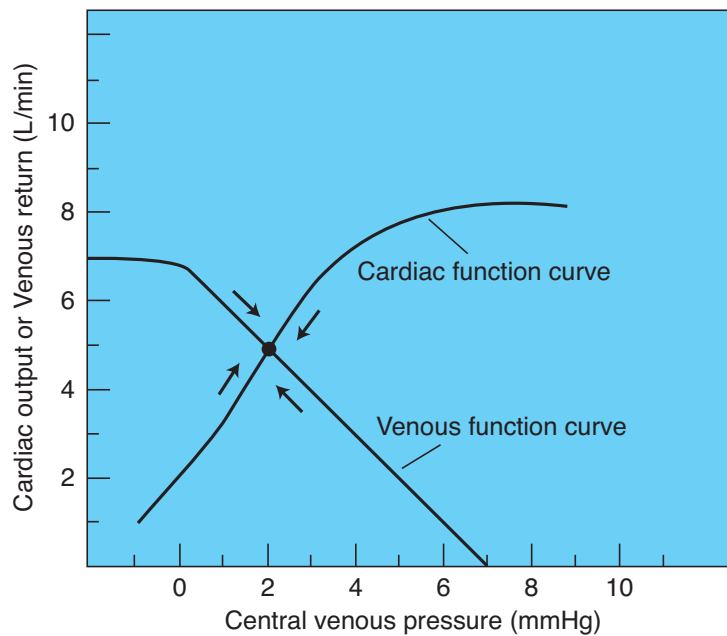


Figure 8-5. Interaction of cardiac output and venous return through central venous pressure.

Central venous pressure, as defined earlier, is the filling pressure of the right heart. Strictly speaking, this pressure directly affects only the stroke volume and output of the *right* heart pump. In most contexts, however, “cardiac output” implies the output of the *left* heart pump. How is it then, as has often been previously implied, that central venous pressure (the filling pressure of the right side of the heart) profoundly affects cardiac output (the output of the left side of the heart)? The short answer is that in the steady state, the right and left sides of the heart have equal outputs. (Because the right and left sides of the heart always beat with identical rates, this implies that their stroke volumes must be equal in the steady state.) The proper answer is that changes in central venous pressure automatically cause essentially parallel changes in the filling pressure of the left side of the heart (ie, in left atrial pressure). Consider, for example, the following sequence of consequences that a small step wise increase in central venous pressure has on a heart that previously was in a steady state:

1. Increased central venous pressure.
2. Increased right ventricular stroke volume via Starling’s law.
3. Increased output of the right side of the heart.
4. The right side of the heart output temporarily exceeds that of the left side of the heart.
5. As long as this imbalance exists, blood accumulates in the pulmonary vasculature and raises pulmonary venous and left atrial pressures.
6. Increased left atrial pressure increases left ventricular stroke volume via Starling’s law.
7. Very quickly, a new steady state will be reached when left atrial pressure has risen sufficiently to make left ventricular stroke volume exactly equal to the increased right ventricular stroke volume.

The major conclusion here is that left atrial pressure will automatically change in the correct direction to match left ventricular stroke volume to the current right ventricular stroke volume. Consequently, it is usually an acceptable simplification to say that central venous pressure affects cardiac output as if the heart consisted only of a single pump.

Note that in Figure 8–5, cardiac output and venous return are equal (at 5 L/min) *only* when the central venous pressure is 2 mmHg. If central venous pressure were to decrease to 0 mmHg for any reason, cardiac output would fall (to 2 L/min) and venous return would increase (to 7 L/min). With a venous return of 7 L/min and a cardiac output of 2 L/min, the volume of the central venous compartment would necessarily be increasing and this would produce a progressively increasing central venous pressure. In this manner, central venous pressure would return to the original level (2 mmHg) in a very short time. Moreover, if central venous pressure were to increase from 2 to 4 mmHg for any reason, venous return would decrease (to 3 L/min) and cardiac output would increase (to 7 L/min). This would quickly reduce the volume of blood in the central venous pool, and the central venous pressure would soon fall back to the original level. The cardiovascular system

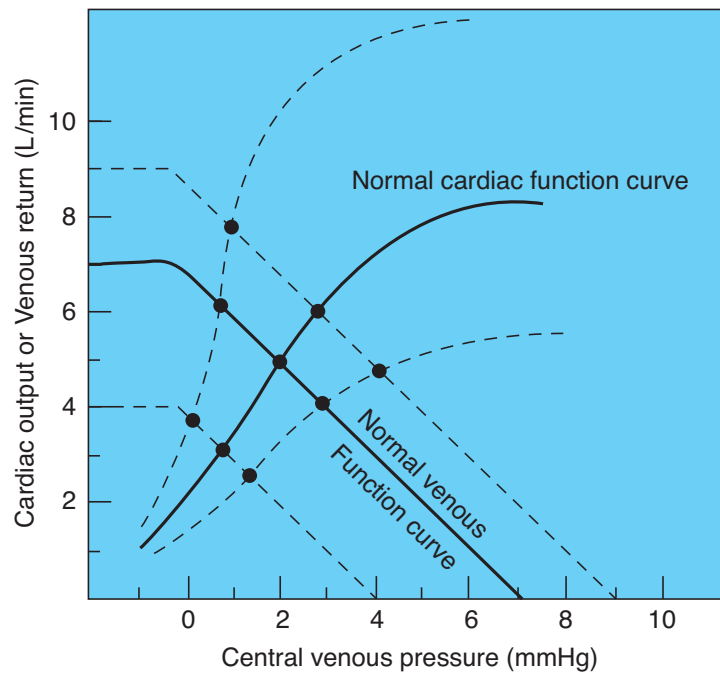


Figure 8-6. Families of cardiac function and venous function curves. Intersection points indicate equilibrium values for cardiac output, venous return, and central venous pressure under various conditions.

automatically adjusts to operate at the point where the cardiac and venous function curves intersect.



Central venous pressure is always inherently driven to the value that makes cardiac output and venous return equal. Cardiac output and venous return always stabilize at the level where the cardiac function and venous function curves intersect.

In order to fulfill its homeostatic role in the body, the cardiovascular system must be able to alter its cardiac output. Recall from Chapter 3 that cardiac output is affected by more than just cardiac filling pressure and that at any moment the heart may be operating on any one of a number of cardiac function curves, depending on the existing level of cardiac sympathetic tone. The family of possible cardiac function curves may be plotted along with the family of possible venous function curves, as shown in Figure 8-6. At a particular moment, the existing influences on the heart dictate the particular cardiac function curve on which it is operating, and similarly, the existing influences on peripheral venous pressure dictate the particular venous function curve that applies. Thus, the influences on the heart and on the peripheral vasculature determine where the cardiac and venous function curves intersect and thus what the central venous pressure and cardiac output (and venous return) are in the steady state. In the intact cardiovascular system, cardiac output can rise only when the point of intersection of the cardiac and venous function curves is raised. *All changes in cardiac output are caused by a shift in the cardiac function curve, a shift in the venous function curve, or both.*

The cardiac function and venous function curves are useful for understanding the complex interactions that occur in the intact cardiovascular system. With the

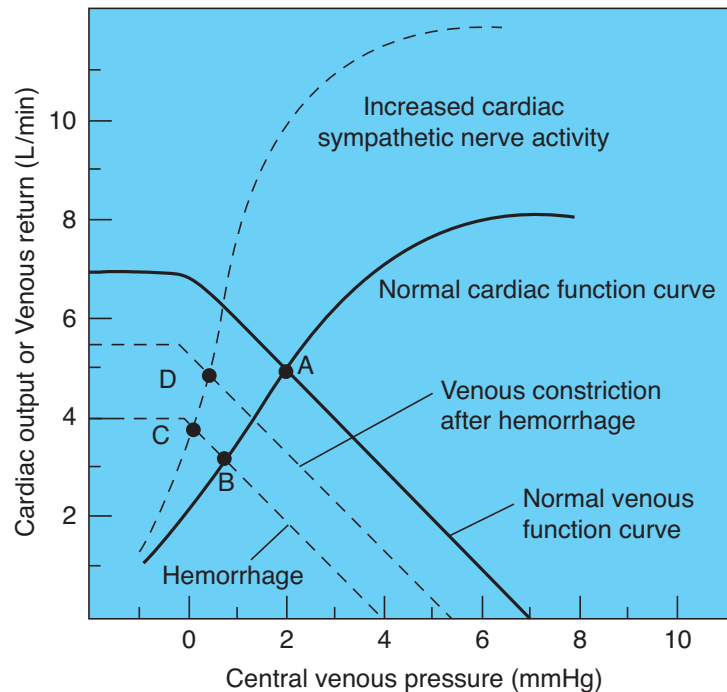


Figure 8-7. Cardiovascular adjustments to hemorrhage.

help of Figure 8-7, let us consider, for example, what happens to the cardiovascular system when there is a significant loss of blood (hemorrhage). Assume that before the hemorrhage, sympathetic activity to the heart and peripheral vessels is normal, as is the blood volume. Therefore, cardiac output is related to central venous pressure as indicated by the “normal” cardiac function curve in Figure 8-7. In addition, venous return is determined by central venous pressure as indicated by the “normal” venous function curve shown. The normal cardiac and venous function curves intersect at point A, so cardiac output is 5 L/min and central venous pressure is 2 mmHg in the normal state. When blood volume decreases because of hemorrhage, the peripheral venous pressure falls and the venous function curve is shifted to the left. In the absence of any cardiovascular responses, the cardiovascular system must switch its operation to point B because this is now the point at which the cardiac function curve and the new venous function curve intersect. This automatically occurs because, at the moment of blood loss, the venous function curve is shifted to the left and venous return falls below cardiac output at the central venous pressure of 2 mmHg. This is what leads to the fall in the central venous compartment’s volume and pressure that causes the shift in operation from point A to point B. Note by comparing points A and B in Figure 8-7 that blood loss itself lowers cardiac output and central venous pressure by shifting the venous function curve. In going from point A to point B, cardiac output falls solely because of decreased filling pressure and Starling’s law of the heart.

Subnormal cardiac output evokes a number of cardiovascular compensatory mechanisms to bring cardiac output back to more normal levels. One of these compensatory mechanisms is an increase in the activity of cardiac sympathetic nerves,

which, as discussed in Chapter 3, shifts the heart's operation to a cardiac function curve that is higher than normal. The effect of increasing cardiac sympathetic activity is illustrated by a shift in cardiovascular operation from point B to point C. In itself, the increased cardiac sympathetic nerve activity increases cardiac output (from 3 to 4 L/min) but causes a further decrease in central venous pressure. This drop in central venous pressure occurs because points B and C lie on the same venous function curve. *Cardiac* sympathetic nerves do not affect the venous function curve.⁴

An additional compensatory mechanism evoked by blood loss is increased activity of the sympathetic nerves leading to veins. Recall that this raises peripheral venous pressure and causes a rightward shift of the venous function curve. Therefore, increased sympathetic activity to veins tends to shift the venous function curve, originally lowered by blood loss, back toward normal. As a consequence of the increased peripheral venous tone and the shift to a more normal venous function curve, the cardiovascular operation shifts from point C to point D in Figure 8–7. Thus, peripheral venous constriction increases cardiac output by raising central venous pressure and moving the heart's operation upward along a fixed cardiac function curve. It must be pointed out that separating the response to hemorrhage into distinct, progressive steps (ie, A to B to C to D) is only a conceptualization for appreciating the individual effects of the different processes involved. In reality, the reflex venous and cardiac responses occur simultaneously and so quickly that they will easily keep up with the blood loss as it occurs. Thus, the actual course of a patient's net response to hemorrhage would follow nearly a straight line from point A to point D.

In summary, point D illustrates that normal cardiac output can be sustained in the face of blood loss by the combined effect of peripheral and cardiac adjustments. Hemorrhage is only one of an almost infinite variety of disturbances to the cardiovascular system. Plots such as those shown in Figure 8–7 are very useful for understanding the many disturbances to the cardiovascular system and the ways in which they may be compensated.

CLINICAL IMPLICATIONS OF ABNORMAL CENTRAL VENOUS PRESSURES



Although, in the clinical situation, there is no way to actually determine the position of either cardiac function or venous function curves, important information about the patient's circulatory status can be obtained from measures of central venous pressure. From what has been presented in this chapter, it is possible to conclude that a patient with *abnormally high* central venous pressure must have a depressed cardiac function curve, a right-shifted venous function curve, or both. As discussed in Chapter 11, very high central venous pressures are a hallmark of patients with congestive heart failure because they have the combination of dysfunctional heart muscle (depressed cardiac function curve) *and* excessive

⁴ Venous return is higher at point C than at point B, but the venous function *curve* has not shifted.

fluid volume (right-shifted venous function curve). *Abnormally low* central venous pressures, on the other hand, could theoretically be caused by either an elevated cardiac function curve or a left-shifted venous function curve. The clinical reality is that abnormally low central venous pressures are invariably the result of a left shift of the venous function curve, caused by either low blood volume or lack of venous tone.



Rough estimates of a patient's central venous pressure can be obtained quite easily by observing the external jugular veins. Because the force of gravity tends to keep veins in the head and neck collapsed when an individual is in an upright position, there should be no distention (or retrograde pulsations from atrial contractions) observed in these neck veins. Conversely, when an individual is fully recumbent, the neck veins should be full and pulsations should be easily detected. If a healthy individual is placed in a semirecumbent position so that the external jugular veins are positioned at ~ 7 cm above the right atrium, the point between the collapsed venous segment and the filled segment can usually be visualized.⁵ Abnormally high central venous pressures will be associated with neck vein distention at a higher level (perhaps even when the patient is upright).

Because of its diagnostic value in critical care situations, central venous pressure is often monitored continuously via a catheter that is inserted in a peripheral vein and advanced centrally until its tip is in the central venous compartment (ie, near or in the right atrium). In some situations, it is desirable to assess *left atrial* pressure, which is the filling pressure for the left side of the heart. This is commonly done with a specialized flow-directed venous catheter that uses a small inflatable balloon at its tip to drag it with the blood flow through the right ventricle and pulmonic valve into the pulmonary artery. The balloon is then deflated and the cannula is advanced further until it wedges into a terminal branch of the pulmonary vasculature. The *pulmonary wedge pressure* recorded at this junction provides a useful estimate of left atrial pressure.

KEY CONCEPTS



Mean circulatory filling pressure is a theoretical measure of pressure in the systemic circuit when flow is stopped and is influenced primarily by blood volume and peripheral venous tone.



Central venous pressure has a negative influence on venous return that can be illustrated graphically as a venous function curve.

⁵ The astute reader will note that 7-cm H₂O is equal to about 5 mmHg. This is significantly higher than the 2-mmHg central venous pressure we have used for argument elsewhere in this text. As discussed in Chapter 10, gravity causes body position-dependent shifts of blood volume between the peripheral and central venous pools. Thus, central venous pressure is normally higher in the recumbent than in the upright position.



Peripheral venous pressure has a positive influence on venous return and can be elevated by increased blood volume and/or increased venous tone.



Because of its opposing influences on cardiac output and venous return, central venous pressure automatically assumes a value that makes cardiac output and venous return equal.



Central venous pressure gives clinically relevant information about circulatory status.



Central venous pressure can be estimated noninvasively by noting the fullness of a patient's jugular veins.



STUDY QUESTIONS

- 8-1. Which of the following will decrease the mean circulatory filling pressure?
 - a. increased circulating blood volume
 - b. decreased arteriolar tone
 - c. increased venous tone
- 8-2. What determines central venous pressure?
- 8-3. According to Starling's law, cardiac output always decreases when central venous pressure decreases. True or false?
- 8-4. In a steady state, venous return will be greater than cardiac output when
 - a. peripheral venous pressure is higher than normal
 - b. blood volume is higher than normal
 - c. cardiac sympathetic nerve activity is lower than normal
- 8-5. What approaches might a physician logically pursue in an attempt to lower a patient's cardiac preload?
- 8-6. In a severely dehydrated patient, you would expect to find
 - a. a depressed cardiac function curve
 - b. an increased mean circulatory filling pressure
 - c. an increased central venous pressure
 - d. distended jugular veins
 - e. decreased cardiac output
- 8-7. If you gave a blood transfusion to a patient who had recently experienced a severe hemorrhage, you would expect
 - a. to expand arterial volume
 - b. to expand venous volume
 - c. to decrease central venous pressure
 - d. to decrease the mean circulatory filling pressure
 - e. to reduce cardiac output

- 8–8. Which of the following would directly (by themselves in the absence of any compensatory responses) tend to decrease central venous (cardiac filling) pressure?
- a. increased sympathetic nerve activity to only the heart
 - b. increased parasympathetic nerve activity to only the heart
 - c. increased blood volume
 - d. decreased total peripheral resistance
 - e. immersion in water up to the waist
-

OBJECTIVES

The student understands the mechanisms involved in the short-term regulation of arterial pressure:

- ▶ *Identifies the sensory receptors, afferent pathways, central integrating centers, efferent pathways, and effector organs that participate in the arterial baroreceptor reflex.*
- ▶ *States the location of the arterial baroreceptors and describes their operation.*
- ▶ *Describes how changes in the afferent input from arterial baroreceptors influence the activity of the sympathetic and parasympathetic preganglionic fibers.*
- ▶ *Describes how the sympathetic and parasympathetic outputs from the medullary cardiovascular centers change in response to changes in arterial pressure.*
- ▶ *Diagrams the chain of events that are initiated by the arterial baroreceptor reflex to compensate for a change in arterial pressure.*
- ▶ *Describes how inputs to the medullary cardiovascular center from cardiopulmonary baroreceptors, arterial and central chemoreceptors, receptors in skeletal muscle, the cerebral cortex, and the hypothalamus influence sympathetic activity, parasympathetic activity, and mean arterial pressure.*
- ▶ *Describes and indicates the mechanisms involved in the Bezold–Jarisch reflex, the cerebral ischemic response, the Cushing reflex, the alerting reaction, blushing, vasovagal syncope, the dive reflex, and the cardiovascular responses to emotion and pain.*

The student comprehends the key elements of the commonly accepted “renal mean arterial pressure” theory of long-term arterial pressure regulation.

- ▶ *Describes baroreceptor adaptation.*
- ▶ *Describes the influence of changes in body fluid volume on arterial pressure and diagrams the steps involved in this process.*
- ▶ *Indicates the mechanisms whereby altered arterial pressure alters glomerular filtration rate and renal tubular function to influence urinary output.*
- ▶ *Describes how mean arterial pressure is adjusted in the long term to that which causes fluid output rate to equal fluid intake rate.*

The student recognizes that our current understanding of all the factors that could be involved in the long-term regulation of arterial pressure is incomplete.

- ▶ *Describes the basic features of the “CNS-MAP set-point” theory of long-term arterial pressure regulation.*



Appropriate systemic arterial pressure is perhaps the single most important requirement for proper operation of the cardiovascular system. Without sufficient arterial pressure, the brain and the heart do not receive adequate blood flow, no matter what adjustments are made in their vascular resistance by local control mechanisms. In contrast, unnecessary demands are placed on the heart by excessive arterial pressure. The elaborate mechanisms that have evolved for regulating this critical cardiovascular variable are discussed in this chapter.

Arterial pressure is continuously monitored by various sensors located within the body. Whenever arterial pressure varies from normal, multiple reflex responses are initiated, which cause the adjustments in cardiac output, and total peripheral resistance needed to return arterial pressure to its normal value. In the short term (seconds), these adjustments are brought about by changes in the activity of the autonomic nerves leading to the heart and peripheral vessels. In the long term (minutes to days), other mechanisms such as changes in cardiac output brought about by changes in blood volume play an increasingly important role in the control of arterial pressure. The short- and long-term regulations of arterial pressure are discussed in this chapter.

SHORT-TERM REGULATION OF ARTERIAL PRESSURE

Arterial Baroreceptor Reflex



The *arterial baroreceptor reflex* is the single most important mechanism providing short-term regulation of arterial pressure. Recall that the usual components of a reflex pathway include sensory receptors, afferent pathways, integrating centers in the central nervous system (CNS), efferent pathways, and effector organs. As shown in Figure 9–1, the efferent pathways of the arterial baroreceptor reflex are the cardiovascular sympathetic and cardiac parasympathetic nerves. The effector organs are the heart and peripheral blood vessels.



EFFERENT PATHWAYS

Previous chapters have discussed the many actions of the sympathetic and parasympathetic nerves leading to the heart and blood vessels. For both systems, *postganglionic fibers*, whose cell bodies are in ganglia outside the CNS, form the terminal link to the heart and vessels. The influences of these postganglionic fibers on key cardiovascular variables are summarized in Figure 9–1.

The activity of the terminal postganglionic fibers of the autonomic nervous system is determined by the activity of *preganglionic fibers* whose cell bodies lie within the CNS. In the sympathetic pathways, the cell bodies of the preganglionic fibers are located within the spinal cord. These preganglionic neurons have spontaneous activity that is modulated by excitatory and inhibitory inputs, which arise from centers in the brainstem and descend in distinct *excitatory* and *inhibitory* spinal pathways. In the parasympathetic system, the cell bodies of the preganglionic fibers are located within the brainstem. Their spontaneous activity is modulated by inputs from adjacent centers in the brainstem.

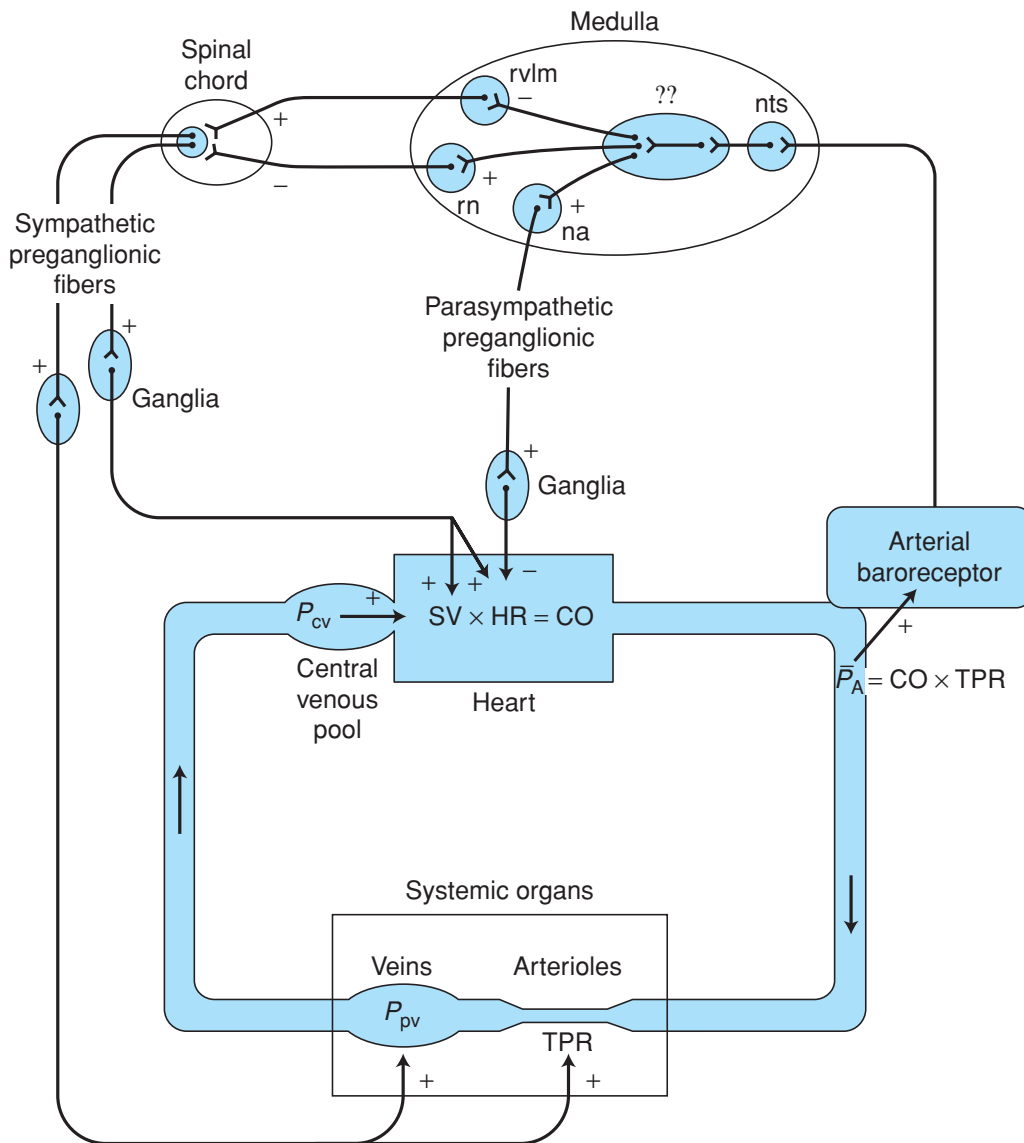


Figure 9-1. Components of the arterial baroreceptor reflex pathway. nts, nucleus tractus solitarius; rvlm, rostral ventrolateral medullary group; rn, raphé nucleus; na, nucleus ambiguus; ??, incompletely mapped integration pathways that may also involve structures outside the medulla.

