

Control Mechanisms in Circulatory Function

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CHAPTER OUTLINE

- AUTONOMIC NEURAL CONTROL OF THE CIRCULATORY SYSTEM
- INTEGRATED SUPRAMEDULLARY CARDIOVASCULAR CONTROL
- HORMONAL CONTROL OF THE CARDIOVASCULAR SYSTEM

- SHORT-TERM AND LONG-TERM CONTROL OF BLOOD PRESSURE COMPARED
- CARDIOVASCULAR CONTROL DURING STANDING

KEY CONCEPTS

1. The sympathetic nervous system acts on the heart primarily via β -adrenergic receptors.
2. The parasympathetic nervous system acts on the heart via muscarinic cholinergic receptors.
3. The sympathetic nervous system acts on blood vessels primarily via α -adrenergic receptors.
4. Reflex control of the circulation is integrated primarily in pools of neurons in the medulla oblongata.
5. The integration of behavioral and cardiovascular responses occurs mainly in the hypothalamus.

6. Baroreceptors and cardiopulmonary receptors are key in the moment-to-moment regulation of arterial pressure.
7. The renin-angiotensin-aldosterone system, arginine vasopressin, and atrial natriuretic peptide are important in the long-term regulation of blood volume and arterial pressure.
8. Pressure diuresis is the mechanism that ultimately adjusts arterial pressure to a set level.
9. The defense of arterial pressure during standing involves the integration of multiple mechanisms.

The mechanisms controlling the circulation can be divided into neural control mechanisms, hormonal control mechanisms, and local control mechanisms. Cardiac performance and vascular tone at any time are the result of the integration of all three control mechanisms. To some extent, this categorization is artificial because each of the three categories affects the other two. This chapter deals with neural and hormonal mechanisms; local mechanisms are covered in Chapter 16.

Central blood volume and arterial pressure are normally maintained within narrow limits by neural and hormonal mechanisms. Adequate central blood volume is necessary to ensure proper cardiac output, and relatively constant arterial blood pressure maintains tissue perfusion in the face of changes in regional blood flow. Neural control involves sympathetic and parasympathetic branches of the autonomic nervous system (ANS). Blood volume and arterial pressure are monitored by stretch receptors in the heart and

arteries. Afferent nerve traffic from these receptors is integrated with other afferent information in the medulla oblongata, which leads to activity in sympathetic and parasympathetic nerves that adjusts cardiac output and systemic vascular resistance (SVR) to maintain arterial pressure. Sympathetic nerve activity and, more importantly, hormones, such as arginine vasopressin (antidiuretic hormone), angiotensin II, aldosterone, and atrial natriuretic peptide, serve as effectors for the regulation of salt and water balance and blood volume. Neural control of cardiac output and SVR plays a larger role in the moment-by-moment regulation of arterial pressure, whereas hormones play a larger role in the long-term regulation of arterial pressure.

In some situations, factors other than blood volume and arterial pressure regulation strongly influence cardiovascular control mechanisms. These situations include the fight-or-flight response, diving, thermoregulation, standing, and exercise.

AUTONOMIC NEURAL CONTROL OF THE CIRCULATORY SYSTEM

Neural regulation of the cardiovascular system involves the firing of postganglionic parasympathetic and sympathetic neurons, triggered by preganglionic neurons in the brain (parasympathetic) and spinal cord (sympathetic and parasympathetic). Afferent input influencing these neurons comes from the cardiovascular system, as well as from other organs and the external environment.

Autonomic control of the heart and blood vessels was described in Chapter 6. Briefly, the heart is innervated by parasympathetic (vagus) and sympathetic (cardioaccelerator) nerve fibers (Fig. 18.1). Parasympathetic fibers release acetylcholine (ACh), which binds to muscarinic receptors of the sinoatrial node, the atrioventricular node, and specialized conducting tissues. Stimulation of parasympathetic fibers causes a slowing of the heart rate and conduction velocity. The ventricles are only sparsely innervated by parasympathetic nerve fibers, and stimulation of these fibers has little direct effect on cardiac contractility. Some cardiac parasympathetic fibers end on sympathetic nerves and inhibit the release of norepinephrine (NE) from sympathetic nerve fibers. Therefore, in the presence of sympa-

thetic nervous system activity, parasympathetic activation reduces cardiac contractility.

Sympathetic fibers to the heart release NE, which binds to β_1 -adrenergic receptors in the sinoatrial node, the atrioventricular node and specialized conducting tissues, and cardiac muscle. Stimulation of these fibers causes increased heart rate, conduction velocity, and contractility.

The two divisions of the autonomic nervous system tend to oppose each other in their effects on the heart, and activities along these two pathways usually change in a reciprocal manner.

Blood vessels (except those of the external genitalia) receive sympathetic innervation only (see Fig. 18.1). The neurotransmitter is NE, which binds to α_1 -adrenergic receptors and causes vascular smooth muscle contraction and vasoconstriction. Circulating epinephrine, released from the adrenal medulla, binds to β_2 -adrenergic receptors of vascular smooth muscle cells, especially coronary and skeletal muscle arterioles, producing vascular smooth muscle relaxation and vasodilation. Postganglionic parasympathetic fibers release ACh and nitric oxide (NO) to blood vessels in the external genitalia. ACh causes the further release of NO from endothelial cells; NO results in vascular smooth muscle relaxation and vasodilation.

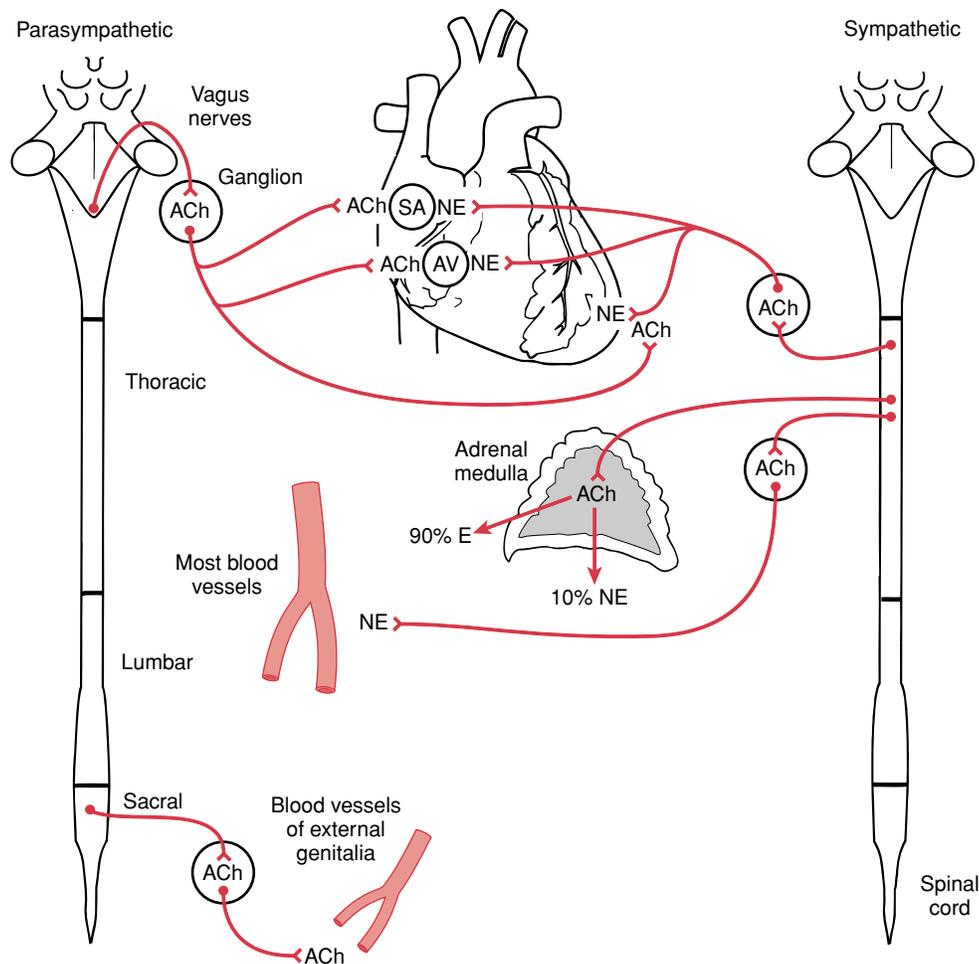


FIGURE 18.1 Autonomic innervation of the cardiovascular system. ACh, acetylcholine; NE, norepinephrine; E, epinephrine; SA, sinoatrial node; AV, atrioventricular node.

The Spinal Cord Exerts Control Over Cardiovascular Function

Preganglionic sympathetic neurons normally generate a steady level of background postganglionic activity (tone). This **sympathetic tone** produces a background level of sympathetic vasoconstriction, cardiac stimulation, and adrenal medullary catecholamine secretion, all of which contribute to the maintenance of normal blood pressure. This tonic activity is generated by excitatory signals from the medulla oblongata. When the spinal cord is acutely transected and these excitatory signals can no longer reach sympathetic preganglionic fibers, their tonic firing is reduced and blood pressure falls—an effect known as **spinal shock**.

Humans have spinal reflexes of cardiovascular significance. For example, the stimulation of pain fibers entering the spinal cord below the level of a chronic spinal cord transection can cause reflex vasoconstriction and increased blood pressure.

The Medulla Is a Major Area for Cardiovascular Reflex Integration

The medulla oblongata has three major cardiovascular functions:

- Generating tonic excitatory signals to spinal sympathetic preganglionic fibers
- Integrating cardiovascular reflexes
- Integrating signals from supramedullary neural networks and from circulating hormones and drugs

Specific pools of neurons are responsible for elements of these functions. Neurons in the **rostral ventrolateral nucleus (RVL)** are normally active and provide tonic excitatory activity to the spinal cord. Specific pools of neurons within the RVL have actions on heart and blood vessels. The cell bodies of cardiac preganglionic parasympathetic neurons are located in the **nucleus ambiguus**; the activity of these neurons is influenced by reflex input, as well as input from respiratory neurons. Respiratory sinus arrhythmia, described in Chapter 13, is primarily the result of the influence of medullary respiratory neurons that inhibit firing of preganglionic parasympathetic neurons during inspiration and excite these neurons during expiration. Other inputs to the RVL and nucleus ambiguus will be described below.

The Baroreceptor Reflex Is Important in the Regulation of Arterial Pressure

The most important reflex behavior of the cardiovascular system originates in mechanoreceptors located in the aorta, carotid sinuses, atria, ventricles, and pulmonary vessels. These mechanoreceptors are sensitive to the stretch of the walls of these structures. When the wall is stretched by increased transmural pressure, receptor firing rate increases. Mechanoreceptors in the aorta and carotid sinuses are called **baroreceptors**. Mechanoreceptors in the atria, ventricles, and pulmonary vessels are referred to as low-pressure baroreceptors or **cardiopulmonary baroreceptors**.

Changes in the firing rate of the arterial baroreceptors and cardiopulmonary baroreceptors initiate reflex responses of the autonomic nervous system that alter cardiac output and SVR. The central terminals for these receptors are located in the **nucleus tractus solitarii (NTS)** in the medulla oblongata. Neurons from the NTS project to the RVL and nucleus ambiguus where they influence the firing of sympathetic and parasympathetic nerves.