AFFERENT PATHWAYS

Sensory receptors, called *arterial baroreceptors*, are found in abundance in the walls of the aorta and carotid arteries. Major concentrations of these receptors are found near the arch of the aorta (the *aortic baroreceptors*) and at the bifurcation of the common carotid artery into the internal and external carotid arteries on either side of the neck (the *carotid sinus baroreceptors*). The receptors themselves are mechanoreceptors that sense arterial pressure indirectly from the degree of stretch of the elastic arterial walls. In general, *increased stretch causes an increased action potential generation rate by the arterial baroreceptors*. Baroreceptors actually sense not only absolute stretch

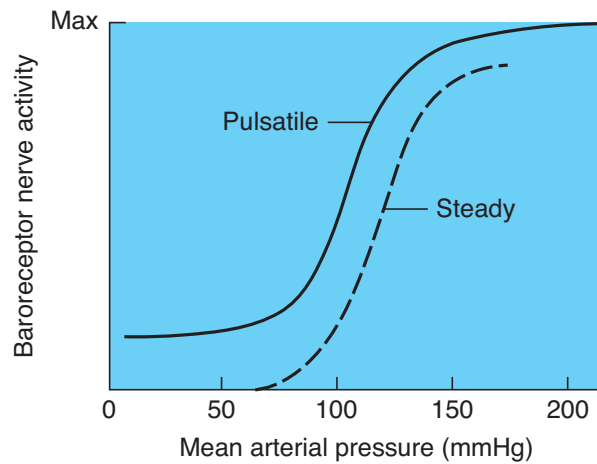


Figure 9–2. The effect of mean arterial pressure on baroreceptor nerve activity.

but also the rate of change of stretch. For this reason, both the mean arterial pressure and the arterial pulse pressure affect baroreceptor firing rate as indicated in Figure 9–2. The dashed curve in Figure 9–2 shows how baroreceptor firing rate is affected by different levels of a steady arterial pressure. The solid curve in Figure 9–2 indicates how baroreceptor firing rate is affected by the mean value of a pulsatile arterial pressure. Note that the presence of pulsations (that of course are normal) increases the baroreceptor firing rate at any given level of mean arterial pressure. Note also that changes in mean arterial pressure near the normal value of 100 mmHg produce the largest changes in baroreceptor discharge rate.

If arterial pressure remains elevated over a period of several days for some reason, the arterial baroreceptor firing rate will gradually return toward normal. Thus, arterial baroreceptors are said to *adapt* to long-term changes in arterial pressure. For this reason, the arterial baroreceptor reflex cannot serve as a mechanism for the long-term regulation of arterial pressure.

Action potentials generated by the carotid sinus baroreceptors travel through the carotid sinus nerves (Hering’s nerves), which join with the glossopharyngeal nerves (IX cranial nerves) before entering the CNS. Afferent fibers from the aortic baroreceptors run to the CNS in the vagus nerves (X cranial nerves). (The vagus nerves contain both afferent and efferent fibers, including, for example, the parasympathetic efferent fibers to the heart.)

CENTRAL INTEGRATION

Much of the central integration involved in reflex regulation of the cardiovascular system occurs in the medulla oblongata in what are traditionally referred to as the *medullary cardiovascular centers*. The neural interconnections between the diffuse structures in this area are complex and not completely mapped. Moreover, these structures appear to serve multiple functions including respiratory control, for example. What is known with a fair degree of certainty is where the cardiovascular afferent and efferent pathways enter and leave the medulla. For example, as indicated in Figure 9–1, the afferent sensory information from the arterial baroreceptors

enters the medullary *nucleus tractus solitarius*, where it is relayed via polysynaptic pathways to other structures in the medulla (and higher brain centers, such as the hypothalamus, as well). The cell bodies of the efferent vagal parasympathetic cardiac nerves are located primarily in the medullary *nucleus ambiguus*. The sympathetic autonomic efferent information leaves the medulla predominantly from the *rostral ventrolateral medulla* group of neurons (via an excitatory spinal pathway) or the *raphé nucleus* (via an inhibitory spinal pathway). The intermediate processes involved in the actual integration of the sensory information into appropriate sympathetic and parasympathetic responses are not well understood at present. Although much of this integration takes place within the medulla, higher centers such as the hypothalamus are probably involved as well. In this context, knowing the details of the integration process is not as important as appreciating the overall effects that changes in arterial baroreceptor activity have on the activities of parasympathetic and sympathetic cardiovascular nerves.

Several functionally important points about the central control of the autonomic cardiovascular nerves are illustrated in Figure 9–1. The major external influence on the cardiovascular centers comes from the arterial baroreceptors. Because the arterial baroreceptors are active at normal arterial pressures, they supply a tonic input to the central integration centers.



As indicated in Figure 9–1, the integration process is such that increased input from the arterial baroreceptors tends to simultaneously (1) inhibit the activity of the spinal sympathetic excitatory tract, (2) stimulate the activity of the spinal sympathetic inhibitory tract, and (3) stimulate the activity of parasympathetic preganglionic nerves. Thus, an increase in the arterial baroreceptor discharge rate (caused by increased arterial pressure) causes a decrease in the tonic activity of cardiovascular sympathetic nerves and a simultaneous increase in the tonic activity of cardiac parasympathetic nerves. Conversely, decreased arterial pressure causes increased sympathetic and decreased parasympathetic activity.

OPERATION OF THE ARTERIAL BARORECEPTOR REFLEX

The arterial baroreceptor reflex is a continuously operating control system that automatically makes adjustments to prevent disturbances on the heart and/or vessels from causing large changes in mean arterial pressure. The arterial baroreceptor reflex mechanism acts to regulate arterial pressure in a *negative feedback* manner that is analogous in many ways to the manner in which a thermostatically controlled home heating system operates to regulate inside temperature despite disturbances such as changes in the weather or open windows.¹



Figure 9–3 shows many events in the arterial baroreceptor reflex pathway that occur in response to a disturbance of decreased mean arterial pressure.

¹ In this analogy, arterial pressure is likened to temperature; the heart is the generator of pressure as the furnace is the generator of heat; dilated arterioles dissipate arterial pressure like open windows lose heat; the arterial baroreceptors monitor arterial pressure as the sensor of a thermostat monitors temperature; and the electronics of the thermostat control the furnace as the medullary cardiovascular centers regulate the operation of the heart. Because home thermostats do not usually also regulate the operation of the windows, there is no analogy to the reflex medullary control of arterioles. The pressure that the arterial baroreflex strives to maintain is analogous to the temperature setting on the thermostat dial.

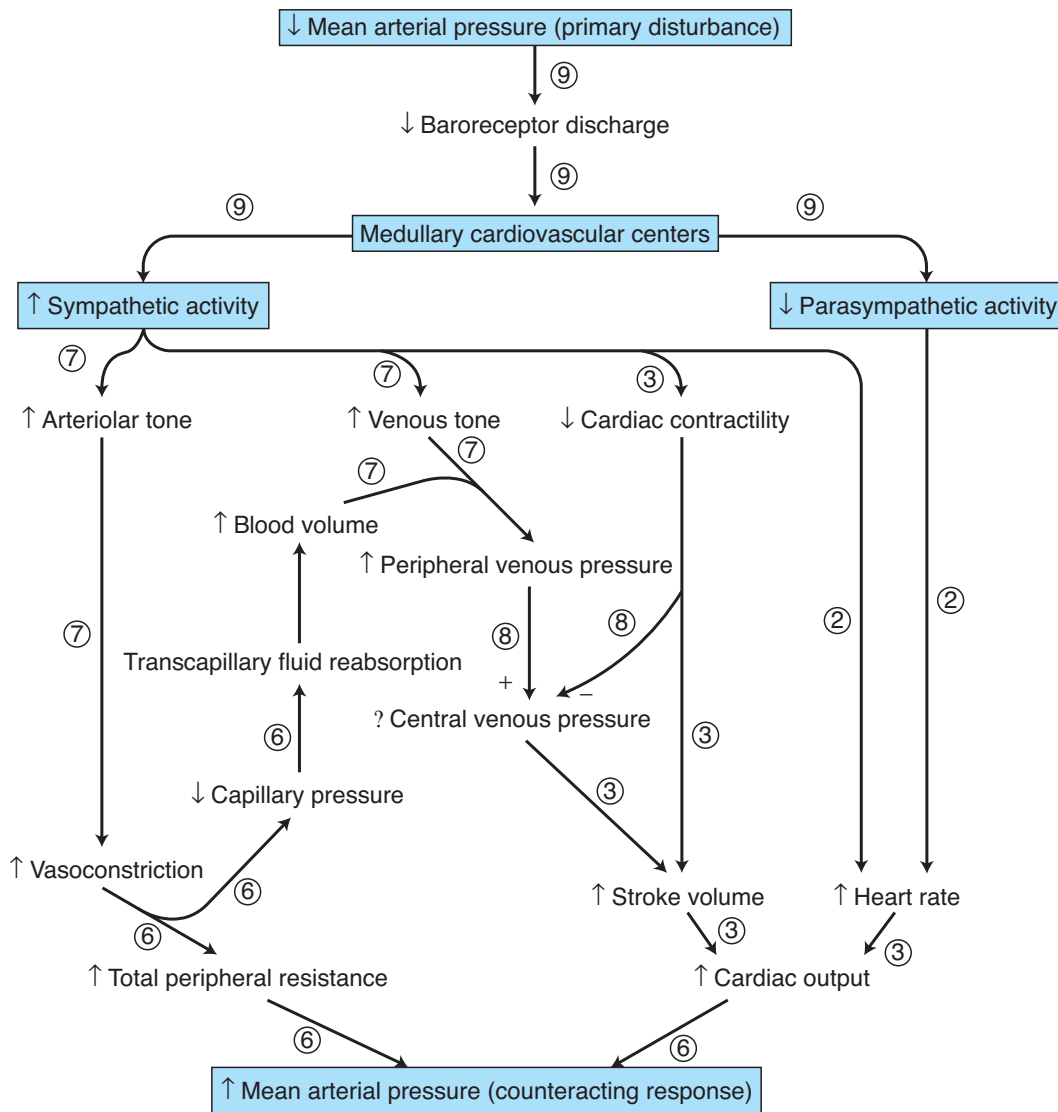


Figure 9-3. Immediate cardiovascular adjustments caused by a decrease in arterial blood pressure. Circled numbers indicate the chapter in which each interaction is discussed.

All the events shown in Figure 9-3 have already been discussed, and each should be carefully examined (and reviewed if necessary) at this point because a great many of the interactions that are essential to understanding cardiovascular physiology are summarized in this figure.

Note that in Figure 9-3 the overall response of the arterial baroreceptor reflex to the disturbance of decreased mean arterial pressure is increased mean arterial pressure (ie, the response tends to counteract the disturbance). A disturbance of increased mean arterial pressure would elicit events exactly opposite to those shown in Figure 9-3 and produce the response of decreased mean arterial pressure; again, the response tends to counteract the disturbance. The homeostatic benefits of the reflex action should be apparent.

One should recall that nervous control of vessels is more important in some areas such as the kidney, the skin, and the splanchnic organs than in the brain and the heart muscle. Thus, the reflex response to a fall in arterial pressure may, for example, include a significant increase in renal vascular resistance and a decrease in renal blood flow without changing the cerebral vascular resistance or blood flow. The peripheral vascular adjustments associated with the arterial baroreceptor reflex take place primarily in organs with strong sympathetic vascular control.

Other Cardiovascular Reflexes and Responses



Seemingly in spite of the arterial baroreceptor reflex mechanism, large and rapid changes in mean arterial pressure occur in certain physiological and pathological situations. These reactions are caused by influences on the medullary cardiovascular centers *other* than those from the arterial baroreceptors. As outlined in the following sections, these inputs on the medullary cardiovascular centers arise from many types of peripheral and central receptors as well as from “higher centers” in the CNS such as the hypothalamus and the cortex.

The analogy was made earlier that the arterial baroreceptor reflex operates to control arterial pressure somewhat as a home heating system acts to control inside temperature. Such a system automatically acts to counteract changes in temperature caused by such things as an open window or a dirty furnace. It does not, however, resist changes in temperature caused by someone’s resetting of the thermostat dial—in fact, the basic temperature-regulating mechanisms cooperate wholeheartedly in adjusting the temperature to the new desired value. The temperature setting on a home thermostat’s dial has a useful conceptual analogy in cardiovascular physiology often referred to as the “*set point*” for arterial pressure. *Most (but not all) of the influences that are about to be discussed influence arterial pressure as if they changed the arterial baroreceptor reflex’s set point for pressure regulation.* Consequently, the arterial baroreceptor reflex does not resist most of these pressure disturbances, but actually assists in producing them.

REFLEXES FROM RECEPTORS IN THE HEART AND LUNGS

A host of mechanoreceptors and chemoreceptors that can elicit reflex cardiovascular responses have been identified in the atria, ventricles, coronary vessels, and lungs. The role of these *cardiopulmonary receptors* in the neurohumoral control of the cardiovascular system is, in most cases, incompletely understood, but evidence is accumulating that they may be involved significantly in many physiological and pathological states.

One general function that the cardiopulmonary receptors perform is sensing the pressure (or volume) in the atria and central venous pool. Increased central venous pressure and volume cause receptor activation by stretch, which elicits a reflex decrease in sympathetic activity. Decreased central venous pressure produces the opposite response. Whatever the details, it is clear that cardiopulmonary baroreflexes normally exert a tonic inhibitory influence on sympathetic activity and play an

arguably important, but not yet completely defined, role in normal cardiovascular regulation.²

CHEMORECEPTOR REFLEXES

Low PO_2 and/or high PCO_2 levels in the arterial blood cause reflex increases in respiratory rate *and* mean arterial pressure. These responses appear to be a result of increased activity of *arterial chemoreceptors*, located in the carotid arteries and the arch of the aorta, and *central chemoreceptors*, located somewhere within the CNS. Chemoreceptors probably play little role in the normal regulation of arterial pressure because arterial blood PO_2 and PCO_2 are normally held very nearly constant by respiratory control mechanisms.

An extremely strong reaction called the *cerebral ischemic response* is triggered by inadequate brain blood flow (ischemia) and can produce a more intense sympathetic vasoconstriction and cardiac stimulation than is elicited by any other influence on the cardiovascular control centers. Presumably the cerebral ischemic response is initiated by chemoreceptors located within the CNS. However, if cerebral blood flow is severely inadequate for several minutes, the cerebral ischemic response wanes and is replaced by marked loss of sympathetic activity. Presumably this situation results when function of the nerve cells in the cardiovascular centers becomes directly depressed by the unfavorable chemical conditions in the cerebrospinal fluid.

Whenever intracranial pressure is increased—for example, by tumor growth or trauma-induced bleeding within the rigid cranium—there is a parallel rise in arterial pressure. This is called the *Cushing reflex*. It can cause mean arterial pressures of more than 200 mmHg in severe cases of intracranial pressure elevation. The obvious benefit of the Cushing reflex is that it prevents collapse of cranial vessels and thus preserves adequate brain blood flow in the face of large increases in intracranial pressure. The mechanisms responsible for the Cushing reflex are not known but could involve the central chemoreceptors. A hallmark of the Cushing reflex is acutely increased arterial pressure in spite of accompanying bradycardia. It seems as if the short-term arterial baroreceptor reflex is attempting to fight this disturbance.

REFLEXES FROM RECEPTORS IN EXERCISING SKELETAL MUSCLE

Reflex tachycardia and increased arterial pressure can be elicited by stimulation of certain afferent fibers from the skeletal muscle. These pathways may be activated by chemoreceptors responding to muscle ischemia, which occurs with strong, sustained static (isometric) exercise. This input may contribute to the marked increase in blood pressure that accompanies such isometric efforts. It is uncertain as to what extent this reflex contributes to the cardiovascular responses to dynamic (rhythmic) muscle exercise.

² Certain other reflexes originating from receptors in the cardiopulmonary region have been described that may be important in specific pathological situations. For example, the *Bezold–Jarisch* reflex that involves marked bradycardia and hypotension is elicited by application of strong stimuli to coronary vessel (or myocardial) chemoreceptors concentrated primarily in the posterior wall of the left ventricle. Activation of this reflex causes certain myocardial infarction patients to present with bradycardia instead of the expected tachycardia.

THE DIVE REFLEX

Aquatic animals respond to diving with a remarkable bradycardia and intense vasoconstriction in all systemic organs except the brain and the heart. The response serves to allow prolonged submersion by limiting the rate of oxygen use and by directing blood flow to essential organs. A similar but less dramatic dive reflex can be elicited in humans by simply immersing the face in water. (Cold water enhances the response.) The response involves the unusual combination of bradycardia produced by enhanced cardiac parasympathetic activity and peripheral vasoconstriction caused by enhanced sympathetic activity that is a rare exception to the general rule that sympathetic and parasympathetic nerves are activated in reciprocal fashion. The dive reflex is sometimes used clinically to reflexly activate cardiac parasympathetic nerves for the purpose of interrupting atrial tachyarrhythmias.

Another, but unrelated, clinical technique for activating parasympathetic nerves in an attempt to interrupt atrial tachyarrhythmias is called *carotid massage*. In essence, massage of the neck is done to cause physical deformation of the carotid sinuses and “trick” them into sending a “high-pressure” alarm to the medullary control centers.

CARDIOVASCULAR RESPONSES ASSOCIATED WITH EMOTION

Cardiovascular responses are frequently associated with certain states of emotion. These responses originate in the cerebral cortex and reach the medullary cardiovascular centers through corticohypothalamic pathways. The least complicated of these responses is the *blushing* that is often detectable in individuals with lightly pigmented skin during states of embarrassment. The blushing response involves a loss of sympathetic vasoconstrictor activity *only* to particular cutaneous vessels, and this produces the blushing by allowing engorgement of the cutaneous venous sinuses.

Excitement or a sense of danger often elicits a complex behavioral pattern called the *alerting reaction* (also called the “defense” or “fight or flight” response). The alerting reaction involves a host of responses such as pupillary dilation and increased skeletal muscle tenseness that are generally appropriate preparations for some form of intense physical activity. The cardiovascular component of the alerting reaction is an increase in blood pressure caused by a general increase in cardiovascular sympathetic nervous activity and a decrease in cardiac parasympathetic activity. Centers in the *posterior hypothalamus* are presumed to be involved in the alerting reaction because many of the components of this multifaceted response can be experimentally reproduced by electrical stimulation of this area. The general cardiovascular effects are mediated via hypothalamic communications with the medullary cardiovascular centers.

Some individuals respond to situations of extreme stress by fainting, a situation referred to clinically as *vasovagal syncope*. The loss of consciousness is due to decreased cerebral blood flow that is itself produced by a sudden dramatic loss of arterial blood pressure that, in turn, occurs as a result of a sudden loss of sympathetic tone and a simultaneous large increase in parasympathetic tone and decrease in the heart rate. The influences on the medullary cardiovascular centers that produce vasovagal syncope appear to come from the cortex via depressor centers in the

anterior hypothalamus. It has been suggested that vasovagal syncope is analogous to the “playing dead” response to peril used by some animals. Fortunately, unconsciousness (combined with becoming horizontal) seems to quickly remove this serious disturbance to the normal mechanisms of arterial pressure control in humans.

The extent to which cardiovascular variables, in particular blood pressure, are normally affected by an emotional state is currently a topic of extreme interest and considerable research. As yet the answer is unclear. However, the therapeutic value of being able, for example, to learn to consciously reduce one’s blood pressure would be incalculable.

CENTRAL COMMAND

The term *central command* is used to imply an input from the cerebral cortex to lower brain centers during voluntary muscle exercise. The concept is that the same cortical drives that initiate somatomotor (skeletal muscle) activity also simultaneously initiate cardiovascular (and respiratory) adjustments appropriate to support that activity. In the absence of any other obvious causes, central command is at present the best explanation as to why both mean arterial pressure and respiration increase during voluntary exercise.

REFLEX RESPONSES TO PAIN

Pain can have either a positive or negative influence on arterial pressure. Generally, superficial or cutaneous pain causes a rise in blood pressure in a manner similar to that associated with the alerting response and perhaps over many of the same pathways. Deep pain from receptors in the viscera or joints, however, often causes a cardiovascular response similar to that which accompanies vasovagal syncope, that is, decreased sympathetic tone, increased parasympathetic tone, and a serious decrease in blood pressure. This response may contribute to the state of shock that often accompanies crushing injuries and/or joint displacement.

TEMPERATURE REGULATION REFLEXES

Certain special cardiovascular reflexes that involve the control of skin blood flow have evolved as part of the body temperature regulation mechanisms. Temperature regulation responses are controlled primarily by the hypothalamus, which can operate through the cardiovascular centers to discretely control the sympathetic activity to cutaneous vessels and thus skin blood flow. The sympathetic activity to cutaneous vessels is extremely responsive to changes in hypothalamic temperature. Measurable changes in cutaneous blood flow result from changes in hypothalamic temperature of tenths of a degree Celsius.

Cutaneous vessels are influenced by reflexes involved in both arterial pressure regulation and temperature regulation. When the appropriate cutaneous vascular responses for temperature regulation and pressure regulation are contradictory, as they are, for example, during strenuous exercise in a hot environment, then the temperature-regulating influences on cutaneous blood vessels usually prevail.

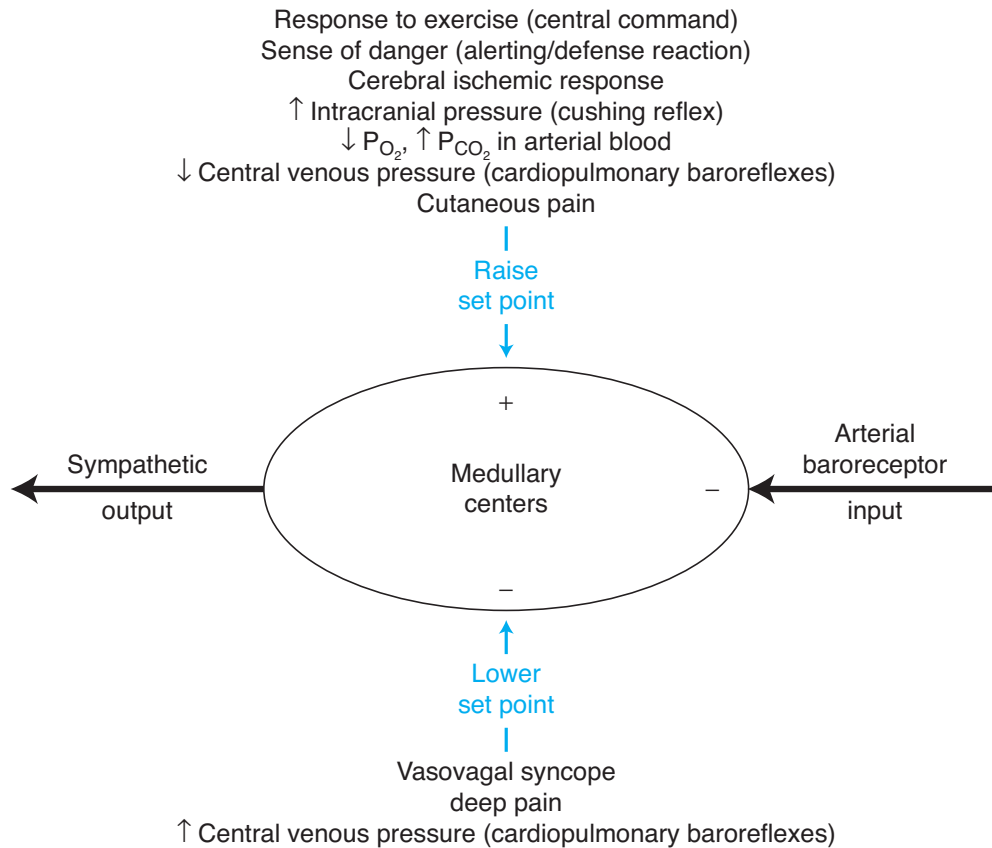


Figure 9–4. Summary of the factors that influence the set point of the arterial baroreceptor reflex.

SUMMARY

Most of the influences on the medullary cardiovascular centers that have been discussed in the preceding sections are summarized in Figure 9–4. This figure is intended first to reemphasize that the arterial baroreceptors normally and continually supply the major input to the medullary centers. The arterial baroreceptor input is shown as inhibitory because an increase in arterial baroreceptor firing rate results in a decrease in sympathetic output. (Decreased sympathetic output should be taken to imply also a simultaneous increase in parasympathetic output that is not shown in this figure.)



As is indicated in Figure 9–4, the *nonarterial baroreceptor influences* on the medullary cardiovascular centers fall into two categories: (1) those that *increase* arterial pressure by raising the set point for the arterial baroreceptor reflex and thus cause an increase in sympathetic activity and (2) those that *decrease* arterial pressure by lowering the set point for the arterial baroreceptor reflex and thus cause a decrease in sympathetic activity. Note that certain responses that have been discussed are not included in Figure 9–4. The complex combination of stimuli involved in the dive reflex causes simultaneous sympathetic and parasympathetic activation and cannot be simply classified as either pressure raising or pressure lowering. Also, temperature stimuli that discretely affect cutaneous vessels but not

general cardiovascular sympathetic and parasympathetic activity have not been included in Figure 9–4.

The nonarterial baroreceptor influences shown in Figure 9–4 may be viewed as disturbances on the cardiovascular system that act on the medullary cardiovascular centers as opposed to disturbances that act on the heart and vessels. These disturbances cause sympathetic activity and arterial pressure to change in the *same direction*. Recall from the discussion of the arterial baroreceptor reflex that cardiovascular disturbances that act on the heart or vessels (such as blood loss or heart failure) produce *reciprocal* changes in arterial pressure and sympathetic activity. These facts are often useful in the clinical diagnoses of blood pressure abnormalities. For example, patients commonly present in the physician's office with high blood pressure in combination with elevated heart rate (implying elevated sympathetic activity). These same-direction changes in arterial pressure and sympathetic activity suggest that the problem lies not in the periphery but rather with an abnormal pressure-raising input to the medullary cardiovascular centers. The physician should immediately think of those set-point raising influences listed in the top half of Figure 9–4 that would simultaneously raise sympathetic activity and arterial pressure. Often, such a patient does not have chronic hypertension but rather is just experiencing a temporary blood pressure elevation due to the anxiety of undergoing a physical examination.

A more rigorous analysis of the operation of the arterial baroreflex is presented in Appendix E. It is not essential reading but the serious students may find it enlightening.

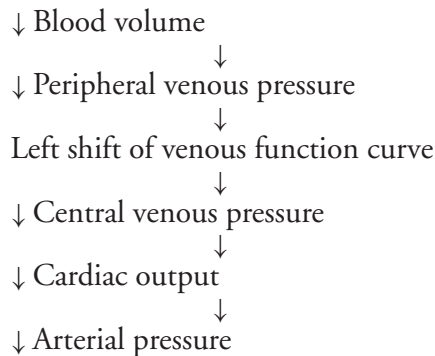
LONG-TERM REGULATION OF ARTERIAL PRESSURE

Long-term regulation of arterial pressure is a topic of extreme clinical relevance because of the prevalence of *hypertension* (sustained excessive arterial blood pressure) in our society. The most long-standing and generally accepted theory of long-term pressure regulation is that it crucially involves the kidneys, their sodium handling, and ultimately the regulation of blood volume. This theory is sometimes referred to as the “renal-MAP set-point” or “fluid balance” model of long-term arterial blood pressure control. In essence, this theory asserts that in the long term, mean arterial pressure is whatever it needs to be to maintain an appropriate blood volume through arterial pressure's direct effects on renal function. At the end of this chapter, we present some alternative hypotheses that argue that the generally accepted “renal-MAP” model of long-term pressure regulation is overly simplistic and incomplete.

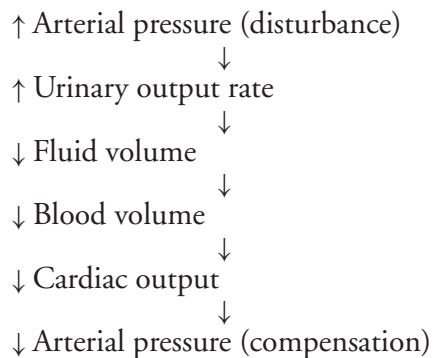
Fluid Balance and Arterial Pressure

Several key factors in the long-term regulation of arterial blood pressure have already been considered. First is the fact that the baroreceptor reflex, however well it counteracts temporary disturbances in arterial pressure, cannot effectively regulate arterial pressure in the long term for the simple reason that the baroreceptor firing rate adapts to prolonged changes in arterial pressure.

The second pertinent fact is that circulating blood volume can influence arterial pressure because:



A fact yet to be considered is that arterial pressure has a profound influence on urinary output rate and thus affects total body fluid volume. Because blood volume is one of the components of the total body fluid, blood volume alterations accompany changes in total body fluid volume. The mechanisms are such that an *increase in arterial pressure* causes an increase in urinary output rate and thus a *decrease in blood volume*. But, as outlined in the preceding sequence, decreased blood volume tends to lower arterial pressure. Thus, the complete sequence of events that are initiated by an increase in arterial pressure can be listed as follows:



Note the negative feedback nature of this sequence of events: increased arterial pressure leads to fluid volume depletion, which tends to lower arterial pressure. Conversely, an initial disturbance of decreased arterial pressure would lead to fluid volume expansion, which would tend to increase arterial pressure. Because of negative feedback, these events constitute a *fluid volume mechanism* for regulating arterial pressure.

As indicated in Figure 9–5, both the arterial baroreceptor reflex and this fluid volume mechanism are negative feedback loops that regulate arterial pressure. Although the arterial baroreceptor reflex is very quick to counteract disturbances in arterial pressure, hours or even days may be required before a change in urinary output rate produces a significant accumulation or loss of total body fluid volume. Whatever this fluid volume mechanism lacks in speed, however, it more than makes

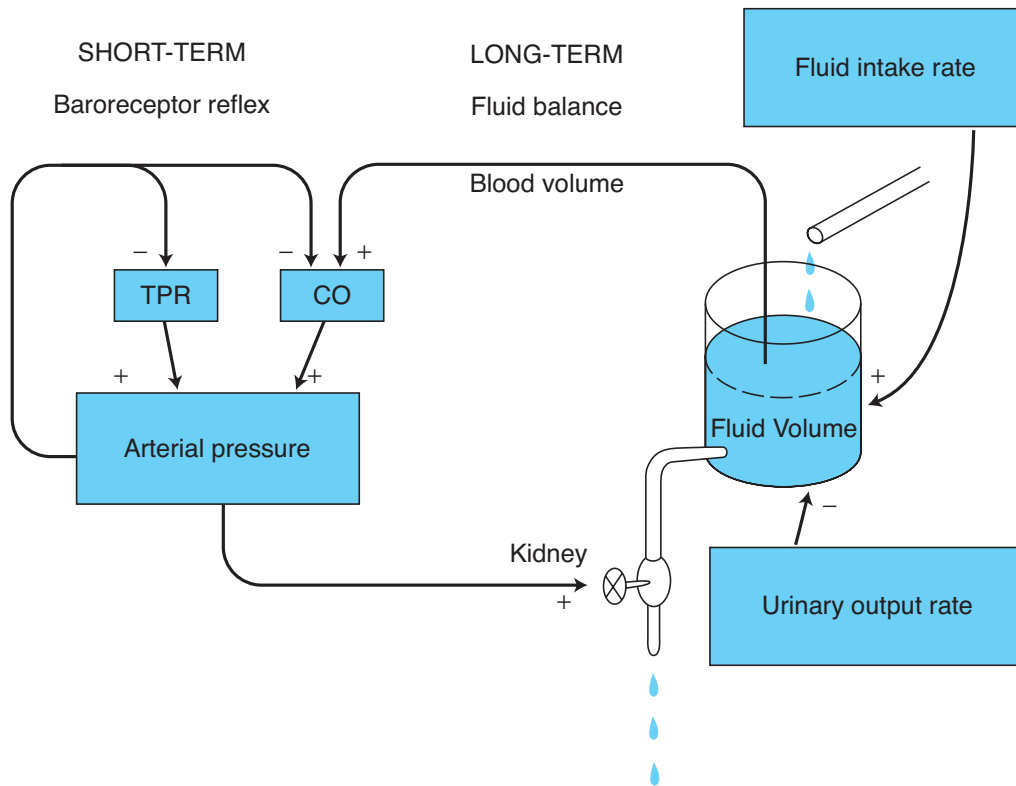


Figure 9–5. Mechanisms of short- and long-term regulations of arterial pressure. TPR, total peripheral resistance; CO, cardiac output.

up for in persistence. As long as there is any inequality between the fluid intake rate and the urinary output rate, fluid volume is changing and this fluid volume mechanism has not completed its adjustment of arterial pressure. The fluid volume mechanism is in equilibrium only when the urinary output rate exactly equals the fluid intake rate.³ *In the long term, the arterial pressure can only be that which makes the urinary output rate equal to the fluid intake rate.*

The baroreceptor reflex is, of course, essential for counteracting rapid changes in arterial pressure. The fluid volume mechanism, however, determines the long-term level of arterial pressure because it slowly overwhelms all other influences. Through adaptation, the baroreceptor mechanism adjusts itself so that it operates to prevent acute changes in blood pressure from the prevailing long-term level as determined through fluid balance.

³ In the present discussion, assume that fluid intake rate represents that in excess of the obligatory fluid losses that normally occur in the feces and by transpiration from the skin and structures in the respiratory tract. The processes that regulate voluntary fluid intake (thirst) are not well understood but seem to involve many of the same factors that influence urinary output (eg, blood volume and osmolality). Angiotensin II may be an important factor in the regulation of thirst.

Effect of Arterial Pressure on Urinary Output Rate

A key element in the fluid balance mechanism of arterial pressure regulation is the effect that arterial pressure has on the renal urine production rate. The mechanisms responsible for this are briefly described here with emphasis on their cardiovascular implications.

As indicated in Chapter 1, the kidneys play a major role in homeostasis by regulating the electrolyte composition of the plasma and thus the entire internal environment. One of the major plasma electrolytes regulated by the kidneys is the sodium ion. To regulate the electrolyte composition, a large fraction of the plasma fluid that flows into the kidneys is filtered across the *glomerular capillaries* so that it enters the *renal tubules*. The fluid that passes from the blood into the renal tubules is called the *glomerular filtrate*, and the rate at which this process occurs is called the *glomerular filtration rate*. Glomerular filtration is a transcapillary fluid movement whose rate is influenced by hydrostatic and oncotic pressures as indicated in Chapter 6. The primary cause of continual glomerular filtration is that glomerular capillary hydrostatic pressure is normally very high (≈ 60 mmHg). The glomerular filtration rate is decreased by factors that decrease glomerular capillary pressure, for example, decreased arterial blood pressure or vasoconstriction of preglomerular renal arterioles.

Once fluid is filtered into the renal tubules, it either (1) is *reabsorbed* and reenters the cardiovascular system or (2) is passed along renal tubules and eventually *excreted* as urine. Thus, urine production is the net result of glomerular filtration and renal tubular fluid reabsorption:

$$\text{Urinary output rate} = \text{glomerular filtration rate} - \text{renal fluid reabsorption rate}$$

Actually, most of the reabsorption of fluid that has entered renal tubules as glomerular filtrate occurs because sodium is actively pumped out of the tubules by cells in the tubular wall. When sodium leaves the tubules, osmotic forces are produced that cause water to leave with it. Thus, any factor that promotes renal tubular sodium reabsorption (sodium retention) tends to increase the renal fluid reabsorption rate and consequently decrease the urinary output rate. The blood concentration of the hormone *aldosterone*, which is produced by the adrenal glands, is the primary regulator of the rate of sodium reabsorption by renal tubular cells. Adrenal release of aldosterone is, in turn, regulated largely by the circulating level of another hormone, *angiotensin II*, whose plasma concentration is determined by the plasma concentration of *renin*, an enzyme that is produced in the kidneys. Renin actually catalyzes the formation of an inactive decapeptide, *angiotensin I*, from *angiotensinogen*, a circulating precursor protein. Angiotensin I then gets quickly converted to angiotensin II (an octapeptide) by the action of *angiotensin-converting enzyme* that is located on the surface of endothelial cells. The combination of elements involved in this whole sequence of events is referred to as the *renin–angiotensin–aldosterone system*.

The rate of renin release by the kidneys is influenced by several factors. An increase in the activity of renal sympathetic nerves causes a direct release of renin through a β_1 -adrenergic mechanism. Also, renin release is triggered by factors associated with a lowered glomerular filtration rate. The activation of sympathetic vasoconstrictor nerves to renal arterioles thus indirectly causes renin release via lowered glomerular capillary hydrostatic pressure and glomerular filtration rate. The important fact to keep in mind, from a cardiovascular standpoint, is that anything that causes renin release causes a decrease in urinary output rate because increased renin causes increased sodium (and therefore fluid) reabsorption from renal tubules.⁴

Urinary output rate is also influenced by vasopressin (antidiuretic hormone) released from the posterior pituitary. Vasopressin regulates the permeability of certain portions of the kidney tubule in such a way that when the blood levels of the hormone are elevated, water is reabsorbed from the tubule and the kidney produces only small volumes of highly concentrated urine. The production of vasopressin in the hypothalamus and its release from the pituitary are stimulated by many factors including increased extracellular fluid osmolality, decreased input from cardiopulmonary baroreceptors, and decreased input from arterial baroreceptors. In the case of the latter two influences on vasopressin release, the overall result is to decrease urinary output rate whenever arterial pressure and/or central blood volume is below normal.

Some major mechanisms that lead to decreased urinary output rate are summarized in Figure 9–6. Most important, this figure shows that urinary output rate is linked to arterial pressure by many synergistic pathways. Because of this, modest changes in arterial pressure are associated with large changes in urinary output rate.

The observed relation between arterial pressure and urinary output for a healthy person is shown in Figure 9–7. Recall that, in the steady state, the urinary output rate must always equal the fluid intake rate and that changes in fluid volume will automatically adjust arterial pressure until this is so. Thus, a healthy person with a normal fluid intake rate will have, as a long-term average, the arterial pressure associated with point A in Figure 9–7. Because of the steepness of the curve shown in Figure 9–7, even rather marked changes in fluid intake rate have minor influences on the arterial pressure of a healthy individual.

Role of the CNS in Long-Term Arterial Pressure Regulation

Many argue that the CNS plays a more important role in the long-term regulation of arterial pressure than is implied by the foregoing “renal fluid balance” model. The crux of the dispute is whether the kidney or the brain is the ultimate controller of long-term blood pressure. In particular, the CNS proponents argue that there is a

⁴ Although the renin–angiotensin–aldosterone system is clearly the primary mechanism for the regulation of renal tubular sodium reabsorption, many believe that other factors are involved. A polypeptide natriuretic (salt-losing) factor has been identified in granules of cardiac atrial cells. Atrial distention causes the release of this *atrial natriuretic peptide* into the blood. The possibility that the heart itself may serve as an endocrine organ in the regulation of body fluid volume is stimulating much research interest.

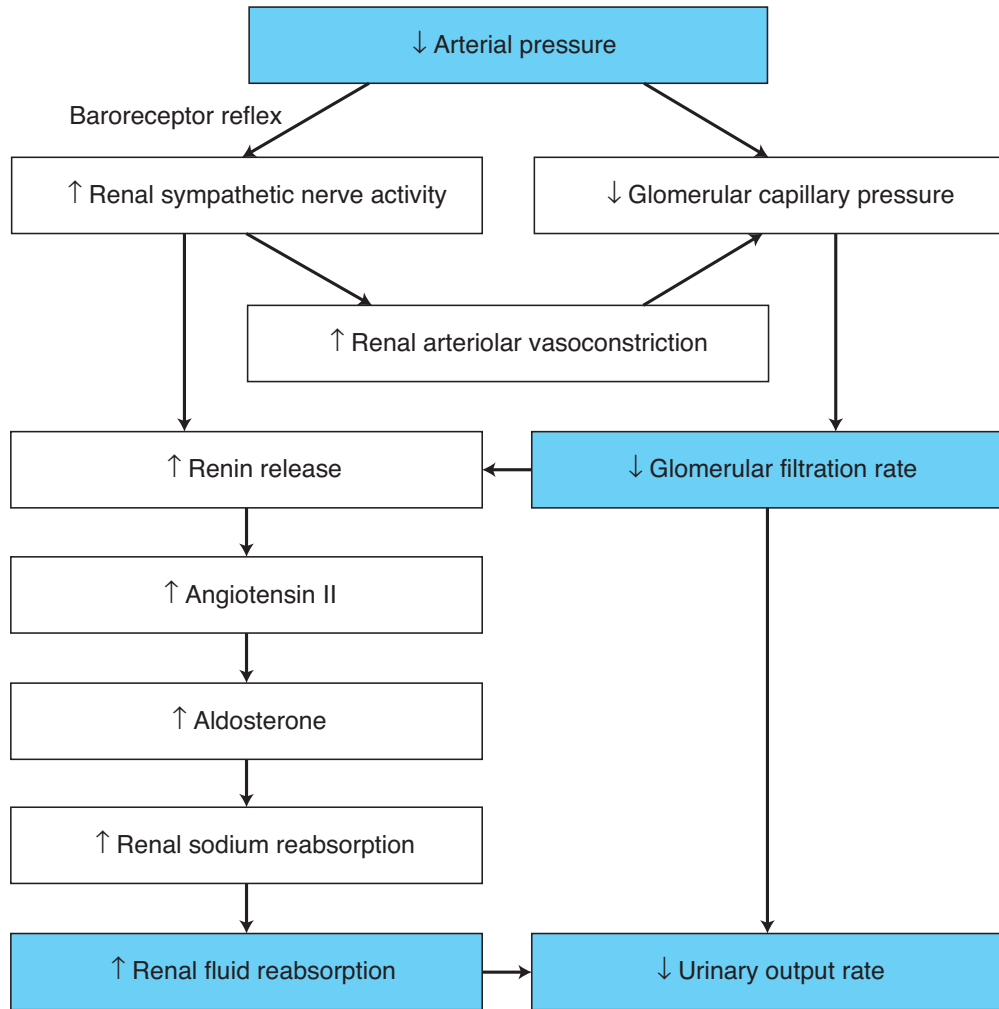


Figure 9-6. Mechanisms by which arterial pressure influences urinary output rate.

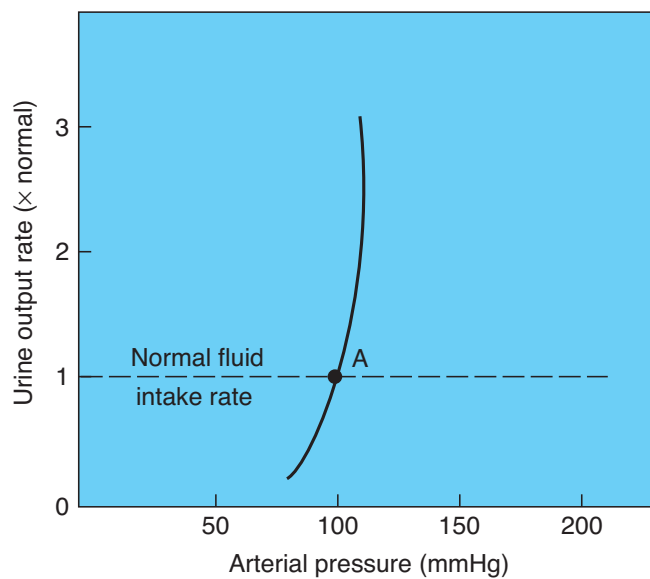


Figure 9-7. The effect of arterial pressure on urinary output rate in a healthy person.

“CNS arterial pressure set point” designed to maintain proper cerebral blood flow and function as opposed to a “renal arterial pressure set point” designed to maintain proper blood volume.

Indeed, even the short-term regulation of arterial pressure is a complex issue that involves many inputs to the medullary cardiovascular control centers in addition to that from the arterial baroreceptors (see Fig. 9–4). It is largely unknown to what extents these “other” influences might be involved in long-term pressure regulation as well. Moreover, the Cushing reflex described earlier clearly indicates the existence of a powerful pressure-regulating mechanism aimed at maintaining adequate brain blood flow.