Baroreceptor Reflex Effects on Cardiac Output and Systemic Vascular Resistance. Increased pressure in the carotid sinus and aorta stretches **carotid sinus baroreceptors** and **aortic baroreceptors** and raises their firing rate. Nerve fibers from carotid sinus baroreceptors join the glossopharyngeal (cranial nerve IX) nerves and travel to the NTS. Nerve fibers from the aortic baroreceptors, located in the wall of the arch of the aorta, travel with the vagus (cranial nerve X) nerves to the NTS.

The increased action potential traffic reaching the NTS leads to excitation of nucleus ambiguus neurons and inhibition of firing of RVL neurons. This results in increased parasympathetic neural activity to the heart and decreased sympathetic neural activity to the heart and resistance vessels (primarily arterioles) (Fig. 18.2), causing decreased cardiac output and SVR. Since mean arterial pressure is the product of SVR and cardiac output (see Chapter 12), mean arterial pressure is returned toward the normal level. This completes a negative-feedback loop by which increases in mean arterial pressure can be attenuated.

Conversely, decreases in arterial pressure (and decreased stretch of the baroreceptors) increase sympathetic neural activity and decrease parasympathetic neural activity, resulting in increased heart rate, stroke volume, and SVR; this

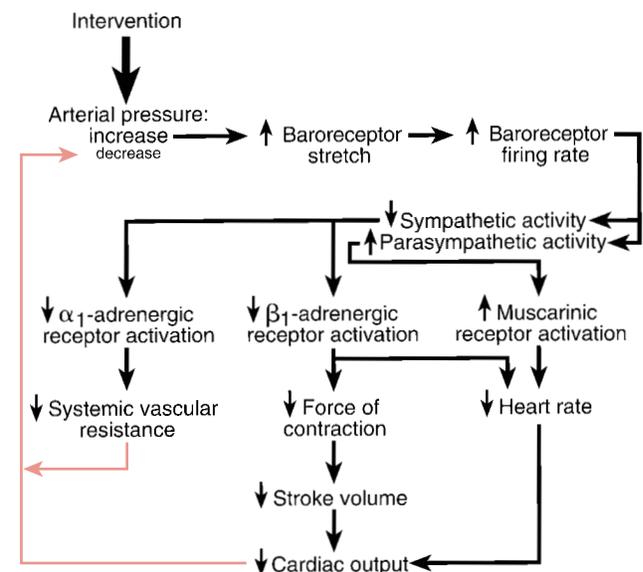


FIGURE 18.2 Baroreceptor reflex response to increased arterial pressure. An intervention elevates arterial pressure (either mean arterial pressure or pulse pressure), stretches the baroreceptors, and initiates the reflex. The resulting reduced systemic vascular resistance and cardiac output return arterial pressure toward the level existing before the intervention.

returns blood pressure toward the normal level. If the fall in mean arterial pressure is very large, increased sympathetic neural activity to veins is added to the above responses, causing contraction of the venous smooth muscle and reducing venous compliance. Decreased venous compliance shifts blood toward the central blood volume, increasing right atrial pressure and, in turn, stroke volume.

Baroreceptor Reflex Effects on Hormone Levels. The baroreceptor reflex influences hormone levels in addition to vascular and cardiac muscle. The most important influence is on the renin-angiotensin-aldosterone system (RAAS). A reduction in arterial pressure and baroreceptor firing results in increased sympathetic nerve activity to the kidneys, which causes the kidneys to release renin, activating the RAAS. The activation of this system causes the kidneys to save salt and water. Salt and water retention increases blood volume and, ultimately, causes blood pressure to rise. The details of the RAAS are discussed later in this chapter and in Chapter 24.

The information on the firing rate of the baroreceptors is also projected to the paraventricular nucleus of the hypothalamus where the release of arginine vasopressin (AVP) by the posterior pituitary is controlled (see Chapter 32). Decreased firing rate of the baroreceptors results in increased AVP release, causing the kidney to save water. The result is an increase in blood volume. An increase in arterial pressure causes decreased AVP release and increased excretion of water by the kidneys.

Hormonal effects on salt and water balance and, ultimately, on cardiac output and blood pressure are powerful, but they occur more slowly (a timescale of many hours to days) than ANS effects (seconds to minutes).

Baroreceptor Reflex Effects on Specific Organs. The defense of arterial pressure by the baroreceptor reflex results in maintenance of blood flow to two vital organs: the heart and brain. If resistance vessels of the heart and brain participated in the sympathetically mediated vasoconstriction found in skeletal muscle, skin, and the splanchnic region, it would lower blood flow to these organs. This does not happen.

The combination of (1) a minimal vasoconstrictor effect of sympathetic nerves on cerebral blood vessels, and (2) a robust autoregulatory response keeps brain blood flow nearly normal despite modest decreases in arterial pressure (see Chapter 17). However, a large decrease in arterial pressure beyond the autoregulatory range causes brain blood flow to fall, accounting for loss of consciousness.

Activation of sympathetic nerves to the heart causes α_1 -adrenergic receptor-mediated constriction of coronary arterioles and β_1 -adrenergic receptor-mediated increases in cardiac muscle metabolism (see Chapter 17). The net effect is a marked increase in coronary blood flow, despite the increased sympathetic constrictor activity. In summary, when arterial pressure drops, the generalized vasoconstriction caused by the baroreflex spares the brain and heart, allowing flow to these two vital organs to be maintained.