We remind the student that, whatever the purpose of long-term arterial pressure regulation, changes in mean arterial pressure can be accomplished only by changing cardiac output and/or total peripheral resistance. Blood volume is undeniably one important determinant of cardiac output. Thus, we (the authors of this text) conclude that there are elements of truth in both the renal and CNS theories of long-term blood pressure control. Hopefully, this debate will ultimately result in some melding of the theories that will improve our understanding of what factors cause chronic hypertension.

KEY CONCEPTS



Arterial pressure is closely regulated to ensure adequate blood flow to the tissues.



The arterial baroreceptor reflex is responsible for regulating arterial pressure in the short term on a second-to-second and moment-to-moment basis.



The arterial baroreceptor reflex involves the following: pressure sensing by stretch-sensitive baroreceptor nerve endings in the walls of arteries; neural integrating centers in the brainstem that adjust autonomic nerve activity in response to the pressure information they receive from the arterial baroreceptors; and responses of the heart and vessels to changes in autonomic nerve activity.



Overall, the arterial baroreflex operates such that increases in arterial pressure lead to an essentially immediate decrease in sympathetic nerve activity and a simultaneous increase in parasympathetic nerve activity (and vice versa).



The brainstem integrating centers also receive nonarterial baroreceptor inputs that can raise or lower the set point for short-term arterial pressure regulation.



In the long term, arterial pressure is regulated by changes in blood volume that come about because arterial pressure has a strong influence on urinary output rate by the kidney.



STUDY QUESTIONS

- 9-1. Consider the various components of the arterial baroreceptor reflex and predict whether the following variables will increase or decrease in response to a rise in arterial pressure.
- arterial baroreceptor firing rate
 - parasympathetic activity to the heart
 - sympathetic activity to the heart
 - arteriolar tone
 - venous tone
 - peripheral venous pressure
 - total peripheral resistance
 - cardiac output
- 9-2. Massage of the neck over the carotid sinus area in a person experiencing a bout of paroxysmal atrial tachycardia is often effective in terminating the episode. Why?
- 9-3. Indicate whether mean arterial pressure, after all adjustments, is increased or decreased by the following stimuli:
- low oxygen in arterial blood
 - increased intracranial pressure
 - increased cardiac filling pressure
 - sense of danger
 - visceral pain
- 9-4. Describe the immediate direct and reflex cardiovascular consequences of giving a healthy person a drug that blocks α_1 -adrenergic receptors.
- 9-5. What net short-term alterations in mean arterial pressure and sympathetic activity would the following produce?
- blood loss through hemorrhage
 - cutaneous pain
 - systemic hypoxia
 - local metabolic vasodilation in the skeletal muscle
- 9-6. Your patient has lower than normal mean arterial pressure and higher than normal pulse rate. Which of the following are possible diagnoses?
- low blood volume
 - anxiety
 - a cardiac valve problem
 - elevated intracranial pressure
- 9-7. In the normal operation of the arterial baroreceptor reflex, a cardiovascular disturbance that lowers mean arterial pressure will evoke a decrease in
- baroreceptor firing rate
 - sympathetic nerve activity
 - the heart rate
 - total peripheral resistance
 - myocardial contractility

- 9–8. *In general, normal kidneys tend to retain sodium and fluid in the body whenever*
- arterial pressure is high*
 - parasympathetic nerve activity is high*
 - sympathetic nerve activity is high*
 - plasma aldosterone levels are low*
 - plasma renin levels are low*
- 9–9. *If your patient's mean systemic arterial pressure changes, it is definitely because of changes in*
- the heart rate and/or myocardial contractility*
 - cardiac output and/or total peripheral resistance*
 - blood volume and/or venous tone*
 - sympathetic and/or parasympathetic nerve activity*
 - arterial compliance and/or stroke volume*
-

Cardiovascular Responses to Physiological Stresses

10

OBJECTIVES

The student understands the general mechanisms involved in the cardiovascular responses to any given normal homeostatic disturbance on the intact cardiovascular system and can predict the resulting alterations in all important cardiovascular variables:

- ▶ *Identifies the primary disturbances that the situation places on the cardiovascular system.*
- ▶ *Lists how the primary disturbances change the influence on the medullary cardiovascular centers from (1) arterial baroreceptors and (2) other sources.*
- ▶ *States what immediate reflex compensatory changes will occur in sympathetic and parasympathetic nerve activities as a result of the altered influences on the medullary cardiovascular centers.*
- ▶ *Indicates what immediate reflex compensatory changes will occur in basic cardiovascular variables such as the heart rate, cardiac contractility, stroke volume, arteriolar tone, venous tone, peripheral venous pressure, central venous pressure, total peripheral resistance, resistance in any major organ, and blood flow through any major organ.*
- ▶ *Predicts what the net effect of the primary disturbance and reflex compensatory influences on the cardiovascular variables listed in the preceding objective will be on mean arterial pressure.*
- ▶ *States whether mean arterial pressure and sympathetic nerve activity will settle above or below their normal values.*
- ▶ *Predicts whether and states how cutaneous blood flow will be altered by temperature regulation reflexes.*
- ▶ *Indicates whether and how transcapillary fluid movements will be involved in the overall cardiovascular response to a given primary disturbance.*
- ▶ *Indicates whether, why, how, and with what time course renal adjustments of fluid balance will participate in the response.*
- ▶ *Predicts how each of the basic cardiovascular variables will be influenced by long-term adjustments in blood volume.*

The student understands how respiratory activities influence the cardiovascular system:

- ▶ *Describes how the “respiratory pump” promotes venous return.*
- ▶ *Identifies the primary disturbances on cardiovascular variables associated with normal respiratory activity.*
- ▶ *Describes the reflex compensatory responses to respiratory activity.*

- ▶ *Defines the causes of “normal sinus arrhythmia.”*
- ▶ *Lists the cardiovascular consequences of the Valsalva maneuver and of positive-pressure artificial ventilation.*

The student understands the specific processes associated with the homeostatic adjustments to the effects of gravity:

- ▶ *States how gravity influences arterial, venous, and capillary pressures at any height above or below the heart in a standing individual.*
- ▶ *Describes and explains the changes in central venous pressure and the changes in transcapillary fluid balance and venous volume in the lower extremities caused by standing upright.*
- ▶ *Describes the operation of the “skeletal muscle pump” and explains how it simultaneously promotes venous return and decreases capillary hydrostatic pressure in the muscle vascular beds.*
- ▶ *Identifies the primary disturbances and compensatory responses evoked by acute changes in body position.*
- ▶ *Describes the chronic effects of long-term bed rest on cardiovascular variables.*

The student understands the specific processes associated with the homeostatic adjustments to exercise:

- ▶ *Identifies the primary disturbances and compensatory responses evoked by acute episodes of dynamic exercise.*
- ▶ *Describes the conflict between pressure reflexes and temperature reflexes on cutaneous blood flow.*
- ▶ *Indicates how the “skeletal muscle pump” and the “respiratory pump” contribute to cardiovascular adjustments during exercise.*
- ▶ *Compares the cardiovascular responses to static exercise with those to dynamic exercise.*
- ▶ *Lists the effects of chronic exercise and physical conditioning on cardiovascular variables.*

The student understands the cardiovascular alterations that accompany pregnancy, birth, growth, and aging:

- ▶ *Identifies the major maternal cardiovascular adjustments that occur during pregnancy.*
- ▶ *Follows the pathway of blood flow through the fetal heart and describes the changes that occur at birth.*
- ▶ *Indicates the normal changes that occur in cardiovascular variables during childhood.*
- ▶ *Identifies age-dependent changes that occur in cardiovascular variables such as cardiac index, arterial pressure, and cardiac workload.*
- ▶ *Describes age-dependent changes in the arterial baroreceptor reflex.*
- ▶ *Distinguishes between age- and disease-dependent alterations that occur in cardiovascular function of the aged.*

The student understands that gender may influence the cardiovascular system:

- ▶ *Describes gender-dependent differences in cardiovascular variables.*

This chapter shows how the basic principles of cardiovascular physiology that have been discussed apply to the intact cardiovascular system. A variety of normal, everyday situations that tend to disturb homeostasis are presented. The key to

understanding the cardiovascular adjustments in each situation is to recall that the arterial baroreceptor reflex and renal fluid balance mechanisms always act to blunt changes in arterial pressure. The overall result is that *adequate blood flow to the brain and the heart muscle is maintained in any circumstance.*



The cardiovascular alterations in each of the following examples are produced by the combined effects of (1) the primary, direct influences of the disturbance on the cardiovascular variables and (2) the reflex compensatory adjustments that are triggered by the primary disturbances. The general pattern of reflex adjustment is similar in all situations. Rather than trying to memorize the cardiovascular alterations that accompany each situation, the student should strive to understand each response in terms of the primary disturbances and reflex compensatory reactions involved. To aid in this process, a list of key cardiovascular variables and their determinants may be found in Appendix C. If the student understands all the relationships indicated in Appendix C, they have mastered the core of cardiovascular physiology.

A list of important study questions is supplied for Chapters 10 and 11. These questions are intended to reinforce the student's understanding of complex cardiovascular responses and provide a review of basic cardiovascular principles.

EFFECT OF RESPIRATORY ACTIVITY



The physical processes associated with inhaling air into and exhaling air out of the lungs can have major effects on venous return and cardiac output. During a normal inspiration, intrapleural pressure falls from approximately -2 mmHg to approximately -7 mmHg (compared to atmospheric pressure) as the diaphragm contracts and the chest wall expands. It rises again by an equal amount during expiration. These periodic pressure fluctuations not only promote air movement into and out of the lungs but also are transmitted through the thin walls of the great veins in the thorax to influence venous return to the heart from the periphery. Because of the venous valves, venous return is increased more by inspiration than it is decreased by expiration. The net effect is that venous return from the periphery is generally facilitated by the periodic fluctuations in central venous pressure caused by respiration. This phenomenon is often referred to as the “respiratory pump.”

Because of these changes in venous return, normal breathing is associated with transient cyclical changes in the heart rate, cardiac output, and arterial pressure. The heart rate in healthy individuals usually fluctuates in synchrony with the respiratory rate. This is referred to as “normal sinus arrhythmia.” Lung mechanoreceptors have a major influence on the cyclical heart rate changes seen with respiration. Stretch of these airway receptors during normal inspiration results in an inhibition of the normal tonic vagal activity to the sinoatrial node, causing a transient increase in the heart rate. In addition to these changes in airway pressures and volumes, the cyclical alterations in intrapleural pressure evoke direct major primary disturbances within the cardiovascular system. Some of these disturbances and compensatory responses are illustrated in Figure 10–1. Filling of the right side of the heart is transiently increased during inspiration and, by Starling's law, stroke volume and thus cardiac

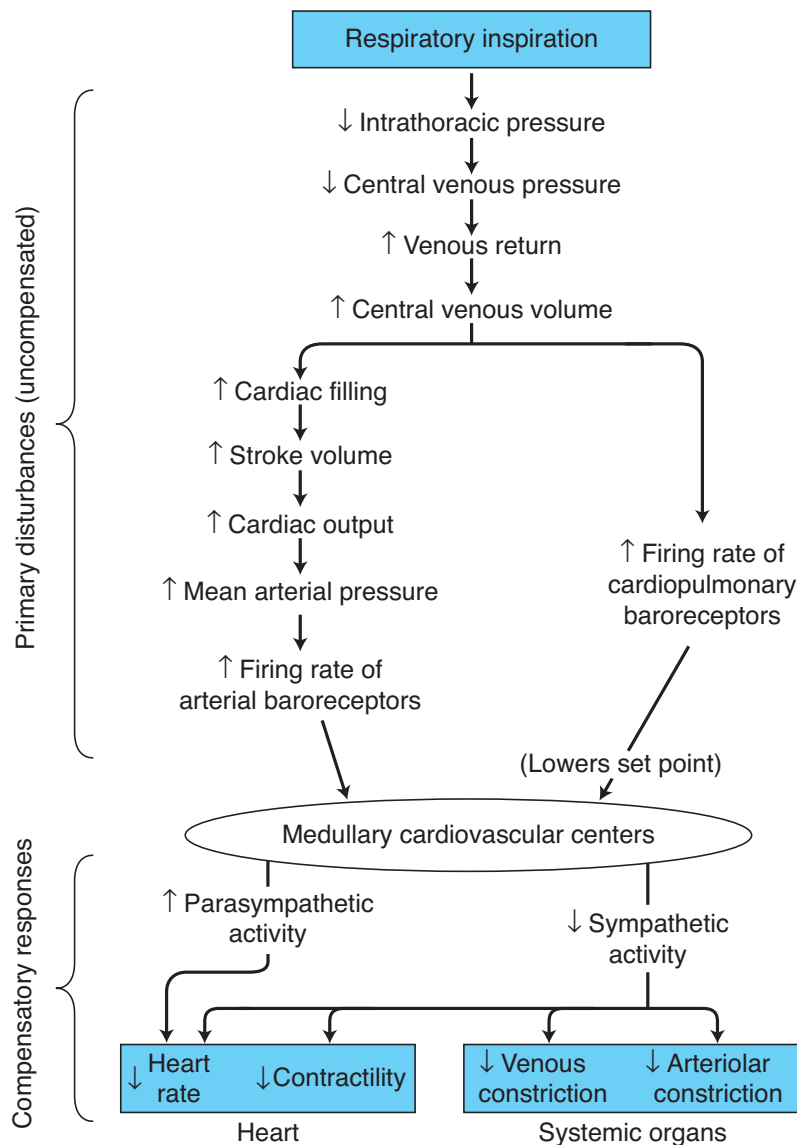


Figure 10–1. Cardiovascular effects of respiratory inspiration.

output are transiently increased. In addition, the reduction in pulmonary vascular resistance that accompanies inspiration reduces the right ventricular afterload and thus contributes to a transient increase in right ventricular stroke volume. Because changes in output of the right side of the heart induce changes in output of the left side of the heart within a few beats, the net effect of inspiration will be a transient increase in stroke volume and cardiac output from the left ventricle. This will lead to a transient increase in arterial pressure and a transient increase in firing of the arterial baroreceptors.

The inspiration-induced decrease in intrathoracic pressure will also stretch the low-pressure cardiopulmonary baroreceptors in the vascular and cardiac walls and will increase their firing rate. These low-pressure baroreceptor inputs will add to the information from the high-pressure arterial baroreceptors and act on the medullary

cardiovascular centers to produce reflex adjustments to *lower* arterial pressure, by increasing cardiac parasympathetic nerve activity and decreasing sympathetic nerve activity. Under normal resting conditions, the cyclic change in the heart rate is the most apparent cardiovascular response to respiration.¹

There are a number of instances when cardiovascular effects of respiratory efforts are extremely important. In *exercise*, for example, a deep and rapid breathing rate contributes significantly to the venous return. *Yawning* is a complex event that includes a significant transient decrease in intrathoracic pressure that is effective in increasing venous return (especially when combined with stretching). In contrast, *coughing* is associated with an *increase* in intrathoracic pressure and, if occurring as a prolonged “fit,” can lead to such severe reductions in cardiac output as to cause fainting.

The cardiovascular consequences of changes in intrathoracic pressure are also important during the *Valsalva maneuver*, which is a forced expiration against a closed glottis. This maneuver is normally performed by individuals during defecation (“straining at stool”), or when attempting to lift a heavy object. There are several phases in this cardiovascular reaction. At the initiation of the Valsalva maneuver, arterial pressure is abruptly elevated for several beats due to the intrathoracic pressure transmitted to the thoracic aorta. The sustained elevation in intrathoracic pressure leads to a fall in venous return and a fall in blood pressure, which evokes a compensatory reflex increase in the heart rate and peripheral vasoconstriction. (During this period, the red face and distended peripheral veins are indicative of high peripheral venous pressures.) At the cessation of the maneuver, there is an abrupt fall in pressure for a couple of beats due to the reduction of intrathoracic pressure. Venous blood then moves rapidly into the central venous pool; stroke volume, cardiac output, and arterial pressure increase rapidly; and a reflex bradycardia occurs. The combination of an episode of high peripheral venous pressure followed by an episode of high arterial pressure and pulse pressure is particularly dangerous for people who are candidates for cerebral vascular accidents (strokes) because this combination may rupture a vessel.

Artificial changes in intrathoracic pressure evoked during forced respiration with a *positive-pressure ventilator* have significant adverse cardiovascular consequences. When the lungs are inflated artificially, intrathoracic pressure goes up (rather than down, as occurs during normal inspiration). Thus, instead of the normal respiratory pump *increasing* venous return during inspiration, the positive-pressure ventilator *decreases* venous return during lung inflation. In addition, the increase in intrathoracic pressure tends to compress the pulmonary microcirculation and this increases right ventricular afterload. Thus, considering the option of putting someone on a respirator, the benefits of improving pulmonary ventilation need to be weighed against the negative effects on the cardiovascular system.

¹ Although the respiratory effects of right heart filling are emphasized in Figure 10–1, respiration also directly affects left heart filling. However, the events are somewhat different because both the left atria and the whole of the pulmonary vascular system are affected by changes in intrathoracic pressure. There are also some time delays between changes in right heart filling and left ventricular stroke volume that are ignored in Figure 10–1. The specific phase relationships between the respiratory cycle and the cardiovascular effects are influenced by respiratory rate and depth as well as the current average heart rate.

EFFECT OF GRAVITY

Responses to Changes in Body Position



Significant cardiovascular readjustments accompany changes in body position because gravity has an effect on pressures within the cardiovascular system. In the preceding chapters, the influence of gravity was ignored and pressure differences between various points in the systemic circulation were related only to flow and vascular resistance ($\Delta P = \dot{Q}R$). As shown in Figure 10–2, this is approximately true only for a recumbent individual. In a standing individual, additional cardiovascular pressure differences exist between the heart and regions that are not at the heart level. This is most important in the lower legs and feet of a standing individual. As indicated in Figure 10–2B, all intravascular pressures in the feet may be increased by 90 mmHg simply from the weight of the blood in the arteries and veins leading to and from the feet. Note by comparing Figure 10–2A and 10–2B that standing upright does not in itself change the flow through the lower extremities, because gravity has the same effect on arterial and venous pressures and thus does not change the *arteriovenous pressure difference* at any one height level. There are however two major direct effects of the increased pressure in the lower extremities, which are shown in Figure 10–2B: (1) the increase in venous transmural pressure distends the compliant peripheral veins and greatly increases peripheral venous volume by as much as 500 mL in a normal adult and (2) the increase in capillary transmural hydrostatic pressure causes a tremendously high transcapillary filtration rate.

For reasons to be described, a reflex activation of sympathetic nerves accompanies the transition from a recumbent to an upright position. However, Figure 10–2C shows how vasoconstriction from sympathetic activation is only marginally effective in ameliorating the adverse effects of gravity on the lower extremities. Arteriolar constriction can cause a greater pressure drop across arterioles, but this has only a limited effect on capillary pressure because venous pressure remains extremely high. Filtration will continue at a very high rate. In fact, the normal cardiovascular reflex mechanisms are alone incapable of dealing with upright posture without the aid of the “skeletal muscle pump.” A person who remained upright without intermittent contraction of the skeletal muscles in the legs would lose consciousness in 10 to 20 minutes because of the decreased brain blood flow that would stem from diminished central blood volume, stroke volume, cardiac output, and arterial pressure.

The effectiveness of the skeletal muscle pump in counteracting venous blood pooling and edema formation in the lower extremities during standing is illustrated in Figures 10–2D and 10–2E. The compression of vessels during skeletal muscle contraction expels both venous blood and lymphatic fluid from the lower extremities (Figure 10–2D). Immediately after a skeletal muscle contraction, both veins and lymphatic vessels are relatively empty because their one-way valves prevent the backflow of previously expelled fluid (Figure 10–2E). Most important, the weight of the venous and lymphatic fluid columns is temporarily supported by the closed one-way valve leaflets. Consequently, venous pressure is drastically lowered immediately

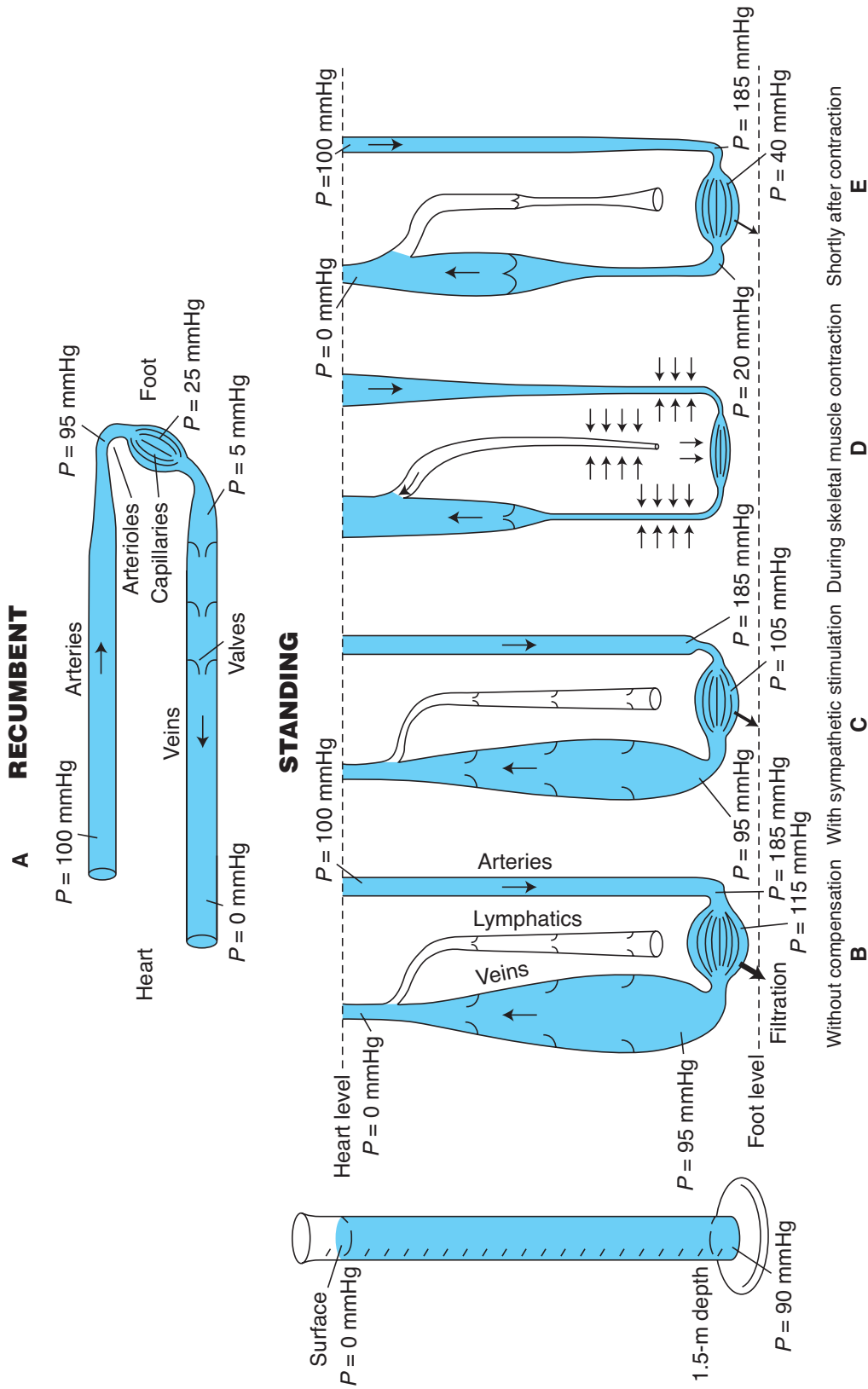


Figure 10-2. The effect of gravity on vascular pressure (A and B) with compensatory influences of sympathetic stimulation (C) and the skeletal muscle pump (D and E)

after skeletal muscle contraction and rises only gradually as veins refill with blood from the capillaries. Thus, capillary pressure and transcapillary fluid filtration rate are dramatically reduced for some period after a skeletal muscle contraction. Periodic skeletal muscle contractions can keep the average value of venous pressure at levels that are only moderately above normal. This, in combination with an increased pressure drop across vasoconstricted arterioles, prevents capillary pressures from rising to intolerable levels in the lower extremities. Some transcapillary fluid filtration is still present, but the increased lymphatic flow resulting from the skeletal muscle pump is normally sufficient to prevent noticeable edema formation in the feet.



The actions of the skeletal muscle pump, however beneficial, do not completely prevent a rise in the average venous pressure and blood pooling in the lower extremities on standing. Thus, assuming an upright position upsets the cardiovascular system and elicits reflex cardiovascular adjustments, as shown in Figure 10–3.

As with all cardiovascular responses, the key to understanding the alterations associated with standing is to distinguish the primary disturbances from the compensatory responses. As shown in the top part of Figure 10–3, the immediate consequence of standing is an increase in both arterial and venous pressures in the lower extremities. The latter causes a major redistribution of blood volume out of the central venous pool. By the chain of events shown, the primary disturbances influence the cardiovascular centers by lessening the normal input from both the arterial and the cardiopulmonary baroreceptors.

The result of a decreased baroreceptor input to the cardiovascular centers will be reflex adjustments (the compensatory response) appropriate to increase blood pressure—that is, decreased cardiac parasympathetic nerve activity and increased activity of the cardiovascular sympathetic nerves as shown in the bottom part of Figure 10–3. The heart rate and cardiac contractility will increase, as will arteriolar and venous constriction in most systemic organs (the brain and the heart excepted).

The heart rate and total peripheral resistance are higher when an individual stands than when the individual is lying down. Note that these particular cardiovascular variables are not directly influenced by standing but *are* changed by the compensatory responses. Stroke volume and cardiac output, conversely, are usually decreased below their recumbent values during quiet standing despite the reflex adjustments that tend to increase them. This is because the reflex adjustments do not quite overcome the primary disturbance on these variables caused by standing. This is in keeping with the general dictum that short-term cardiovascular compensations never completely correct the initial disturbance.

Mean arterial pressure is often found to increase when a person changes from the recumbent to the standing position. At first glance, this is a violation of many rules of cardiovascular system operation. How can a compensation be more than complete? Moreover, how is increased sympathetic activity compatible with higher than normal mean arterial pressure in the first place? In the case of standing, there are many answers to these apparent puzzles. First, the average arterial baroreceptor discharge rate can actually decrease in spite of a small increase in mean arterial pressure *if* there is simultaneously a sufficiently large decrease in pulse pressure. Second, the

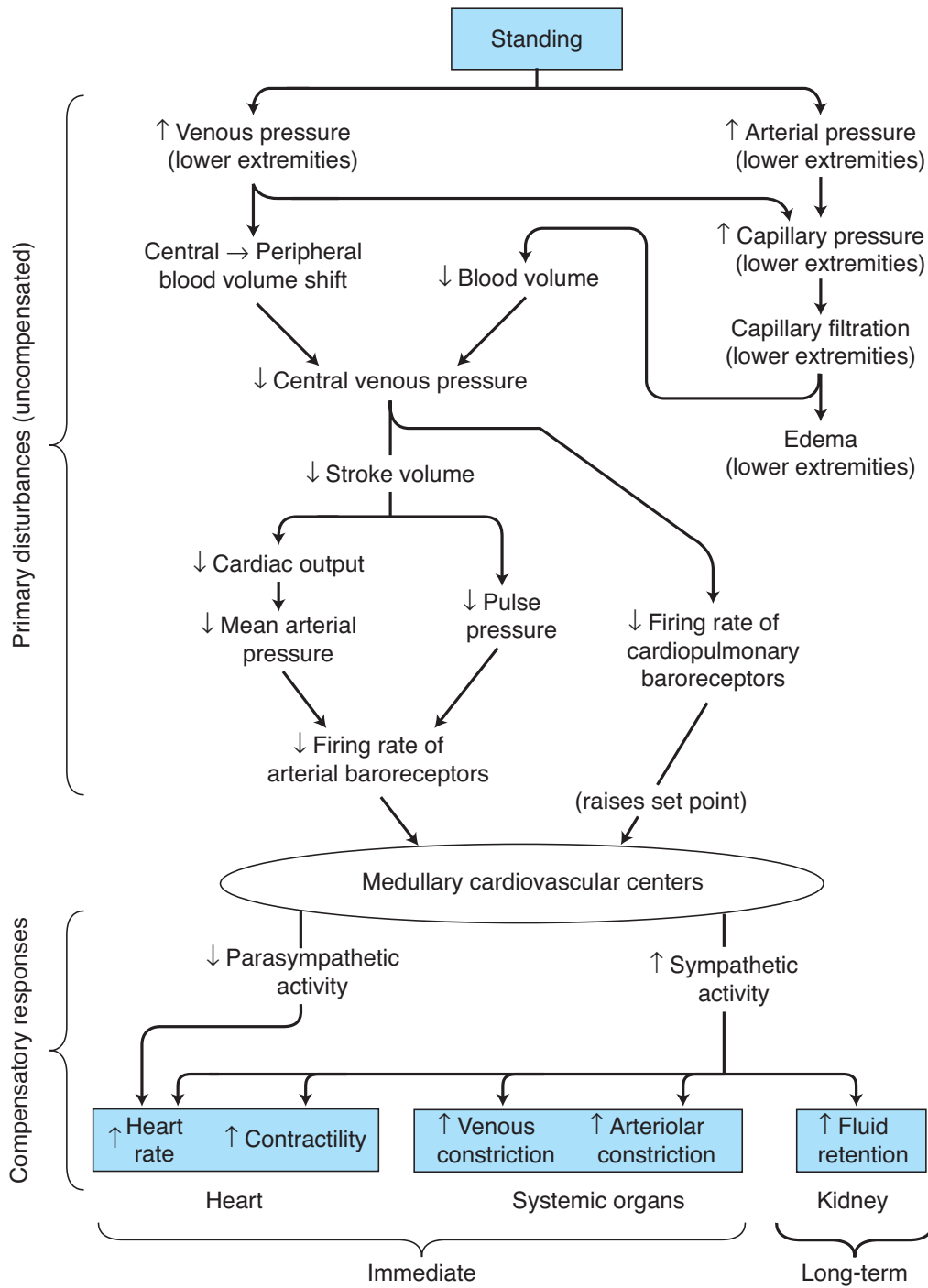


Figure 10-3. Cardiovascular mechanisms involved when changing from a recumbent to a standing position.

influence on the medullary cardiovascular centers from cardiopulmonary receptors is interpreted as a decrease in blood volume and may raise arterial pressure by mechanisms raising the set point. Third, mean arterial pressure determined by sphygmomanometry from the arm of a standing individual *overestimates* the mean arterial pressure actually being sensed by the baroreceptors in the carotid sinus region of the neck because of gravitational effects.

The kidney is especially susceptible to changes in sympathetic nerve activity (as discussed in the previous chapter and shown in Figure 9–6). Consequently, as shown in Figure 10–3, every reflex alteration in sympathetic activity has influences on fluid balance that become important in the long term. Standing, which is associated with an increase in sympathetic tone, ultimately results in an increase in fluid volume. The ultimate benefit of this is that an increase in blood volume generally reduces the magnitude of the reflex alterations required to tolerate upright posture.

Responses to Long-Term Bed Rest (or to Zero Gravity)

The cardiovascular system of an individual who is subjected to long-term bed rest undergoes a variety of adaptive changes that are quite similar to those experienced by people who travel outside the earth's atmosphere at zero gravity. In both cases, the consequences of these adjustments are substantial.



The most significant immediate change that occurs on assuming a recumbent position (or entering a gravity-free environment) is a shift of fluid from the lower extremities to the upper portions of the body. The consequences of this shift include distention of the head and neck veins, facial edema, nasal stuffiness, and decreases in calf girth and leg volume. In addition, the increase in central blood volume stimulates the cardiopulmonary mechanoreceptors, which influence renal function by neural and hormonal pathways to reduce sympathetic drive and promote fluid loss. The individual begins to lose weight and, within a few days, becomes hypovolemic (by normal earth standards).

When the bedridden patient initially tries to stand up (or when the space traveler reenters the earth's gravitational field), the normal responses to gravity as described in Figure 10–3 are not as effective, primarily because of the substantial decrease in circulating blood volume. Upon standing, blood shifts out of the central venous pool into the peripheral veins, stroke volume falls, and the individual often becomes dizzy and may faint because of a dramatic fall in blood pressure. This phenomenon is referred to as *orthostatic* or *postural hypotension*. Because there are other cardiovascular changes that may accompany bed rest (or space travel), complete reversal of this orthostatic intolerance may take several days or even weeks.

Efforts made to diminish the cardiovascular changes for the bedridden patient may include intermittent sitting up or tilting the bed to lower the legs and trigger fluid retention mechanisms. Efforts made in space to accomplish the same end may include exercise programs, lower body negative-pressure devices, and salt and water loading. (To date, these interventions have met with limited success.)

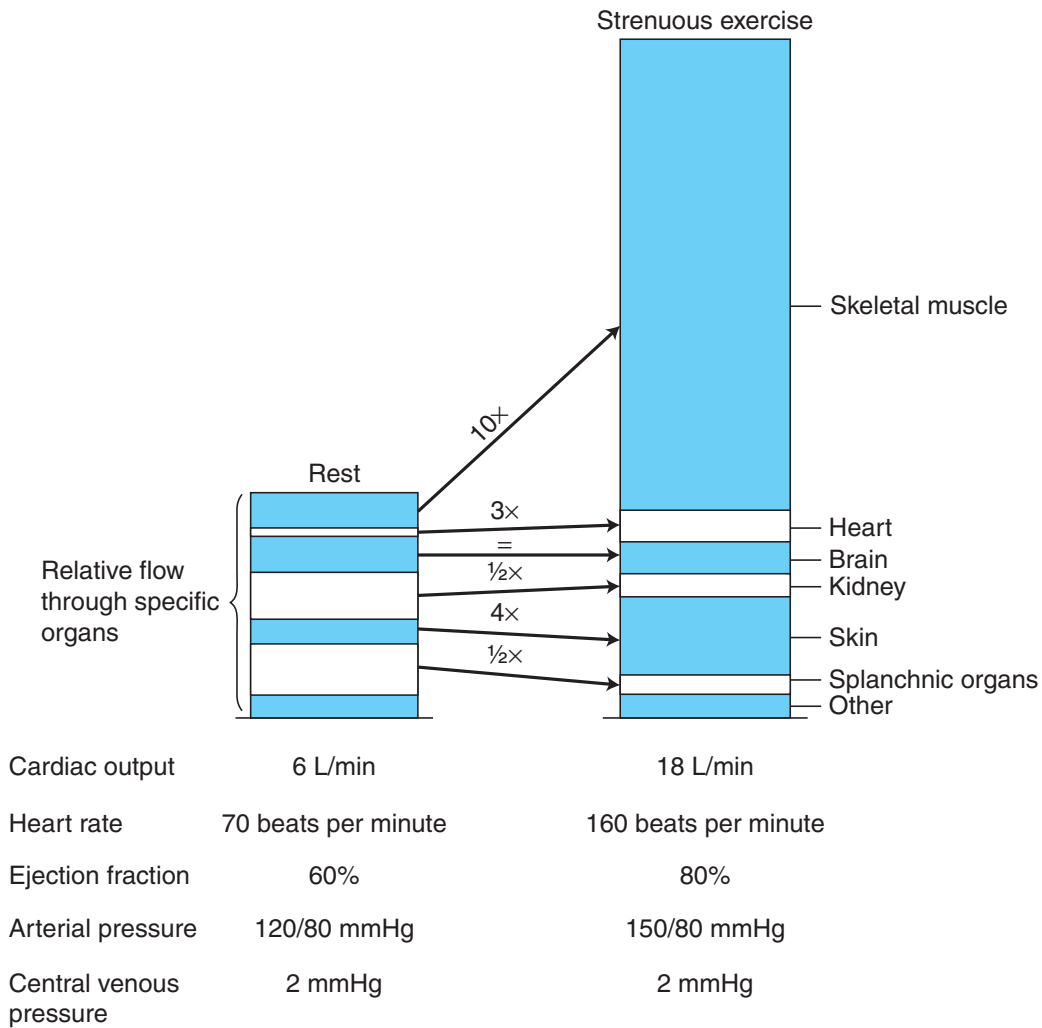


Figure 10–4. Cardiovascular adjustments to strenuous exercise.

EFFECT OF EXERCISE

Responses to Acute Exercise

Physical exercise is one of the most ordinary, yet taxing, situations with which the cardiovascular system must cope. The specific alterations in cardiovascular function that occur during exercise depend on several factors including (1) the type of exercise—that is, whether it is predominantly “dynamic” (rhythmic or isotonic) or “static” (isometric); (2) the intensity and duration of the exercise; (3) the age of the individual; and (4) the level of “fitness” of the individual. The example shown in Figure 10–4 is typical of the cardiovascular alterations that might occur in a normal, untrained, middle-aged adult doing a dynamic-type exercise such as running or dancing. Note especially that the heart rate and cardiac output increase greatly during exercise and that mean arterial pressure and pulse pressure also increase significantly. These alterations ensure that the increased metabolic demands

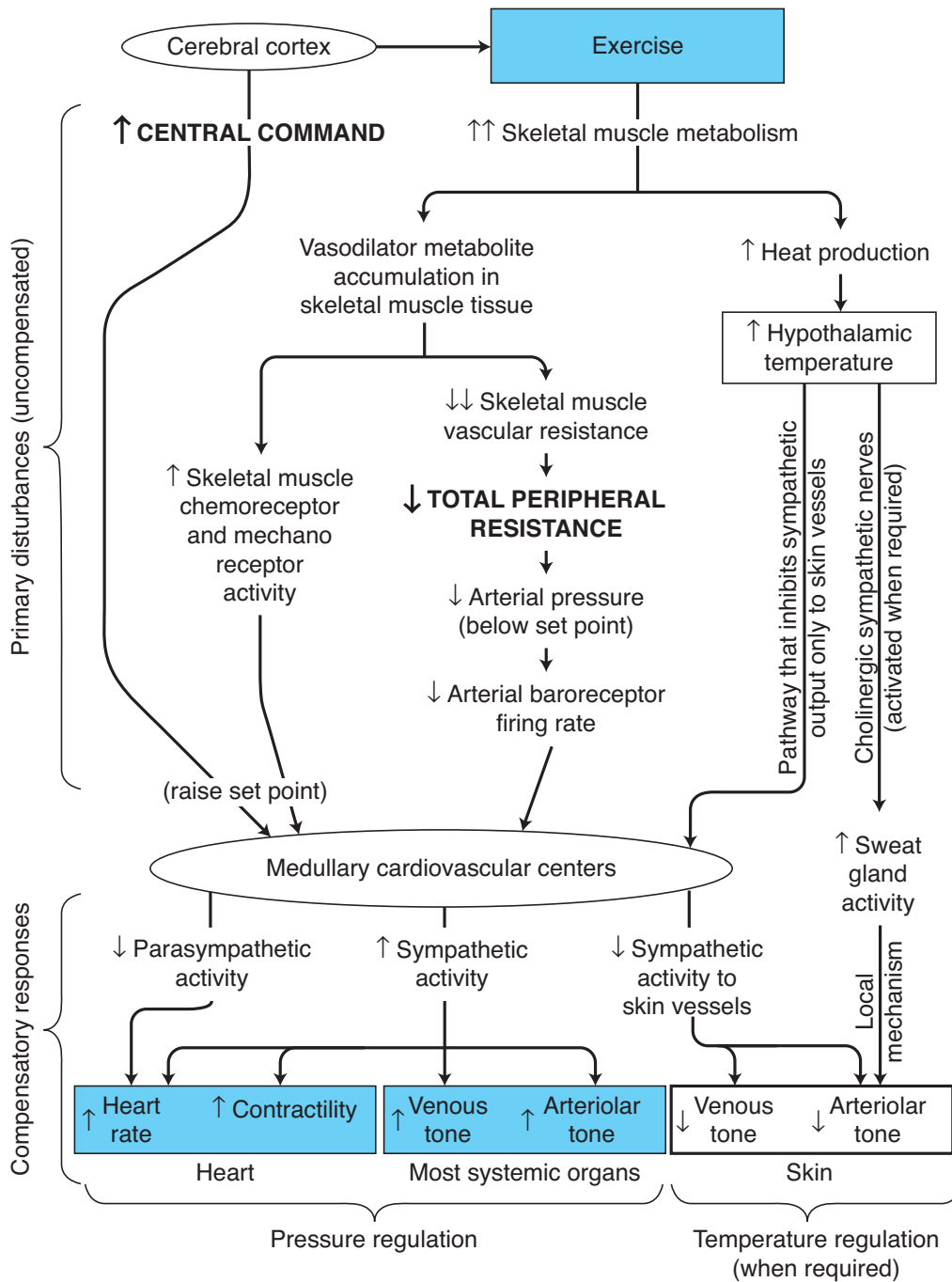


Figure 10–5. Cardiovascular mechanisms involved during exercise.

of the exercising skeletal muscle are met by appropriate increases in skeletal muscle blood flow.



Many of the adjustments to exercise are due to a large increase in sympathetic activity, which results from the mechanisms outlined in Figure 10–5. One of the primary disturbances associated with the stress and/or anticipation

of exercise originates within the cerebral cortex and exerts an influence on the medullary cardiovascular centers through corticohypothalamic pathways. This set-point-raising influence, referred to as the “central command,” causes mean arterial pressure to be regulated to a higher than normal level (see Appendix E, Figure E-1). Also indicated in Figure 10-5 is the possibility that a second set-point-raising influence may reach the cardiovascular centers from chemoreceptors and mechanoreceptors in the active skeletal muscles. Such inputs would also contribute to the elevations in sympathetic activity and mean arterial pressure that accompany exercise.



A major primary disturbance on the cardiovascular system during dynamic exercise, however, is the great decrease in total peripheral resistance caused by metabolic vasodilator accumulation and decreased vascular resistance in the active skeletal muscle. As indicated in Figure 10-5, decreased total peripheral resistance is a pressure-lowering disturbance that elicits a strong increase in sympathetic activity through the arterial baroreceptor reflex.

Although mean arterial pressure is above normal during exercise, the decreased total peripheral resistance causes it to fall below the elevated level to which it would be regulated by the set-point-raising influences on the cardiovascular center alone. The arterial baroreceptor reflex pathway responds to this circumstance with a large increase in sympathetic activity. Thus, the arterial baroreceptor reflex is responsible for a large portion of the increase in sympathetic activity that accompanies exercise despite the seemingly contradictory fact that arterial pressure is higher than normal. In fact, were it not for the arterial baroreceptor reflex, the decrease in total peripheral resistance that occurs during exercise would cause mean arterial pressure to fall well below normal.

As discussed in Chapter 9 and indicated in Figures 10-4 and 10-5, cutaneous blood flow may increase during exercise despite a generalized increase in sympathetic vasoconstrictor tone because thermal reflexes can override pressure reflexes in the special case of skin blood flow control. Temperature reflexes, of course, are usually activated during strenuous exercise to dissipate the excess heat being produced by the active skeletal muscles. Often cutaneous flow decreases at the onset of exercise (as part of the generalized increase in arteriolar tone from increased sympathetic vasoconstrictor activity) and then increases later during exercise as body heat builds up.

In addition to the increases in the skeletal muscle and skin blood flow, coronary blood flow increases substantially during strenuous exercise. This is primarily due to local metabolic vasodilation of coronary arterioles as a result of increased cardiac work and myocardial oxygen consumption.

Two important mechanisms that participate in the cardiovascular response to dynamic exercise are not shown in Figure 10-5. The first is the skeletal muscle pump, which was discussed in connection with upright posture. The skeletal muscle pump is a very important factor in promoting venous return during dynamic exercise preventing the reflex-induced increase in cardiac output from drastically lowering central venous pressure. The second factor is the respiratory pump, which also promotes venous return during exercise. Exaggerated respiratory movements that

occur during exercise increase the effectiveness of the respiratory pump and thus enhance venous return and cardiac filling.

As indicated in Figure 10–4, the average central venous pressure does not change much, if at all, during strenuous dynamic exercise. This is because the cardiac output and the venous return curves are both shifted upward during exercise. Therefore, the cardiac output and venous return will be elevated without a significant change in central venous pressure. Thus, the increase in stroke volume that accompanies exercise largely reflects the increased myocardial contractility and increased ejection fraction with decreased end-systolic ventricular volume.



In summary, the profound cardiovascular adjustments to dynamic exercise shown in Figure 10–5 all occur automatically as a consequence of the operation of the normal cardiovascular control mechanisms. The tremendous increase in skeletal muscle blood flow is accomplished largely by increased cardiac output but also in part by diverting flow away from the kidneys and the splanchnic organs.

Static exercise (ie, isometric) presents a much different disturbance on the cardiovascular system than does dynamic exercise. As discussed in the previous section, dynamic exercise produces large reductions in total peripheral resistance because of local metabolic vasodilation in exercising muscles. Static efforts, even of moderate intensity, cause a compression of the vessels in the contracting muscles and a reduction in the blood flow through them. Thus, total peripheral resistance does not usually fall during strenuous static exercise and may even increase significantly. The primary disturbances on the cardiovascular system during static exercise seem to be set-point-raising inputs to the medullary cardiovascular centers from the cerebral cortex (central command) and from chemoreceptors and mechanoreceptors in the contracting muscle. These inputs result in another example of what is termed the “exercise pressor response.”

Cardiovascular effects of static exercise include increases in the heart rate, cardiac output, and arterial pressure—all of which are the result of increases in sympathetic drive. Static exercise, however, produces less of an increase in the heart rate and cardiac output and more of an increase in diastolic, systolic, and mean arterial pressure than does dynamic exercise. Because of the higher afterload on the heart during static exercise, cardiac work is significantly higher than during dynamic exercise.

The time course of recovery of the various cardiovascular variables after a bout of exercise depends on many factors, including the type, duration, and intensity of the exercise as well as the overall fitness of the individual. Muscle blood flow normally returns to a resting value within a few minutes after dynamic exercise. However, if an abnormal arterial obstruction prevents a normal *active hyperemia* from occurring during dynamic exercise, the recovery will take much longer than normal. After isometric exercise, muscle blood flow often rises to near maximum levels before returning to normal with a time course that varies with the duration and intensity of the effort. Part of the increase in muscle blood flow that follows isometric exercise might be classified as *reactive hyperemia* in response to the blood flow restriction caused by compressional forces within the muscle during the exercise.