Pressure Range for Baroreceptors. The effective range of the carotid sinus baroreceptor mechanism is approxi-

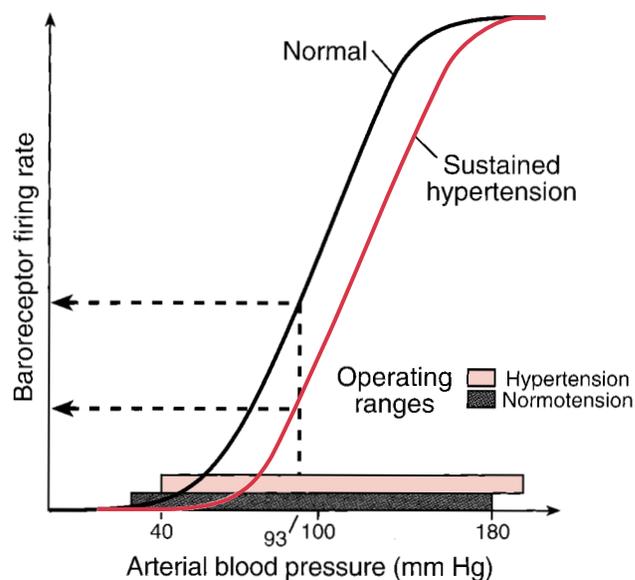


FIGURE 18.3 Carotid sinus baroreceptor nerve firing rate and mean arterial pressure. With normal conditions, a mean arterial pressure of 93 mm Hg is near the midrange of the firing rates for the nerves. Sustained hypertension causes the operating range to shift to the right, putting 93 mm Hg at the lower end of the firing range for the nerves.

mately 40 mm Hg (when the receptor stops firing) to 180 mm Hg (when the firing rate reaches a maximum) (Fig. 18.3). Pulse pressure also influences the firing rate of the baroreceptors. For a given mean arterial pressure, the firing rate of the baroreceptors increases with pulse pressure.

Baroreceptor Adaptation. An important property of the baroreceptor reflex is that it adapts during a period of 1 to 2 days to the prevailing mean arterial pressure. When the mean arterial pressure is suddenly raised, baroreceptor firing increases. If arterial pressure is held at the higher level, baroreceptor firing declines during the next few seconds. Firing rate then continues to decline more slowly until it returns to the original firing rate, between 1 and 2 days. Consequently, if the mean arterial pressure is maintained at an elevated level, the tendency for the baroreceptors to initiate a decrease in cardiac output and SVR quickly disappears. This occurs, in part, because of the reduction in the rate of baroreceptor firing for a given mean arterial pressure mentioned above (see Fig. 18.3). This is an example of **receptor adaptation**. A “resetting” of the reflex in the central nervous system (CNS) occurs as well. Consequently, the baroreceptor mechanism is the “first line of defense” in the maintenance of normal blood pressure; it makes the rapid control of blood pressure needed with changes in posture or blood loss possible, but it does not provide for the long-term control of blood pressure.

Cardiopulmonary Baroreceptors Are Stretch Receptors That Sense Central Blood Volume

Cardiopulmonary baroreceptors are located in the cardiac atria, at the junction of the great veins and atria, in the ven-

tricular myocardium, and in pulmonary vessels. Their nerve fibers run in the vagus nerve to the NTS, with projections to supramedullary areas as well. Unloading (i.e., decreasing the stretch) of the cardiopulmonary receptors by reducing central blood volume results in increased sympathetic nerve activity and decreased parasympathetic nerve activity to the heart and blood vessels. In addition, the cardiopulmonary reflex interacts with the baroreceptor reflex. Unloading of the cardiopulmonary receptors enhances the baroreceptor reflex, and loading the cardiopulmonary receptors, by increasing central blood volume, inhibits the baroreceptor reflex.

Like the arterial baroreceptors, the decreased stretch of the cardiopulmonary baroreceptors activates the RAAS and increases the release of AVP.

Chemoreceptors Detect Changes in PCO_2 , pH, and PO_2

The reflex response to changes in blood gases and pH begins with **chemoreceptors** located peripherally in the **carotid bodies** and **aortic bodies** and centrally in the medulla (see Chapter 22). The peripheral chemoreceptors of the carotid bodies and aortic bodies are specialized structures located in approximately the same areas as the carotid sinus and aortic baroreceptors. They send nerve impulses to the NTS and are sensitive to elevated PCO_2 , as well as decreased pH and PO_2 . Peripheral chemoreceptors exhibit an increased firing rate when (1) the PO_2 or pH of the arterial blood is low, (2) the PCO_2 of arterial blood is increased, (3) the flow through the bodies is very low or stopped, or (4) a chemical is given that blocks oxidative metabolism in the chemoreceptor cells. The central medullary chemoreceptors increase their firing rate primarily in response to elevated arterial PCO_2 , which causes a decrease in brain pH.

The increased firing of both peripheral and central chemoreceptors (via the NTS and RVL) leads to profound peripheral vasoconstriction. Arterial pressure is significantly elevated. If respiratory movements are voluntarily stopped, the vasoconstriction is more intense and a striking bradycardia and decreased cardiac output occur. This response pattern is typical of the diving response (discussed later). As in the case of the baroreceptor reflex, the coronary and cerebral circulations are not subject to the sympathetic vasoconstrictor effects and instead exhibit vasodilation, as a result of the combination of the direct effect of the abnormal blood gases and local metabolic effects.

In addition to its importance when arterial blood gases are abnormal, the chemoreceptor reflex is important in the cardiovascular response to severe hypotension. As blood pressure falls, blood flow through the carotid and aortic bodies decreases and chemoreceptor firing increases—probably because of changes in local PCO_2 , pH, and PO_2 .