Responses to Chronic Exercise

Physical training or “conditioning” produces substantial beneficial effects on the cardiovascular system. The specific alterations that occur depend on the type of exercise, the intensity and duration of the training period, the age of the individual, and his or her original level of fitness.



In general, however, repeated physical exercise over a period of several weeks is associated with an increase in the individual’s work capacity. Cardiovascular alterations associated with conditioning may include increases in circulating blood volume, decreases in the heart rate, increases in cardiac stroke volume, and decreases in arterial blood pressure at rest.² During exercise, a trained individual will be able to achieve a given workload and cardiac output with a lower heart rate and higher stroke volume than will be possible by an untrained individual. These changes produce a general decrease in myocardial oxygen demand and an increase in the *cardiac reserve* (potential for increasing cardiac output) that can be called on during times of stress. Ventricular chamber enlargement often accompanies dynamic exercise conditioning regimens (endurance training), whereas increases in myocardial mass and ventricular wall thickness are more pronounced with static exercise conditioning regimens (strength training). These structural alterations improve the pumping capabilities of the myocardium.³ Deconditioning occurs with the cessation of the exercise program and the changes rapidly reverse.

It is clear that exercise and physical conditioning can significantly reduce the incidence and mortality of cardiovascular disease. Although studies have not established specific mechanisms for these beneficial effects, there is a positive correlation between physical inactivity and the incidence rate and intensity of coronary heart disease. It is increasingly evident that recovery from a myocardial infarction or cardiac surgery is enhanced by an appropriate increase in physical activity. The benefits of cardiac rehabilitation programs include improvement in various indices of cardiac function as well as improvements in physical work capacity, percent body fat, serum lipids, psychological sense of well-being, and quality of life.

NORMAL CARDIOVASCULAR ADAPTATIONS

Up to this point, the cardiovascular system of a healthy adult has been described. However, there are some important cardiovascular alterations that accompany pregnancy, birth, growth, and aging. The material in the following section is a brief overview of these changes.

² Much of the benefit of exercise “conditioning” can be attributed to the increase in circulating blood volume. This process represents the opposite end of a functional spectrum from the “deconditioning” effects of long-term bed rest that decreases circulating blood volume.

³ However, as described in the next chapter, ventricular chamber enlargement and myocardial hypertrophy are not always hallmarks of improved cardiac performance but may be adaptive responses to various pathological states that, if extreme, may not be helpful.

Cardiovascular Changes during Pregnancy



Pregnancy causes alterations in vascular structure and blood flow to many maternal organs in order to support growth of the developing fetus. These organs include not only the uterus and developing placenta but also the kidneys and the gastrointestinal organs. However, one of the most striking cardiovascular changes of pregnancy is the nearly 50% increase in circulating blood volume. The placenta, being a low-resistance organ added in parallel with the other systemic organs, reduces the overall systemic total peripheral resistance by approximately 40%. Without the substantial increase in circulating blood volume to support cardiac filling, the necessary elevation in cardiac output to balance the decrease in total peripheral resistance would not be possible and pregnancy would result in a substantial decrease in mean arterial pressure. At birth, the loss of the placenta contributes to the return of maternal total peripheral resistance back toward normal levels.

Fetal Circulation and Changes at Birth



During fetal development, the exchange of nutrients, gases, and waste products between fetal and maternal blood occurs in the placenta. This exchange occurs by diffusion between separate fetal and maternal capillaries without any direct connection between the fetal and maternal circulations. From a hemodynamic standpoint, the placenta represents a temporary additional large systemic organ for both the fetus and the mother. The fetal component of the placenta has a low vascular resistance and receives a substantial portion of the fetal cardiac output.

Blood circulation in the developing fetus completely bypasses the collapsed fetal lungs. No blood flows into the pulmonary artery because the vascular resistance in the collapsed fetal lungs is essentially infinite. By the special structural arrangements shown in Figure 10–6, the right and left sides of the fetal hearts actually operate in parallel to pump blood through the systemic organs and the placenta. As shown in Figure 10–6A, fetal blood returning from the systemic organs and placenta fills both the left and right sides of the hearts together because of an opening in the intra-atrial septum called the *foramen ovale*. As indicated in Figure 10–6B, blood that is pumped by the right side of the fetal heart does not enter the occluded pulmonary circulation but rather is diverted into the aorta through a vascular connection between the pulmonary artery and the aorta called the *ductus arteriosus*.

An abrupt decrease in pulmonary vascular resistance occurs at birth with the onset of lung ventilation. This permits blood to begin flowing into the lungs from the pulmonary artery and tends to lower pulmonary arterial pressure. Meanwhile, total systemic vascular resistance increases greatly because of the interruption of flow through the placenta. This causes a rise in aortic pressure, which retards or even reverses the flow through the ductus arteriosus. Through mechanisms that are incompletely understood but clearly linked to a rise in blood oxygen tension, the ductus arteriosus gradually constricts and completely closes over time, normally ranging from hours to a few days. The circulatory changes that occur at birth tend to simultaneously increase the pressure afterload on the left side of the heart and

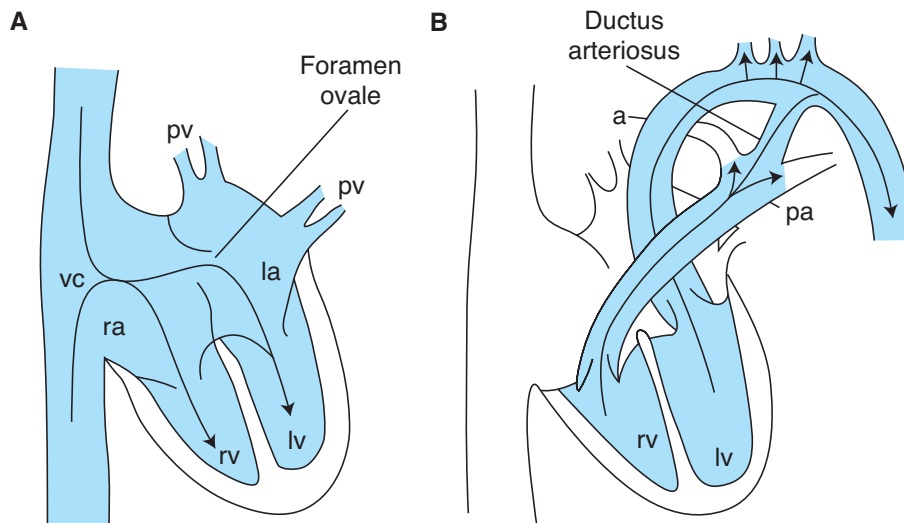


Figure 10–6. Fetal circulation during (A) cardiac filling and (B) cardiac ejection. pv, pulmonary veins; la, left atrium; lv, left ventricle; rv, right ventricle; ra, right atrium; vc, venae cavae; a, aorta; pa, pulmonary artery.

decrease that on the right. This indirectly causes left atrial pressure to increase above that in the right atrium so that the pressure gradient for flow through the foramen ovale is reversed. Reverse flow through the foramen ovale is, however, prevented by a flap-like valve that covers the opening in the left atrium. Normally, the foramen ovale is eventually closed permanently by the growth of fibrous tissue.

Pediatric Cardiovascular Characteristics



Cardiovascular variables change significantly between birth and adulthood. The healthy neonate has, by adult standards, a high resting heart rate (average of 140 beats per minute) and a low arterial blood pressure (average of 60/35 mmHg). These average values rapidly change over the first year (to 120 beats per minute and 100/65 mmHg, respectively). By the time the child enters adolescence, these values are near adult levels.

Pulmonary vascular resistance decreases precipitously at birth as described earlier and then continues to decline during the first year, at which time pulmonary pressures resemble adult levels. These resistance changes appear to be due to a progressive remodeling of the microvascular arterioles from thick-walled, small-diameter vessels to thin-walled, large-diameter microvessels.

It is noteworthy that distinct differences between right and left ventricular mass and wall thickness develop only after birth. Presumably they arise because of a hypertrophic response of the left ventricle to the increased afterload it must assume at birth. Accordingly, the electrocardiogram of children shows an early right ventricular dominance (electrical axis orientation) that converts to the normal left ventricular dominance during childhood.

Heart murmurs are also quite common in childhood and have been reported to be present in as many as 50% of healthy children. Most of these murmurs fall in the category of “innocent” murmurs, resulting from normal cardiac tissue vibrations, high flow through valves, and thin chest walls that make noises from the vasculature easy to hear. Less than 1% of them result from various congenital heart defects.

Growth and development of the vascular system parallels growth and development of the body with most of the local and reflex regulatory mechanisms operational shortly after birth.

Cardiovascular Changes with Normal Aging

In general, as persons get older, they get slower, stiffer, and drier. Connective tissue becomes less elastic, capillary density decreases in many tissues, mitotic activity of dividing cells becomes slower, and fixed postmitotic cells (such as nerve and muscle fibers) are lost. Although these changes do not, in general, alter the basic physiological processes, they do have an influence on the rate at which various homeostatic mechanisms operate.



Age-dependent changes that occur in the heart include (1) a decrease in the resting and maximum cardiac index, (2) a decrease in the maximum heart rate, (3) an increase in the contraction and relaxation time of the heart muscle, (4) an increase in the myocardial stiffness during diastole, (5) a decrease in the number of functioning myocytes, and (6) an accumulation of pigment in the myocardial cells.

Changes that occur in the vascular bed with age include a decrease in capillary density in some tissues, a decrease in arterial and venous compliance, and an increase in total peripheral vascular resistance. These changes combine to produce the age-dependent increases in arterial pulse pressure and mean arterial pressure that are discussed in Chapter 6 (see Figure 6–10). The increases in arterial pressure impose a greater afterload on the heart, which may be partially responsible for the age-dependent decreases in cardiac index.

Arterial baroreceptor-induced responses to changes in blood pressure are blunted with age. This is due in part to a decrease in afferent activity from the arterial baroreceptors because of the age-dependent increase in arterial rigidity. In addition, the total amount of norepinephrine contained in the sympathetic nerve endings of the myocardium decreases with age, and the myocardial responsiveness to catecholamines declines. Thus, the efferent component of the reflex is also compromised. These changes may partially account for the apparent age-dependent sluggishness in the responses to postural changes and recovery from exercise.

It is important (although often difficult) to separate age-dependent alterations from disease-induced changes in physiological function. Cardiovascular diseases are the major cause of death in an aging population. Atherosclerosis and hypertension are the primary culprits in many populations. These “diseases” lack the universality necessary to be categorized as aging processes but generally occur with increasing incidence in the older population. Pharmacological interventions and reduction of risk factors (smoking, obesity, inactivity, and high-fat or high-sodium diets) by

modification of lifestyle can alter the incidence, intensity, and progression of these diseases. It is also possible that some of the previously mentioned interventions may prevent early expression of some of the normal aging processes and prolong the lifespan of a given individual. No practical intervention, however, is currently available that will increase the maximum potential lifespan of humans.

EFFECT OF GENDER



There are a few well-documented gender-dependent differences in the cardiovascular system. Compared with age-matched men, premenopausal women have a lower left ventricular mass to body mass ratio, which may reflect a lower cardiac afterload in women. This may result from their lower arterial blood pressure, greater aortic compliance, and improved ability to induce vasodilatory mechanisms (such as endothelial-dependent flow-mediated vasodilation). These differences are thought to be related to protective effects of estrogen and may account for the lowered risk of premenopausal women for developing cardiovascular disease. After menopause, these gender differences disappear. In fact, older women with ischemic heart disease often have a worse prognosis than men.

There are also gender-dependent differences in cardiac electrical properties. Women often have lower intrinsic heart rates and longer QT intervals than do men. They are at greater risk of developing long-QT syndrome and torsades de pointes. They are also twice as likely as men to have atrioventricular nodal reentry tachycardias.

However, it should be noted that most basic cardiovascular physiological processes are not greatly influenced by gender and that individual differences in physiological responses within genders are usually as large as, or larger than, differences between genders.

KEY CONCEPTS



Cardiovascular responses to physiological stresses should be evaluated in terms of the initial effects of the primary disturbance and the subsequent effects of the reflex compensatory responses.



Changes in intrathoracic pressure due to respiratory activity have significant effects on the cardiovascular system, partly by influencing venous return and cardiac filling.



Gravity, and hence body position, has a significant effect on the cardiovascular system, and various reflex compensatory mechanisms are required to overcome peripheral venous pooling and reduced cardiac filling that accompanies the upright position.



Long-term bed rest causes decreases in circulating blood volume that contributes to orthostatic hypotension.



The primary cardiovascular disturbances of exercise (central command and muscle vasodilation) evoke immediate reflex compensatory activity, which permits major changes in muscle blood flow and cardiac output.



Chronic exercise (training) evokes compensatory adjustments in blood volume, cardiovascular characteristics and muscle metabolic processes, permitting greater exercise efficiency.



Pregnancy-induced cardiovascular changes, including a major decrease in total peripheral resistance due to the developing placenta, evoke a significant increase in circulating maternal blood volume.



Circulatory pathways in the fetus are significantly different from those of the newborn and change abruptly at birth with the first breath.



Pediatric cardiovascular characteristics (high resting heart rates and low arterial blood pressures) gradually change to reach the normal adult levels during early adolescence.



Aging results in decreases in the maximal capabilities of cardiovascular responses that are distinct from any disease processes.




Gender influences several cardiovascular characteristics and disease susceptibility particularly before the age of menopause in women.



STUDY QUESTIONS

- 10-1. How are the thin-walled capillaries in the feet able to withstand pressures greater than 100 mmHg in a standing individual without rupturing?
- 10-2. Soldiers faint when standing at attention on a very hot day more often than on a cooler day. Why?
- 10-3. For several days after an extended period of bed rest, patients often become dizzy when they stand upright quickly because of an exaggerated transient fall in arterial pressure (orthostatic hypotension). Why might this be so?
- 10-4. Vertical immersion to the neck in tepid water produces a diuresis in many individuals. What mechanisms might account for this phenomenon?
- 10-5. How is the decrease in skeletal muscle vascular resistance evident from the data presented in Figure 10-4?
- 10-6. Is a decrease in total peripheral resistance implied in Figure 10-4?
- 10-7. What in Figure 10-4 implies increased sympathetic activity?
- 10-8. From the information given in Figure 10-4,
 - a. Calculate the resting and exercising stroke volumes (SVs).
 - b. Calculate the resting and exercising end-diastolic volumes (EDVs).
 - c. Calculate the resting and exercising end-systolic volumes (ESVs).
 - d. Construct a sketch that indicates, as accurately as possible, how this exercise affects the left ventricular volume–pressure cycle.

- 10-9. The "iron lung," used to help polio victims breathe in the mid-20th century, applied an external intermittent negative pressure to the patient's thoracic cavity. How is this better than positive-pressure ventilation of the patient's lungs?
- 10-10. Blood pressure can rise to extremely high levels during strenuous isometric exercise maneuvers like weight lifting. Why?
- 10-11. All the following tend to occur when a person lies down. Which one is the primary disturbance that causes all the others to happen?
- The heart rate will decrease.
 - Stroke volume will increase.
 - Sympathetic activity will decrease.
 - Parasympathetic activity will increase.
 - Central venous pressure will increase.
- 10-12. Which of the following represents a normal compensatory response to chronic endurance exercise training?
- an increase in circulating blood volume
 - an increase in the resting heart rate
 - an increase in mean arterial pressure
 - a decrease in resting stroke volume
 - a decrease in resting blood flow to the kidneys
- 10-13. Total systemic peripheral vascular resistance of a newborn baby undergoes an abrupt and sustained increase at birth. This is because
- Circulating blood volume increases.
 - The high-resistance lungs inflate.
 - The low-resistance placental circulation is removed.
 - Sympathetic neural stimulation is elevated.
 - Cardiac output rises.
- 

Cardiovascular Function in Pathological Situations

11

OBJECTIVES

The student understands the primary disturbances, compensatory responses, decompensatory processes, and possible therapeutic interventions that pertain to various abnormal cardiovascular situations.

- ▶ *Defines circulatory shock.*
- ▶ *Identifies the primary disturbances that can account for cardiogenic, hypovolemic, anaphylactic, septic, and neurogenic shock states.*
- ▶ *Lists the compensatory processes that may arise during shock.*
- ▶ *Identifies the decompensatory processes that may arise during shock and describes how these lead to irreversible shock states.*
- ▶ *Indicates how coronary artery disease may lead to abnormal cardiac function.*
- ▶ *Defines the term angina pectoris and describes the mechanisms that promote its development.*
- ▶ *Indicates the mechanisms by which various therapeutic interventions may alleviate angina and myocardial ischemia in association with coronary artery disease.*
- ▶ *Defines the term heart failure and differentiates between systolic and diastolic dysfunction.*
- ▶ *Identifies the short-term and long-term compensatory processes that accompany heart failure.*
- ▶ *Describes the advantages and disadvantages of the fluid accumulation that accompanies heart failure.*
- ▶ *Defines pulmonary and systemic arterial hypertension.*
- ▶ *Identifies the various factors that may contribute to the development of systemic hypertension.*
- ▶ *Describes the role of the kidney in establishing and/or maintaining systemic hypertension.*

In this last chapter, some of the pathological situations that can interfere with the homeostatic functions of the cardiovascular system are introduced. It is not intended as an in-depth coverage of cardiovascular diseases but rather as an introductory presentation of how the physiological processes described previously are evoked and/or altered during various abnormal cardiovascular states. In each case there is generally

a primary disturbance that evokes appropriate compensatory reflex responses. Often, however, pathological situations also lead to inappropriate “decompensatory processes,” which tend to accelerate the deterioration of cardiovascular function. Therapeutic interventions may be required and are often designed to limit or reverse these decompensatory processes. Students are again encouraged to review the summary of cardiovascular variables and their determinants in Appendix C because a thorough knowledge of this material will greatly help to understand the physiological consequences of these abnormalities.

CIRCULATORY SHOCK



A state of circulatory shock exists whenever there is a generalized, severe reduction in blood supply to the body tissues and the metabolic needs of the tissues are not met. Even with all cardiovascular compensatory mechanisms activated, arterial pressure is usually (though not always) low in shock.

Primary Disturbances



In general, the shock state is precipitated either by severely depressed myocardial functional ability, by grossly inadequate cardiac filling due to low mean circulatory filling pressure or by profound systemic vasodilation. The first situation is called *cardiogenic shock* and occurs whenever cardiac pumping ability is compromised (eg, severe arrhythmias, abrupt valve malfunction, coronary occlusions, and myocardial infarction). The latter situations can be caused by any of the conditions itemized as follows that decrease central venous volume, ventricular filling or total peripheral resistance:

1. *Hypovolemic shock* accompanies significant hemorrhage (usually greater than 20% of blood volume), severe burns, chronic diarrhea, or prolonged vomiting. These situations can induce shock by depleting body fluids and thus circulating blood volume.

The occurrence of a *pulmonary embolus* (a clot mobilized from systemic veins lodging in a pulmonary vessel) may evoke a shock state that resembles hypovolemic shock in that left ventricular filling may be compromised. Although small emboli have minor functional consequences, large emboli not only reduce cardiac output but also interfere with adequate gas exchange in the lungs.

2. *Anaphylactic shock* occurs as a result of a severe allergic reaction to an antigen to which the patient has developed a sensitivity (eg, insect bites, antibiotics, and certain foods). This immunological event, also called an “immediate hypersensitivity reaction,” is mediated by several substances (such as histamine, prostaglandins, leukotrienes, and bradykinin) that, by multiple mechanisms not well understood, results in substantial peripheral vasodilation with reduction in total peripheral resistance and increases microvascular permeability.
3. *Septic shock* is caused by vasodilator effects of substances released into the circulating blood by infective agents. One of the most common is *endotoxin*, a lipopolysaccharide released from bacteria. This substance induces the formation

of a nitric oxide synthase (called *inducible* nitric oxide synthase to distinguish it from the normally present *constitutive* nitric oxide synthase) in endothelial cells, vascular smooth muscle, and macrophages that then produce large amounts of the potent vasodilator nitric oxide.

4. *Neurogenic shock* is produced by loss of vascular tone due to inhibition of the normal tonic activity of the sympathetic vasoconstrictor nerves and often occurs with deep general anesthesia or in reflex response to deep pain associated with traumatic injuries. The transient vasovagal syncope that may be evoked by strong emotions is a mild form of neurogenic shock.

As shown in the top half of Figure 11–1, the common primary disturbances in all forms of shock are decreased cardiac output and decreased mean arterial pressure. Generally, the reduction in arterial pressure is substantial, and so, therefore, is the influence on the cardiovascular centers from reduced arterial baroreceptor discharge rate. In addition, in the case of hypovolemic, anaphylactic, and septic shock, diminished activity of the cardiopulmonary baroreceptors due to a decrease in central venous pressure and/or volume acts on the medullary cardiovascular centers to stimulate sympathetic output.¹ If arterial pressure falls below approximately 60 mmHg, brain blood flow begins to fall and this elicits the cerebral ischemic response. As indicated in Chapter 9, the cerebral ischemic response causes the most intense of all activation of the sympathetic nerves.

Compensatory Mechanisms



In general, the various forms of shock elicit the compensatory responses in the autonomic nervous system that we would expect from a fall in blood pressure.² These are indicated in the bottom half of Figure 11–1. These compensatory responses to shock, however, may be much more intense than those that accompany more ordinary cardiovascular disturbances. Many of the commonly recognized symptoms of shock (eg, pallor, cold clammy skin, rapid heart rate, muscle weakness, and venous constriction) are a result of greatly increased sympathetic nerve activity. When the immediate compensatory processes are inadequate, the individual may also show signs of abnormally low arterial pressure, such as dizziness, confusion, or loss of consciousness.

There are some additional compensatory processes that are initiated during the shock state:

1. Breathing is rapid and may be shallow, which promotes venous return to the heart by action of the respiratory pump.

¹ In the case of cardiogenic shock, central venous pressure will increase; and in the case of neurogenic shock, central venous pressure cannot be predicted because both cardiac output and venous return are likely to be depressed. Thus, in these instances, it is not clear how the cardiopulmonary baroreceptors affect autonomic output.

² Two primary exceptions to this statement include (1) neurogenic shock, where reflex responses may be absent or lead to further depression of blood pressure, and (2) certain instances of cardiogenic shock associated with inferoposterior myocardial infarctions, which elicit a reflex bradycardia and decrease sympathetic drive (the Bezold–Jarisch reflex).