Pain Receptors Produce Reflex Responses in the Cardiovascular System

Two reflex cardiovascular responses to pain occur. In the most common reflex, pain causes increased sympathetic activity to the heart and blood vessels, coupled with de-

creased parasympathetic activity to the heart. These events lead to increases in cardiac output, SVR, and mean arterial pressure. An example of this reaction is the **cold pressor response**—the elevated blood pressure that normally occurs when an extremity is placed in ice water. The increase in blood pressure produced by this challenge is exaggerated in several forms of hypertension.

A second type of response is produced by deep pain. The stimulation of deep pain fibers associated with crushing injuries, disruption of joints, testicular trauma, or distension of the abdominal organs results in diminished sympathetic activity and enhanced parasympathetic activity with decreased cardiac output, SVR, and blood pressure. This hypotensive response contributes to certain forms of cardiovascular shock.

Activation of Chemoreceptors in the Ventricular Myocardium Causes Reflex Bradycardia and Vasodilation

An injection of bradykinin, 5-hydroxytryptamine (serotonin), certain prostaglandins, or various other compounds into the coronary arteries supplying the posterior and inferior regions of the ventricles causes reflex bradycardia and hypotension. The chemoreceptor afferents are carried in the vagus nerves. The bradycardia results from increased parasympathetic tone. Dilation of systemic arterioles and veins is caused by withdrawal of sympathetic tone. This reflex is also elicited by myocardial ischemia and is responsible for the bradycardia and hypotension that can occur in response to acute infarction of the posterior or inferior myocardium.

INTEGRATED SUPRAMEDULLARY CARDIOVASCULAR CONTROL

The highest levels of organization in the ANS are the **supramedullary networks** of neurons with way stations in the limbic cortex, amygdala, and hypothalamus. These supramedullary networks orchestrate cardiovascular correlates of specific patterns of emotion and behavior by their projections to the ANS.

Unlike the medulla, supramedullary networks do not contribute to the tonic maintenance of blood pressure, nor are they necessary for most cardiovascular reflexes, although they modulate reflex reactivity.

The Fight-or-Flight Response Includes Specific Cardiovascular Changes

Upon stimulation of certain areas in the hypothalamus, cats demonstrate a stereotypical rage response, with spitting, clawing, tail lashing, back arching, and so on. This is accompanied by the autonomic **fight-or-flight response** described in Chapter 6. Cardiovascular responses include elevated heart rate and blood pressure.

The initial behavioral pattern during the fight-or-flight response includes increased skeletal muscle tone and general alertness. There is increased sympathetic neural activity to blood vessels and the heart. The result of this cardiovascular response is an increase in cardiac output (by

increasing both heart rate and stroke volume), SVR, and arterial pressure. When the fight-or-flight response is consummated by fight or flight, arterioles in skeletal muscle dilate because of accumulation of local metabolites from the exercising muscles (see Chapter 17). This vasodilation may outweigh the sympathetic vasoconstriction in other organs and SVR may actually fall. With a fall in SVR, mean arterial pressure returns toward normal despite the increase in cardiac output.

Emotional situations often provoke the fight-or-flight response in humans, but it is usually not accompanied by muscle exercise (e.g., medical students taking an examination). It seems likely that repeated elevations in arterial pressure caused by dissociation of the cardiovascular component of the fight-or-flight response from muscular exercise component are harmful.

Fainting Can Be a Cardiovascular Correlate of Emotion

Vasovagal syncope (fainting) is a somatic and cardiovascular response to certain emotional experiences. Stimulation of specific areas of the cerebral cortex can lead to a sudden relaxation of skeletal muscles, depression of respiration, and loss of consciousness. The cardiovascular events accompanying these somatic changes include profound parasympathetic-induced bradycardia and withdrawal of resting sympathetic vasoconstrictor tone. There is a dramatic drop in heart rate, cardiac output, and SVR. The resultant decrease in mean arterial pressure results in unconsciousness because of lowered cerebral blood flow. Vasovagal syncope appears in lower animals as the "playing dead" response typical of the opossum.

The Cardiovascular Correlates of Exercise Require Integration of Central and Peripheral Mechanisms

Exercise causes activation of supramedullary neural networks that inhibit the activity of the baroreceptor reflex. The inhibition of medullary regions involved in the baroreceptor reflex is called **central command**. Central command results in withdrawal of parasympathetic tone to the heart with a resulting increase in heart rate and cardiac output. The increased cardiac output supplies the added requirement for blood flow to exercising muscle. As exercise intensity increases, central command adds sympathetic tone that further increases heart rate and contractility. It also recruits sympathetic vasoconstriction that redistributes blood flow away from splanchnic organs and resting skeletal muscle to exercising muscle. Finally, afferent impulses from exercising skeletal muscle terminate in the RVL where they further augment sympathetic tone.

During exercise, blood flow of the skin is largely influenced by temperature regulation, as described in Chapter 17.

The Diving Response Maintains Oxygen Delivery to the Heart and Brain

The **diving response** is best observed in seals and ducks, but it also occurs in humans. An experienced diver can exhibit intense slowing of the heart rate (parasympathetic)

and peripheral vasoconstriction (sympathetic) of the extremities and splanchnic regions when his or her face is submerged in cold water. With breath holding during the dive, arterial PO_2 and pH fall and PCO_2 rises, and the chemoreceptor reflex reinforces the diving response. The arterioles of the brain and heart do not constrict and, therefore, cardiac output is distributed to these organs. This heart-brain circuit makes use of the oxygen stored in the blood that would normally be used by the other tissues, especially skeletal muscle. Once the diver surfaces, the heart rate and cardiac output increase substantially; peripheral vasoconstriction is replaced by vasodilation, restoring nutrient flow and washing out accumulated waste products.