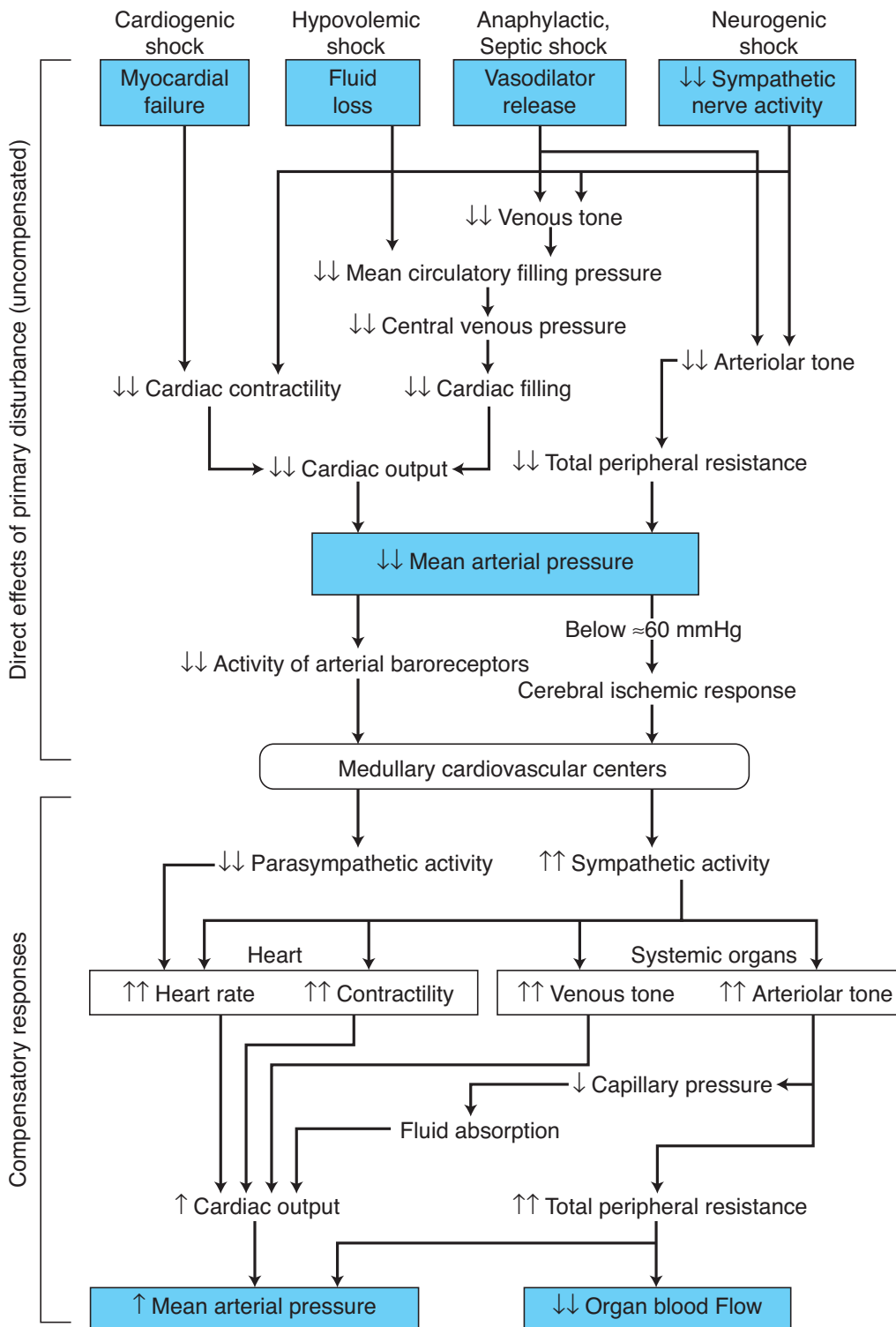


Figure 11-1. Cardiovascular alterations in shock.

2. The release of renin from the kidney as a result of sympathetic stimulation promotes the formation of the hormone, angiotensin II, which is a potent vasoconstrictor and participates in the increase in total peripheral resistance even in mild shock states.
3. The circulating level of vasopressin (also known as, antidiuretic hormone) from the posterior pituitary gland increases and, being a potent vasoconstrictor, contributes to the increase in total peripheral resistance. This hormone is released in response to decreased firing of the cardiopulmonary and arterial baroreceptors.
4. Circulating levels of epinephrine from the adrenal medulla increase in response to sympathetic stimulation and contribute to the vasoconstriction.
5. The increase in arteriolar constriction reduces capillary hydrostatic pressure. Because plasma oncotic pressure has not changed (at least initially), there is a net shift of fluid from the interstitial space into the vascular space.
6. Glycogenolysis in the liver induced by epinephrine and norepinephrine results in a release of glucose and a rise in blood (and interstitial) glucose levels and, more importantly, a rise in extracellular osmolarity by as many as 20 mOsm. This will induce a shift of fluid from the intracellular space into the extracellular (including intravascular) space.

The latter two processes result in a sort of “autotransfusion” that can move as much as a liter of fluid into the vascular space in the first hour after the onset of the shock episode. This fluid shift accounts for the reduction in hematocrit that is commonly observed in hemorrhagic shock.

In addition to the immediate compensatory responses shown in Figure 11–1, fluid retention mechanisms are evoked by hypovolemic states that affect the situation in the long term. The production and release of the antidiuretic hormone (vasopressin) from the posterior pituitary promote water retention by the kidneys. Furthermore, activation of the renin–angiotensin–aldosterone pathway promotes renal sodium retention (via aldosterone) and the thirst sensation and drinking behavior (via angiotensin II). These processes contribute to the replenishment of extracellular fluid volume within a few days of the shock episode.

Decompensatory Processes



Often the strong compensatory responses elicited during shock are capable of preventing drastic reductions in arterial pressure. However, because the compensatory mechanisms involve intense arteriolar vasoconstriction, perfusion of tissues other than the heart and brain may be inadequate despite nearly normal arterial pressure. For example, blood flow through organs such as the liver and kidneys may be reduced nearly to zero by intense sympathetic activation. The possibility of permanent renal or hepatic ischemic damage is a very real concern even in seemingly mild shock situations. Patients who have apparently recovered from a state of shock may die several days later because of renal failure and uremia.

The immediate danger with shock is that it may enter the *progressive stage*, wherein the general cardiovascular situation progressively degenerates, or, worse yet, enter the *irreversible stage*, where no intervention can halt the ultimate collapse of cardiovascular function that results in death.

The mechanisms behind progressive and irreversible shock are not completely understood. However, it is clear from the mechanisms shown in Figure 11–2 that bodily homeostasis can progressively deteriorate with prolonged reductions in organ blood flow. These homeostatic disturbances, in turn, adversely affect various components of the cardiovascular system so that arterial pressure and organ blood flow

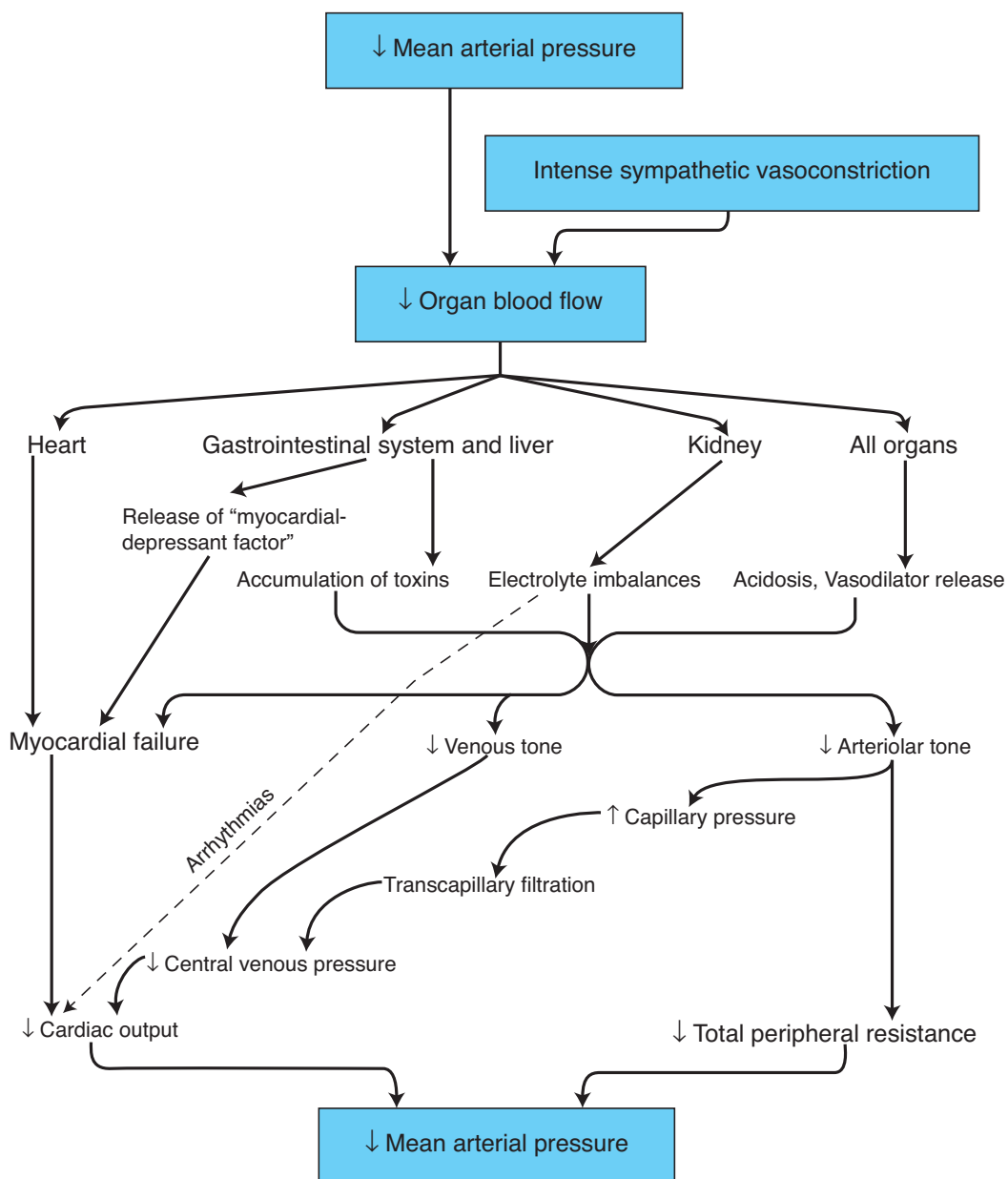


Figure 11–2. Decompensatory mechanisms in shock.

are further reduced. Note that the events shown in Figure 11–2 are *decompensatory mechanisms*. Reduced arterial pressure leads to alterations that further reduce arterial pressure rather than correct it (ie, a *positive feedback process*). These decompensatory mechanisms that are occurring at the tissue level to lower blood pressure are eventually further compounded by a reduction in sympathetic drive and a change from vasoconstriction to vasodilation with a further lowering of blood pressure. The factors that lead to this unexpected reduction in sympathetic drive from the medullary cardiovascular centers are not clearly understood. If the shock state is severe enough and/or has persisted long enough to enter the progressive stage, the self-reinforcing decompensatory mechanisms progressively drive arterial pressure down. Unless corrective measures are taken quickly, death will ultimately result.

CARDIAC DISTURBANCES

Coronary Artery Disease



Whenever coronary blood flow falls below that required to meet the metabolic needs of the heart, the myocardium is said to be *ischemic* and the pumping capability of the heart is impaired. The most common cause of myocardial ischemia is atherosclerotic disease of the large coronary arteries. In atherosclerotic disease, localized lipid deposits called *plaques* develop within the arterial walls. With severe disease, these plaques may become calcified and so large that they physically narrow the lumen of arteries (producing a stenosis) and thus greatly and permanently increase the normally low vascular resistance of these large arteries. This extra resistance adds to the resistance of other coronary vascular segments and tends to reduce coronary flow. If the coronary artery stenosis is not too severe, local metabolic vasodilator mechanisms may reduce arteriolar resistance sufficiently to compensate for the abnormally large arterial resistance. Thus, an individual with coronary artery disease may have perfectly normal coronary blood flow when resting. A coronary artery stenosis of any significance will, however, limit the extent to which coronary flow can increase above its resting value by reducing maximum achievable coronary flow. This occurs because, even with very low arteriolar resistance, the overall vascular resistance of the coronary vascular bed is high if arterial resistance is high.

Coronary artery disease can jeopardize cardiac function in several ways. Ischemic muscle cells are electrically irritable and unstable, and the danger of fibrillation is enhanced. During ischemia, the normal cardiac electrical excitation pathways may be altered and often ectopic pacemaker foci develop. Electrocardiographic manifestations of myocardial ischemia can be observed in individuals with coronary artery disease during exercise stress tests. In addition, there is evidence that platelet aggregation and clotting function may be abnormal in atherosclerotic coronary arteries and the danger of thrombus or emboli formation is enhanced. It appears that certain platelet suppressants or anticoagulants such as aspirin may be beneficial in the treatment of this consequence of coronary artery disease. (Details of the blood-clotting process are included in Appendix D.)

Myocardial ischemia not only impairs the pumping ability of the heart but also produces intense, debilitating chest pain called *angina pectoris*. Anginal pain is often absent in individuals with coronary artery disease when they are resting but is induced during physical exertion or emotional excitement. Both of these situations elicit an increase in sympathetic tone that increases myocardial oxygen consumption. Myocardial ischemia and chest pain will result if coronary blood flow cannot keep pace with the increase in myocardial metabolism.

Primary treatment of coronary artery disease (and atherosclerosis, in general) should include attempts to lower blood lipids by dietary and pharmacological techniques that prevent (and possibly reverse) further development of the plaques. The interested student should consult medical biochemistry and pharmacology texts for a complete discussion of this very important topic.

Treatment of angina that is a result of coronary artery disease may involve several different pharmacological approaches. First, quick-acting vasodilator drugs such as nitroglycerin may be used to provide primary relief from an anginal attack. These drugs may act directly on coronary vessels to acutely increase coronary blood flow. In addition to increasing myocardial oxygen delivery, nitrates may reduce myocardial oxygen demand by dilating systemic veins which reduces venous return, central venous filling and cardiac preload and by dilating systemic arterioles which reduces arterial resistance, arterial pressure and cardiac afterload. Second, β -adrenergic blocking agents such as propranolol may be used to block the effects of cardiac sympathetic nerves on the heart rate and contractility. These agents limit myocardial oxygen consumption and prevent it from increasing above the level that the compromised coronary blood flow can sustain. Third, calcium channel blockers such as verapamil may be used to dilate coronary and systemic blood vessels. These drugs, which block entry of calcium into the vascular smooth muscle cell, interfere with normal excitation–contraction coupling. They have been found to be useful for treating the angina caused by vasoconstrictive spasms of large coronary arteries (Prinzmetal's angina).

Invasive or surgical interventions are commonly used to eliminate coronary artery stenosis. X-ray techniques combined with radio-opaque dye injections can be used to visualize a balloon-tipped catheter as it is threaded into the coronary artery to the occluded region. Rapid inflation of the balloon squeezes the plaque against the vessel wall and improves the patency of the vessel. This technique, called *coronary angioplasty*, may also be effective in opening occlusions produced by intravascular clots associated with acute myocardial infarction.³ A small tube-like expandible device called a *stent* is often implanted inside the vessel at the angioplasty site. This rigid implant promotes continued patency of the vessel over a longer period than angioplasty alone. If angioplasty and stent placement are inappropriate or unsuccessful, coronary bypass surgery may be performed. The stenotic coronary artery segments are bypassed by implanting parallel low-resistance pathways formed from either natural (eg, saphenous vein or mammary artery) or artificial vessels.

³ Another method for treatment of *acute* myocardial infarction has been the intravascular injection of thrombolytic substances (eg, streptokinase or tissue plasminogen-activating factors) that dissolve blood clots. This method is most successful when these clot busters are given within a few hours of the infarction.

Chronic Heart Failure—Systolic Dysfunction



Heart (or cardiac or myocardial) *failure* is said to exist whenever ventricular function is depressed through myocardial damage, insufficient coronary flow, or any other condition that directly impairs the mechanical performance of the heart muscle. By definition, *systolic* heart failure is associated with a left ventricular ejection fraction of less than 40%. This also implies that the heart is operating on a *lower-than-normal cardiac function curve*, that is, a reduced cardiac output at any given filling pressure. Acute heart failure has already been discussed in the context of cardiogenic shock and as part of the decompensatory mechanisms operating in progressive and irreversible shock. Often, however, sustained cardiac “challenges” may induce a chronic state of heart failure. Such challenges might include (1) progressive coronary artery disease, (2) sustained elevation in cardiac afterload as that which accompanies arterial hypertension or aortic valve stenosis, or (3) reduced functional muscle mass following myocardial infarction. In some instances, external causes of cardiac failure cannot be identified and some primary myocyte abnormality is to blame. This situation is referred to as *primary cardiomyopathy*. Regardless of the precipitating cause, most forms of failure are associated eventually with a reduced myocyte function. Many specific structural, functional, and biochemical myocyte alterations accompany severe systolic heart failure. Some of the more well-documented abnormalities include (1) reduced calcium sequestration by the sarcoplasmic reticulum and upregulation of the sarcolemmal Na/Ca exchanger (leading to low intracellular calcium levels for excitation–contraction coupling), (2) low affinity of troponin for calcium (leading to reduced cross-bridge formation and contractile ability), (3) altered substrate metabolism from fatty acid to glucose oxidation, and (4) impaired respiratory chain activity (leading to impaired energy production).

The primary disturbance in systolic heart failure (acute or chronic) is depressed cardiac output and thus lowered arterial pressure. Consequently, all the compensatory responses important in shock (Figure 11–1) are also important in heart failure. In chronic heart failure, however, the cardiovascular disturbances may not be sufficient to produce a state of shock. Moreover, long-term compensatory mechanisms are especially important in chronic heart failure.

The circumstances of chronic systolic heart failure are well illustrated by cardiac output and venous function curves such as those shown in Figure 11–3. The normal cardiac output and normal venous function curves intersect at point A in Figure 11–3. A cardiac output of 5 L/min at a central venous pressure of less than 2 mmHg is indicated by the normal operating point (A). With heart failure, the heart operates on a much lower than normal cardiac output curve. Thus, acute heart failure alone (uncompensated) shifts the cardiovascular operation from the normal point (A) to a new position, as illustrated by point B in Figure 11–3—that is, cardiac output falls below normal while central venous pressure rises above normal. The decreased cardiac output leads to decreased arterial pressure and reflex activation of the cardiovascular sympathetic nerves. Increased sympathetic nerve activity tends to (1) raise the cardiac function curve toward normal and (2) increase peripheral

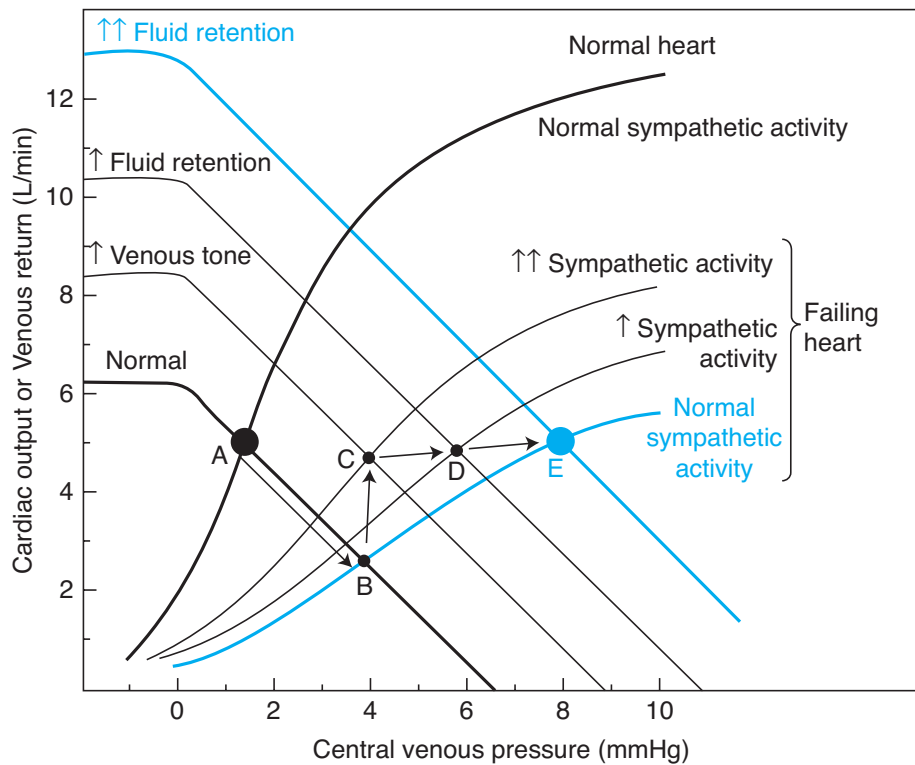


Figure 11–3. Cardiovascular alterations with compensated chronic systolic heart failure.

venous pressure through venous constriction, and thus raises the venous function curve above normal. Cardiovascular operation will shift from point B to point C in Figure 11–3. Thus, the depressed cardiac output is substantially improved by the immediate consequences of increased sympathetic nerve activity. Note, however, that the cardiac output at point C is still below normal. The arterial pressure associated with cardiovascular operation at point C is likely to be near normal, however, because higher than normal total peripheral resistance will accompany higher than normal sympathetic nerve activity.



In the long term, cardiovascular operation cannot remain at point C in Figure 11–3. Operation at point C involves higher than normal sympathetic activity, and this will inevitably cause a gradual increase in blood volume by the mechanisms that are described in Chapter 9. Over several days, there is a progressive rise in the venous function curve as a result of increased blood volume and, consequently, increased mean circulatory filling pressure. Recall that this process involves a sympathetically induced release of renin from the kidney, which activates the renin–angiotensin–aldosterone system that promotes fluid retention. This will progressively shift the cardiovascular operating point from C to D to E as shown in Figure 11–3.

Note that increased fluid retention (C → D → E in Figure 11–3) causes a progressive increase in cardiac output toward normal and simultaneously allows a *reduction in sympathetic nerve activity toward the normal value*. Reduced sympathetic activity

is beneficial for several reasons. First, decreased arteriolar constriction permits renal and splanchnic blood flow to return toward more normal values. Second, myocardial oxygen consumption may fall as sympathetic nerve activity falls, even though cardiac output tends to increase. Recall that the increased heart rate and increased cardiac contractility greatly increase myocardial oxygen consumption. Reduced myocardial oxygen consumption is especially beneficial in situations where inadequate coronary blood flow is the cause of the heart failure. In any case, once a normal cardiac output has been achieved, the individual is said to be in a “compensated” state of chronic heart failure.⁴

Unfortunately, the consequences of fluid retention in chronic cardiac failure are not all beneficial. Note that in Figure 11–3 fluid retention (C → D → E) will cause both peripheral and central venous pressures to be much higher than their normal values. Chronically high central venous pressure causes chronically increased end-diastolic volume (cardiac dilation). Up to a point, cardiac performance is improved by increased cardiac filling volume through Starling’s law. Excessive cardiac dilation, however, can impair cardiac function because increased total wall tension is required to generate pressure within an enlarged ventricular chamber ($T = P \times r$, Chapter 2). This increases the myocardial oxygen demand.

The high venous pressure associated with fluid retention also adversely affects organ function because high venous pressure produces transcapillary fluid filtration, edema formation, and congestion (hence the commonly used term *congestive heart failure*). Pulmonary edema with dyspnea (shortness of breath)⁵ and respiratory crisis often accompanies left-sided heart failure. Common signs of right-sided heart failure include distended neck veins, ankle edema, and fluid accumulation in the abdomen (ascites) with liver congestion and dysfunction.⁶

In the example shown in Figure 11–3, the depression in the cardiac output curve because of heart failure is only moderately severe. Thus, it is possible, through moderate fluid retention, to achieve a normal cardiac output with essentially normal sympathetic activity (point E). The situation at point E is relatively stable because the stimuli for further fluid retention have been removed. If, however, the heart failure is more severe, the cardiac output curve may be so depressed that normal cardiac output cannot be achieved by any amount of fluid retention. In these cases fluid retention is extremely marked, as is the elevation in venous pressure, and the complications of congestion are very serious problems.

⁴ The extracellular fluid volume remains expanded after reaching the compensated state even though sympathetic activity may have returned to near normal levels. Net fluid loss requires a period of *less than normal* sympathetic activity, which does not occur. For reasons not well understood, the cardiopulmonary baroreceptor reflexes apparently become less responsive to the increased central venous pressure and volume associated with heart failure.

⁵ Patients often complain of difficulty breathing especially during the night (paroxysmal nocturnal dyspnea). Being recumbent promotes a fluid shift from the extremities into the central venous pool and lungs, making the patient’s pulmonary problems worse. Such patients often sleep more comfortably when propped up.

⁶ Plasma volume expansion combines with abnormal liver function to reduce the concentration of plasma proteins by as much as 30%. This reduction in plasma oncotic pressure contributes to the development of interstitial edema of congestive heart failure.

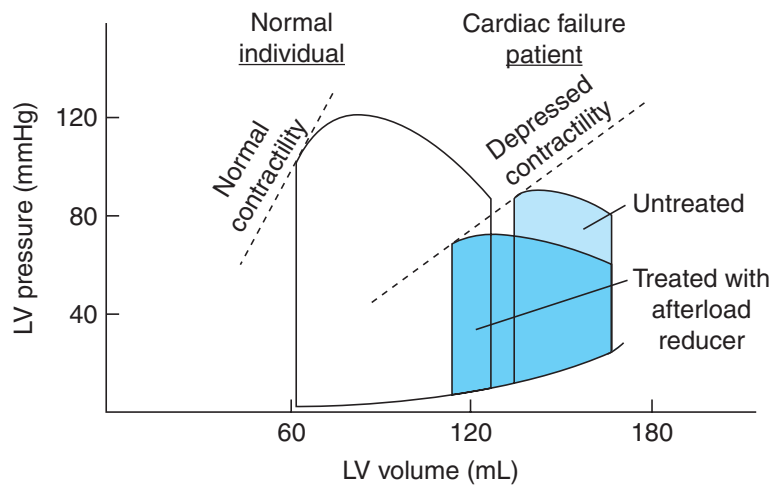


Figure 11-4. Left ventricular pressure–volume loops showing systolic heart failure (loops to the right) characterized by depressed contractility, increased end-diastolic volume, and reduced ejection fraction.

Another way of looking at the effects of left ventricular cardiac failure is given in Figure 11-4. The left ventricular pressure–volume loops describing the events of a cardiac cycle from a failing heart are displaced far to the right of those from normal hearts. The untreated patient described in this figure is in serious trouble with a reduced stroke volume and ejection fraction and high filling pressure. Furthermore, the slope of the line describing the end-systolic pressure–volume relationship is shifted downward and is less steep, indicating the reduced contractility of the cardiac muscle. However, because of this flatter relationship, small reductions in cardiac afterload (ie, arterial blood pressure) will produce substantial increases in stroke volume as indicated in Fig 11-4 and will significantly help this patient.

As might be expected from the previous discussion, the most common symptoms of patients with congestive heart failure are associated with the inability to increase cardiac output (low exercise tolerance and fatigue) and with the compensatory fluid accumulation (tissue congestion, shortness of breath, peripheral swelling). In severe cases, the ability of the cardiac cells to respond to increases in sympathetic stimulation is diminished by a reduction in the effective number (downregulation) of the myocyte β_1 -adrenergic receptors. This further reduces the ability of the myocytes to increase their contractility as well as the ability of the heart to increase its beating rate in response to sympathetic stimulation. Thus, low maximal heart rates contribute to the reduced exercise tolerance.

Treatment of the patient with congestive systolic heart failure is a difficult challenge. Treatment of the precipitating condition is of course the ideal approach, but often this cannot be done effectively. The cardiac glycosides (eg, digitalis)⁷ have

⁷ A “tea” made from the leaves of the foxglove plant (*Digitalis purpurea*) was used for centuries as a common folk remedy for the treatment of “dropsy” (congestive heart failure with significant peripheral edema). With the formal recognition of its medicinal benefits in the late-18th century by the English physician Sir William Withering, digitalis became a valuable official pharmacological tool.

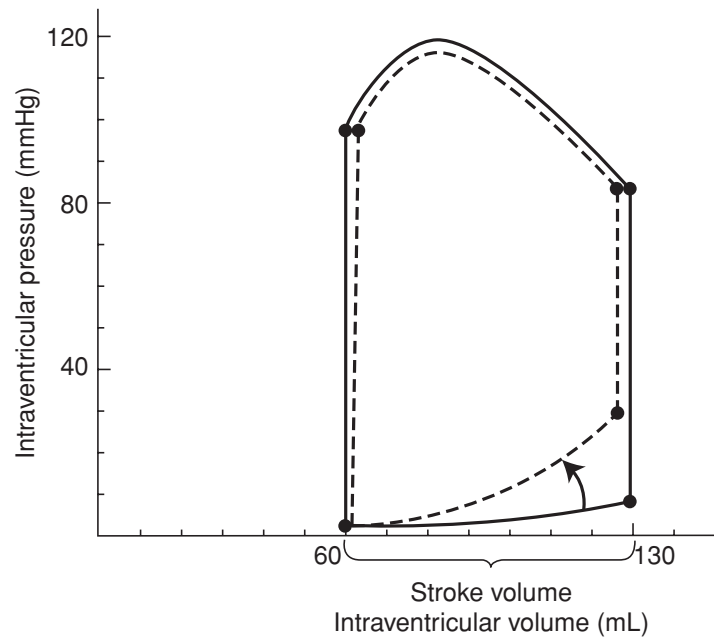


Figure 11–5. Left ventricular pressure–volume loops showing diastolic heart failure (*dashed lines*) characterized by increased diastolic stiffness, increased end-diastolic pressure, and normal ejection fraction.

been used to improve cardiac contractility (ie, to shift the cardiac function curve upward, increasing contractile force of the myocyte at any given starting length).⁸ These drugs are unfortunately quite toxic and often have undesirable side effects.

Treatment of the congestive symptoms involves balancing the need for enhanced cardiac filling with the problems of too much fluid. Drugs that promote renal fluid loss (diuretics such as furosemide or thiazides) are extremely helpful as are the angiotensin-converting enzyme (ACE) inhibitors and the angiotensin II receptor blockers (ARBs).⁹ A potent diuretic can quickly save a patient from drowning in the pulmonary exudate and reduce diastolic volume of the dilated heart to acceptable levels, but it can also lower blood pressure to dangerous levels.

Chronic Heart Failure—Diastolic Dysfunction



Although systolic dysfunction is often the primary cause of heart failure, some degree of diastolic dysfunction is also commonly present. As shown in Figure 11–5, diastolic dysfunction implies a stiffened heart during diastole

⁸ The mechanism of cardiac glycoside action is thought to involve the inhibition of the sodium/potassium adenosine triphosphatase (Na^+/K^+ -ATPase) leading to increases in intracellular $[\text{Na}^+]$, which is then exchanged for extracellular calcium via the $\text{Na}^+/\text{Ca}^{2+}$ exchanger. This results in “loading” of the sarcoplasmic reticulum during diastole and increased calcium release for subsequent excitation–contraction coupling.

⁹ The ACE inhibitors are very helpful to the congestive heart failure patient for several reasons. By inhibiting the conversion of angiotensin I into its more active form, angiotensin II, peripheral vasoconstriction is reduced (which improves cardiac pumping by afterload reduction) and aldosterone levels are reduced (which promotes diuresis). In addition, ACE inhibitors as well as the ARBs seem to prevent some of the apparently inappropriate myocyte and collagen growth (ie, remodeling) that occurs with cardiac overload and failure.

such that increases in cardiac filling pressure do not produce normal increases in end-diastolic volume. Some individuals (primarily elderly patients with hypertension and cardiac hypertrophy) who have some symptoms of cardiac failure (exertional dyspnea, fluid retention, pulmonary edema, and high end-diastolic pressures) seem to have normal systolic function (ejection fractions >40%), and normal or even reduced ventricular end-diastolic volumes despite increased cardiac filling pressure. Thus, the terms *diastolic heart failure* and *heart failure with preserved systolic function* have been used to describe this situation.

Potential causes of altered diastolic properties in heart failure include (1) decreased cardiac tissue passive compliance due to extracellular remodeling, collagen cross-linking, and other extracellular matrix protein alterations (2) increased myofibrillar passive stiffness due to alterations in the myofibrillar protein titin, (3) delayed myocyte relaxation early in diastole due to slow cytosolic calcium removal processes, (4) inadequate adenosine triphosphate levels required to disconnect the myofilament cross-bridges rapidly, and (5) residual, low-grade cross-bridge cycling during diastole due to calcium leaking from the sarcoplasmic reticulum.

At this point, therapeutic strategies that directly influence diastolic properties are not well developed. Attempts to reduce interstitial fibrosis (with ACE inhibitors and/or angiotensin receptor antagonists) and to reduce diastolic calcium leak from the sarcoplasmic reticulum (with β -adrenergic blockers) have had limited success.

HYPERTENSION

Hypertension is defined as a chronic elevation in arterial blood pressure and can exist in either the pulmonary or the systemic vascular system.



Pulmonary hypertension is much less common than systemic hypertension and less is known about its causes, progression, and treatments. Pulmonary hypertension is designated when mean pulmonary artery pressure is greater than 20 mmHg. It is relatively hard to diagnose until the consequences of the elevated pulmonary arterial pressures (systemic edema, chest pain, fatigue) are fairly well advanced. Right-sided heart failure resulting from chronic pulmonary hypertension is called *cor pulmonale*. Although there is a genetic component to its incidence, it seems to be highly correlated with conditions involving chronic hypoxia (eg, chronic obstructive pulmonary disease, cystic fibrosis, and pneumoconiosis).¹⁰ The increased prevalence of obesity with accompanying obstructive sleep apnea may account for a recent increase in reported incidence of this disease. There is no cure at present and strategies for treatment of systemic hypertension have little or no effect on pulmonary hypertension. However, recent pharmacological approaches using blockers of the receptors for the vasoconstrictor, endothelin, are promising.

¹⁰ It is noteworthy that *acute* pulmonary hypertension and pulmonary edema are recognized risks of mountain climbing to extreme altitudes without the aid of supplemental oxygen.



Systemic hypertension is defined as an elevation of mean systemic arterial pressure above 140/90 mmHg. It is an extremely common cardiovascular problem, affecting more than 20% of the adult population of the western world. It has been established beyond doubt that hypertension increases the risk of coronary artery disease, myocardial infarction, heart failure, stroke, and many other serious cardiovascular problems. Moreover, it has been clearly demonstrated that the risk of serious cardiovascular incidents is reduced by proper treatment of hypertension.¹¹

In approximately 90% of cases, the primary abnormality that produces high blood pressure is unknown. This condition is sometimes referred to as primary or essential hypertension because the elevated level was thought to be “essential” to drive the blood through the systemic circulation. In the remaining 10% of hypertensive patients, the cause can be traced to a variety of sources, including epinephrine-producing tumors (pheochromocytomas), aldosterone-producing tumors (in primary hyperaldosteronism), certain forms of renal disease (eg, renal artery stenosis, glomerular nephritis, and toxemia of pregnancy), certain neurological disorders (eg, brain tumors that increase intracranial pressure), certain thyroid and parathyroid disorders, aortic coarctation, lead poisoning, drug side effects, abuse of certain drugs, or even unusual dietary habits. The high blood pressure that accompanies such known causes is referred to as secondary hypertension. Most often, however, the true cause of the hypertension remains a mystery, and it is only the symptom of high blood pressure that is treated.

Facts about Systemic Hypertension

In the midst of an enormous amount of information about systemic hypertension, a few universally accepted facts stand out:

1. Genetic factors contribute importantly to the development of hypertension. Familial tendencies for high blood pressure are well documented. In addition, hypertension is generally more common in men than in women and in blacks than in whites.
2. Environmental factors can influence the development of hypertension. High-salt diets and/or certain forms of psychological stress may either aggravate or precipitate hypertension in genetically susceptible individuals.
3. Structural changes in the left side of the heart and arterial vessels occur in response to hypertension. Early alterations include hypertrophy of muscle cells and thickening of the walls of the ventricle and systemic resistance vessels. Late changes associated with deterioration of function include increases in connective tissue and loss of elasticity.

¹¹ Because an increased risk of cardiovascular complications with even mildly elevated blood pressure has been identified, a category designated *prehypertension* has been added to include blood pressures ranging from 120 to 139 mmHg systolic and 80 to 89 mmHg diastolic.

4. The established phase of hypertension is associated with an increase in total peripheral resistance. Cardiac output and/or blood volume may be elevated during the early developmental phase, but these variables are usually normal after the hypertension is established.
5. The increased total peripheral resistance associated with established hypertension may be due to (a) *rarefaction* (decrease in density) of microvessels, (b) the pronounced structural adaptations that occur in the peripheral vascular bed, (c) a continuously increased activity of the vascular smooth muscle cells,¹² (d) an increased sensitivity and reactivity of the vascular smooth muscle cells to external vasoconstrictor stimuli, and/or (e) diminished production and/or effect of endogenous vasodilator substances (eg, nitric oxide).
6. The chronic elevation in blood pressure does not appear to be due to a sustained elevation in sympathetic vasoconstrictor neural discharge nor is it due to a sustained elevation of any blood-borne vasoconstrictive factor. (Both neural and hormonal influences, however, may help initiate primary hypertension.)
7. Blood pressure-regulating reflexes (both the short-term arterial and cardiopulmonary baroreceptor reflexes and the long-term, renal-dependent, pressure-regulating reflexes) become adapted or “reset” to regulate blood pressure at a higher than normal level.
8. Disturbances in renal function contribute importantly to the development and maintenance of primary hypertension. Recall that the urinary output rate is influenced by arterial pressure, and, in the long term, arterial pressure can stabilize only at the level that makes urinary output rate equal to fluid intake rate. As shown by point N in Figure 11–6, this pressure is approximately 100 mmHg in a normal individual.

All forms of hypertension involve an alteration somewhere in the chain of events by which changes in arterial pressure produce changes in urinary output rate (see Figure 9–6) such that the renal function curve is shifted rightward as indicated in Figure 11–6. The important feature to note is that *higher than normal arterial pressure is required to produce a normal urinary output rate in a hypertensive individual*. Although this condition is always present with hypertension, it is not clear whether it could be the common cause of hypertension or simply another one of the many adaptations to it.

Consider that the untreated hypertensive individual in Figure 11–6 would have a very low urinary output rate at the normal mean arterial pressure of 100 mmHg. Recall from Figure 9–5 that whenever the fluid intake rate exceeds the urinary output rate, fluid volume must rise and consequently so will cardiac output and mean arterial pressure. With a normal fluid intake rate, this untreated hypertensive patient will ultimately stabilize at point A (mean arterial pressure 150 mmHg).

¹² Continuous activation of vascular smooth muscle might be evoked by autoregulatory responses to increased blood pressure, as discussed in Chapter 6. A *total body autoregulation* could produce an increase in total peripheral resistance so that total systemic flow (ie, cardiac output) would remain nearly normal in the presence of increased mean arterial pressure.

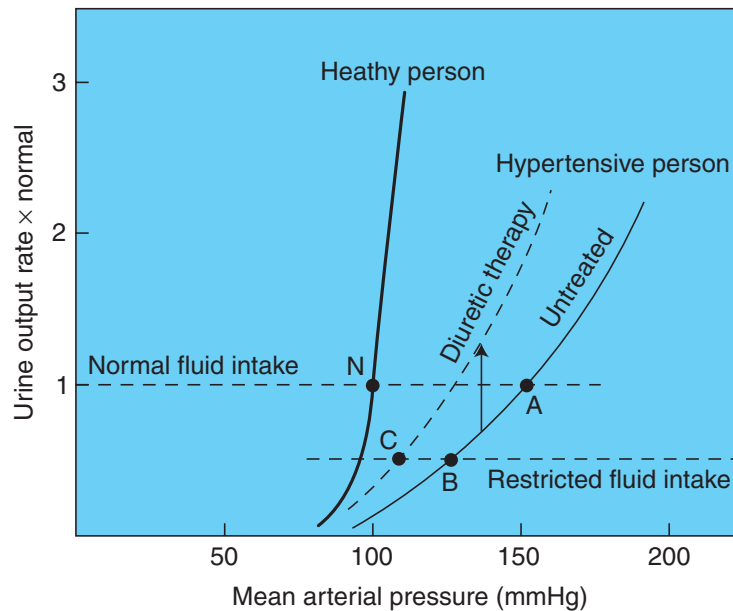


Figure 11–6. Renal function curves in healthy and hypertensive people.

Recall from Chapter 9 that the baroreceptors adapt within days so that they have a normal discharge rate at the *prevailing* average arterial pressure. Thus, once the hypertensive individual has been at point A for a week or more, even the baroreceptor mechanism will begin resisting acute changes from the 150-mmHg pressure level.

A most important fact to realize is that, although either high cardiac output or high total peripheral resistance must always ultimately sustain high blood pressure, neither needs be the primary cause. A shift in the relationship between arterial pressure and urinary output rate, as illustrated in Figure 11–6, however, will always produce hypertension. The possibility that the kidneys actually “set” the blood pressure is supported by evidence accumulating from kidney transplant studies. In these studies, the blood pressure is shown to “follow” the kidney (ie, putting a hypertensive kidney in a normotensive individual produces a hypertensive individual, whereas putting a normotensive kidney in a hypertensive individual produces a normotensive individual).

Therapeutic Strategies for Treatment of Systemic Hypertension

In certain hypertensive individuals, restricting salt intake produces a substantial reduction in blood pressure because of the reduced requirement for water retention to osmotically balance the salt load. In the example in Figure 11–6, this effect is illustrated by a shift from point A to point B. The efficacy of lowering salt intake to lower arterial pressure depends heavily on the slope of the renal function curve in the hypertensive individual. The arterial pressure of a healthy individual, for example, is affected only slightly by changes in salt intake because the normal renal function curve is so steep.

A second common treatment of hypertension is diuretic therapy. Many diuretic drugs are available, but most have the effect of inhibiting renal tubular salt (and therefore fluid) reabsorption. The net effect of diuretic therapy, as shown in Figure 11–6, is that the urinary output rate for a given arterial pressure is increased; that is, diuretic therapy raises the renal function curve. The combined result of restricted fluid intake and diuretic therapy for the hypertensive individual in Figure 11–6 is illustrated by point C.

A third therapeutic intervention is treatment with β -adrenergic blockers that inhibit sympathetic influences on the heart and renal renin release. This approach is most successful in hypertensive patients who have high circulating renin levels.

A fourth antihypertensive strategy is to block the effects of the renin–angiotensin system either with ACE inhibitors blocking the formation of the vasoconstrictor angiotensin II or with angiotensin II receptor blockers. Other pharmacological interventions may include use of α -adrenergic receptor blockers, which prevent the vasoconstrictive effects of catecholamines, and calcium channel blockers, which act directly to decrease vascular smooth muscle tone.

Alterations in life style, including reduction of stress, decreases in caloric intake, limitation of the amount of saturated fats in the diet, and establishment of a regular exercise program, may help reduce blood pressure in certain individuals.

KEY CONCEPTS



1 Circulatory shock is defined as a generalized, severe reduction in tissue blood flow so that metabolic needs are not met.



2 The primary disturbances that can lead to shock can be categorized as those that directly interfere with pump function (cardiogenic shock) or those that interfere with ventricular filling (hypovolemia, pulmonary embolus), or those that cause sustained vascular dilation.



3 Shock is usually accompanied by a compensatory increase in sympathetic activity aimed at maintaining arterial pressure via augmented cardiac output and vascular resistance.



4 Decompensatory processes precipitated by the shock state are generally caused by inadequate tissue blood flow, loss of local homeostasis, and tissue damage leading to a progressive and irreversible fall in arterial pressure.



5 Coronary artery disease, usually associated with development of atherosclerotic plaques, results in a progressive compromise in coronary blood flow that becomes inadequate to meet the tissue's metabolic needs.



6 Systolic heart failure is defined as a reduction of cardiac muscle contractility and results in a depressed cardiac output at all preloads.



Compensatory fluid retention mechanisms are evoked in heart failure to improve cardiac filling, but when fluid retention is excessive, congestive complications arise (eg, pulmonary edema and abdominal ascites).



Diastolic dysfunction resulting from reduced cardiac compliance often accompanies (and may precipitate) heart failure.



Elevation of pulmonary arterial pressure accompanies acute or chronic conditions of hypoxia.



Chronic elevation of systemic arterial blood is a common and serious condition influenced by multiple genetic and environmental factors.



STUDY QUESTIONS

- 11-1. Clinical signs of hypovolemic shock often include pale and cold skin, dry mucous membranes, weak but rapid pulse, muscle weakness, and mental disorientation or unconsciousness. What are the physiological conditions that account for these signs?
- 11-2. Which of the following would be helpful to hemorrhagic shock victims?
 - a. Keep them on their feet
 - b. Warm them up
 - c. Give them fluids to drink
 - d. Maintain their blood pressure with catecholamine-type drugs
- 11-3. What happens to hematocrit?
 - a. during hypovolemic shock resulting from prolonged diarrhea
 - b. during acute cardiogenic shock
 - c. during septic shock
 - d. with chronic bleeding
- 11-4. Left ventricular chamber enlargement with congestive heart failure increases the wall tension required to generate a given systolic pressure. True or false?
- 11-5. Why are diuretic drugs often helpful in treating patients with congestive heart failure?
- 11-6. What is the potential danger of vigorous diuretic therapy for the patient with heart failure?
- 11-7. Why does renal artery stenosis produce hypertension?
- 11-8. Your 70-year-old, 70-kg patient has an ejection fraction of 70%. Left ventricular end-diastolic volume is 60 mL. Which of the following statements best fits these data?
 - a. Stroke volume is approximately 70 mL.
 - b. Left ventricular end-systolic volume is approximately 60 mL.
 - c. Your patient may be severely hypovolemic.
 - d. Your patient may be suffering from chronic systolic heart failure.
 - e. These are normal values for someone this age.

- 11-9. All the following are compensatory processes that help maintain circulation during states of hypovolemic shock except
- a. hepatic glycogenolysis to increase blood glucose
 - b. rapid respiratory effort to promote venous return of blood to the heart
 - c. vasoconstrictive contributions from increases in circulating epinephrine
 - d. autotransfusion of interstitial fluid into capillary beds
 - e. transcapillary filtration of plasma into interstitial space
- 11-10. Chronic systemic hypertension is usually accompanied by a chronic increase in
- a. cardiac output
 - b. the heart rate
 - c. arterial pulse pressure
 - d. total peripheral resistance
 - e. renal urinary output
- 