Behavioral Conditioning Affects Cardiovascular Responses

Cardiovascular responses can be conditioned (as can other autonomic responses, such as those observed in Pavlov's famous experiments). Both classical and operant conditioning techniques have been used to raise and lower the blood pressure and heart rate of animals. Humans can also be taught to alter their heart rate and blood pressure, using a variety of behavioral techniques, such as biofeedback.

Behavioral conditioning of cardiovascular responses has significant clinical implications. Animal and human studies indicate that psychological stress can raise blood pressure, increase atherogenesis, and predispose to fatal cardiac arrhythmias. These effects are thought to result from an inappropriate fight-or-flight response. Other studies have shown beneficial effects of behavior patterns designed to introduce a sense of relaxation and well-being. Some clinical regimens for the treatment of cardiovascular disease take these factors into account.

Not All Cardiovascular Responses Are Equal

Supramedullary responses can override the baroreceptor reflex. For example, the fight-or-flight response causes the heart rate to rise above normal levels despite a simultaneous rise in arterial pressure. In such circumstances, the neurons connecting the hypothalamus to medullary areas inhibit the baroreceptor reflex and allow the corticohypothalamic response to predominate. Also, during exercise, input from supramedullary regions inhibits the baroreceptor reflex, promoting increased sympathetic tone and decreased parasympathetic tone despite an increase in arterial pressure.

Moreover, the various cardiovascular response patterns do not necessarily occur in isolation, as previously described. Many response patterns interact, reflecting the extensive neural interconnections between all levels of the CNS and interaction with various elements of the local control systems. For example, the baroreceptor reflex interacts with thermoregulatory responses. Cutaneous sympathetic nerves participate in body temperature regulation (see Chapter 29), but also serve the baroreceptor reflex. At moderate levels of heat stress, the baroreceptor reflex can cause cutaneous arteriolar constriction despite elevated core temperature. However, with severe heat stress, the baroreceptor reflex cannot overcome the cutaneous vasodilation; as a result, arterial pressure regulation may fail.

HORMONAL CONTROL OF THE CARDIOVASCULAR SYSTEM

Various hormones play a role in the control of the cardiovascular system. Important sites of hormone secretion include the adrenal medulla, posterior pituitary gland, kidney, and cardiac atrium.

Circulating Epinephrine Has Cardiovascular Effects

When the sympathetic nervous system is activated, the adrenal medulla releases epinephrine (> 90%) and norepinephrine (< 10%), which circulate in the blood (see Chapter 6). Changes in the circulating NE concentration are small relative to changes in NE resulting from the direct release from nerve endings close to vascular smooth muscle and cardiac cells. Increased circulating epinephrine, however, contributes to skeletal muscle vasodilation during the fight-or-flight response and exercise. In these cases, epinephrine binds to β_2 -adrenergic receptors of skeletal muscle arteriolar smooth muscle cells and causes relaxation. In the heart, circulating epinephrine binds to cardiac cell β_1 -adrenergic receptors and reinforces the effect of NE released from sympathetic nerve endings.

A comparison of the responses to infusions of epinephrine and norepinephrine illustrates not only the different effects of the two hormones but also the different reflex response each one elicits (Fig. 18.4). Epinephrine and norepinephrine have similar direct effects on the heart, but NE elicits a powerful baroreceptor reflex because it causes sys-

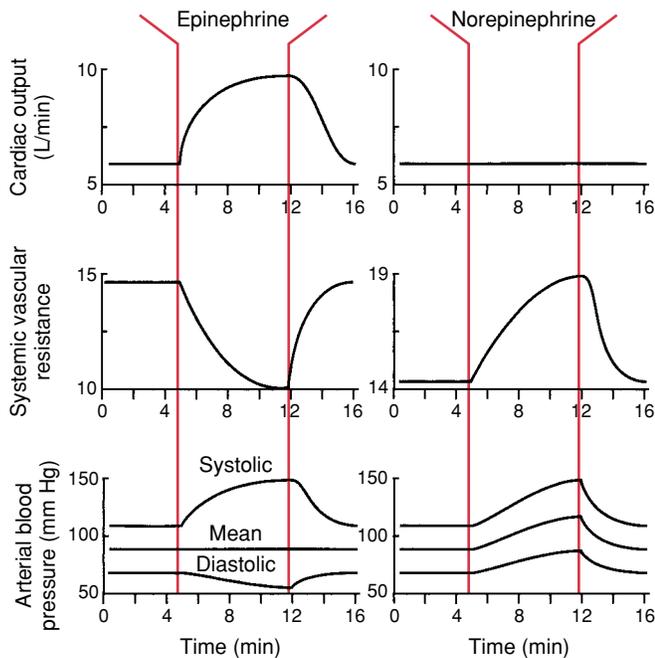


FIGURE 18.4 A comparison of the effects of intravenous infusions of epinephrine and norepinephrine. (See text for details). (Modified from Rowell LB. Human Circulation: Regulation During Physical Stress. New York: Oxford University Press, 1986.)

temic vasoconstriction and increases mean arterial pressure. The reflex masks some of the direct cardiac effects of NE by significantly increasing cardiac parasympathetic tone. In contrast, epinephrine causes vasodilation in skeletal muscle and splanchnic beds. SVR may actually fall and mean arterial pressure does not rise. The baroreceptor reflex is not elicited, parasympathetic tone to the heart is not increased, and the direct cardiac effects of epinephrine are evident. At high concentrations, epinephrine binds to α_1 -adrenergic receptors and causes peripheral vasoconstriction; this level of epinephrine is probably never reached except when it is administered as a drug.

Denervated organs, such as transplanted hearts, are very responsive to circulating levels of epinephrine and norepinephrine. This increased sensitivity to neurotransmitters is referred to as **denervation hypersensitivity**. Several factors contribute to denervation hypersensitivity, including the absence of sympathetic nerve endings to take up circulating norepinephrine and epinephrine actively, leaving more transmitter available for binding to receptors. In addition, denervation results in **up-regulation** of neurotransmitter receptors in target cells. During exercise, circulating levels of norepinephrine and epinephrine increase. Because of their enhanced response to circulating catecholamines, transplanted hearts can perform almost as well as normal hearts.

The Renin-Angiotensin-Aldosterone System Helps Regulate Blood Pressure and Volume

The control of total blood volume is extremely important in regulating arterial pressure. Because changes in total blood volume lead to changes in central blood volume, the long-term influence of blood volume on ventricular end-diastolic volume and cardiac output is paramount. Cardiac output, in turn, strongly influences arterial pressure. Hormonal control of blood volume depends on hormones that regulate salt and water intake and output as well as red blood cell formation.

Reduced arterial pressure and blood volume cause the release of **renin** from the kidneys. Renin release is mediated by the sympathetic nervous system and by the direct effect of lowered arterial pressure on the kidneys. Renin is a proteolytic enzyme that catalyzes the conversion of angiotensinogen, a plasma protein, to angiotensin I (Fig. 18.5). Angiotensin I is then converted to angiotensin II by **angiotensin-converting enzyme (ACE)**, primarily in the lungs. Angiotensin II has the following actions:

- It is a powerful arteriolar vasoconstrictor, and in some circumstances, it is present in plasma in concentrations sufficient to increase SVR.
- It reduces sodium excretion by increasing sodium reabsorption by proximal tubules of the kidney.
- It causes the release of **aldosterone** from the adrenal cortex.
- It causes the release of **AVP** from the posterior pituitary gland.

Angiotensin II is a significant vasoconstrictor in some circumstances. Angiotensin II directly stimulates contraction of vascular smooth muscle and also augments NE release from sympathetic nerves and sensitizes vascular smooth muscle to the constrictor effects of NE. It plays an

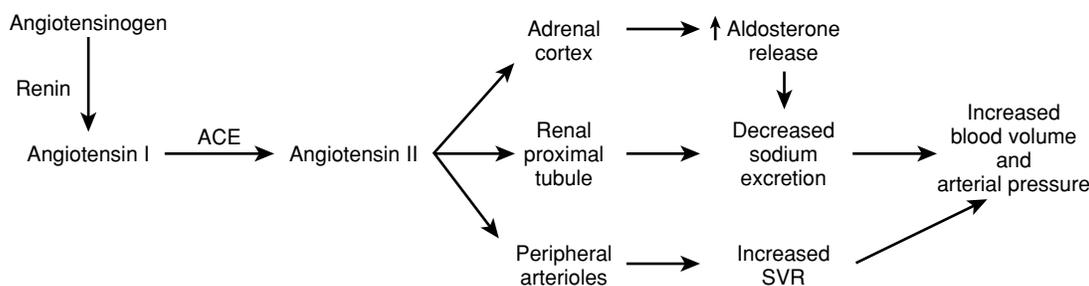


FIGURE 18.5 **Renin-angiotensin-aldosterone system.** This system plays an important role in the regulation of arterial blood pressure and blood volume. ACE, angiotensin-converting enzyme; SVR, systemic vascular resistance.

important role in increasing SVR, as well as blood volume, in individuals on a low-salt diet. If an ACE inhibitor is given to such individuals, blood pressure falls. Renin is released during blood loss, even before blood pressure falls, and the resulting rise in plasma angiotensin II increases the SVR.

One of the effects of aldosterone is to reduce renal excretion of sodium, the major cation of the extracellular fluid. Retention of sodium paves the way for increasing blood volume. Renin, angiotensin, aldosterone, and the factors that control their release and formation are discussed in Chapter 24. The RAAS is important in the normal maintenance of blood volume and blood pressure. It is critical when salt and water intake is reduced.

Rarely, renal artery stenosis causes hypertension that can be attributed solely to elevated renin and angiotensin II levels. In addition, the renin-angiotensin system plays an important (but not unique) role in maintaining elevated pressure in more than 60% of patients with essential hypertension. In patients with congestive heart failure, renin and angiotensin II are increased and contribute to elevated SVR as well as sodium retention.

Arginine Vasopressin Contributes to the Regulation of Blood Volume

Arginine vasopressin (AVP) is released by the posterior pituitary gland controlled by the hypothalamus. Three primary classes of stimuli lead to AVP release: increased plasma osmolality; decreased baroreceptor and cardiopulmonary receptor firing; and various types of stress, such as physical injury or surgery. In addition, circulating angiotensin II stimulates AVP release. Although AVP is a vasoconstrictor, it is not ordinarily present in plasma in high enough concentrations to exert an effect on blood vessels. However, in special circumstances (e.g., severe hemorrhage) it probably contributes to increased SVR. AVP exerts its major effect on the cardiovascular system by causing the retention of water by the kidneys (see Chapter 24)—an important part of the neural and humoral mechanisms that regulate blood volume.

Atrial Natriuretic Peptide Helps Regulate Blood Volume

Atrial natriuretic peptide (ANP) is a 28-amino acid polypeptide synthesized and stored in the atrial muscle

cells and released into the bloodstream when the atria are stretched. By increasing sodium excretion, it decreases blood volume (see Chapter 24). It also inhibits renin release as well as aldosterone and AVP secretion. Increased ANP (along with decreased aldosterone and AVP) may be partially responsible for the reduction in blood volume that occurs with prolonged bed rest. When central blood volume and atrial stretch are increased, ANP secretion rises, leading to higher sodium excretion and a reduction in blood volume.

Erythropoietin Increases the Production of Erythrocytes

The final step in blood volume regulation is production of erythrocytes. **Erythropoietin** is a hormone released by the kidneys that causes bone marrow to increase production of red blood cells, raising the total mass of circulating red cells. The stimuli for erythropoietin release include hypoxia and reduced hematocrit. An increase in circulating AVP and aldosterone enhances salt and water retention and results in an elevated plasma volume. The increased plasma volume (with a constant volume of red blood cells) results in a lower hematocrit. The decrease in hematocrit stimulates erythropoietin release, which stimulates red blood cell synthesis and, therefore, balances the increase in plasma volume with a larger red blood cell mass.

COMPARISON OF SHORT-TERM AND LONG-TERM BLOOD PRESSURE CONTROL

Different mechanisms are responsible for the short-term and long-term control of blood pressure. Short-term control depends on activation of neural and hormonal responses by the baroreceptor reflexes (described earlier).

Long-term control depends on salt and water excretion by the kidneys. Excretion of salt and water by the kidneys is regulated by some neural and hormonal mechanisms, most of which have been mentioned earlier in this chapter. However, it is also regulated by arterial pressure. Increased arterial pressure results in increased excretion of salt and water—a phenomenon known as **pressure diuresis** (Fig. 18.6). Because of pressure diuresis, as long as mean arterial pressure is elevated, salt and water excretion will exceed the normal rate; this will tend to lower extracellular fluid vol-

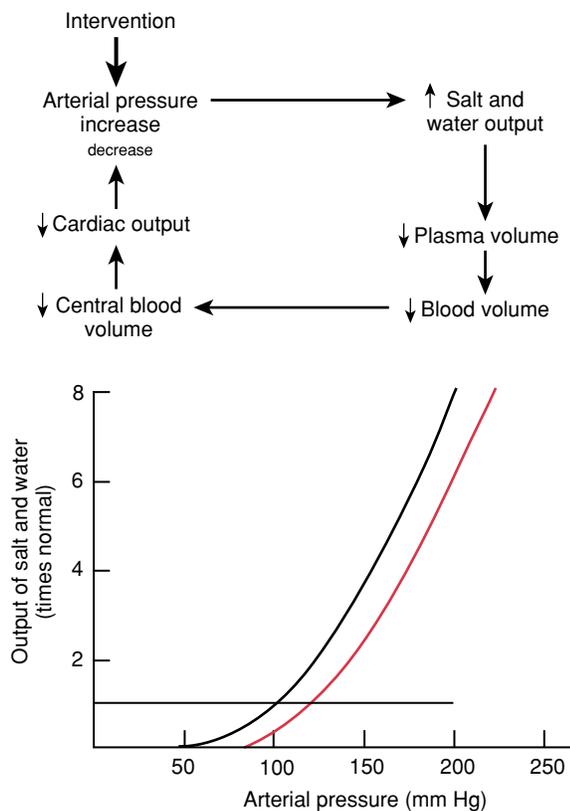


FIGURE 18.6 Regulation of arterial pressure by pressure diuresis. A higher output of salt and water in response to increased arterial pressure reduces blood volume. Blood volume is reduced until pressure returns to its normal level. The curve on the left shows the relationship in a person with normal blood pressure. The curve on the right shows the same relationship in an individual who is hypertensive. Note that the hypertensive individual has an elevated arterial pressure at a normal output of salt and water. (Modified from Guyton AC, Hall JE. *Medical Physiology*. 10th Ed. Philadelphia: WB Saunders, 2000, p. 203.)

ume and, ultimately, blood volume. As discussed earlier in this chapter and in Chapter 15, a decrease in blood volume reduces stroke volume by lowering the end-diastolic filling of the ventricles. Decreased stroke volume lowers cardiac output and arterial pressure. Pressure diuresis persists until it lowers blood volume and cardiac output sufficiently to return mean arterial pressure to a set level. A decrease in mean arterial pressure has the opposite effect on salt and water excretion. Reduced pressure diuresis increases blood volume and cardiac output until mean arterial pressure is returned to a set level.

Pressure diuresis is a slow but persistent mechanism for regulating arterial pressure. Because it persists in altering salt and water excretion and blood volume as long as arterial pressure is above or below a set level, it will eventually return pressure to that level. In hypertensive patients, the curve shown in Figure 18.6 is shifted to the right, so that salt and water excretion are normal at a higher arterial pressure. If this were not the case, pressure diuresis would inexorably bring arterial pressure back to normal.

CARDIOVASCULAR CONTROL DURING STANDING

An integrated view of the cardiovascular system requires an understanding of the relationships among cardiac output, venous return, and central blood volume and how these relationships are influenced by interactions among various neural, hormonal, and other control mechanisms. Consideration of the responses to standing erect provides an opportunity to explore these elements in detail. Figure 18.7 compares venous pressures for the recumbent and standing positions. When a person is recumbent, pressure in the veins of the legs is only a few mm Hg above the pressure in the right atrium. The pressure distending the veins—transmural pressure—is equal to the pressure within the veins of the legs because the pressure outside the veins is atmospheric pressure (the zero-reference pressure).

When a person stands, the column of blood above the lower extremities raises venous pressure to about 50 mm Hg at the femoral level and 90 mm Hg at the foot. This is

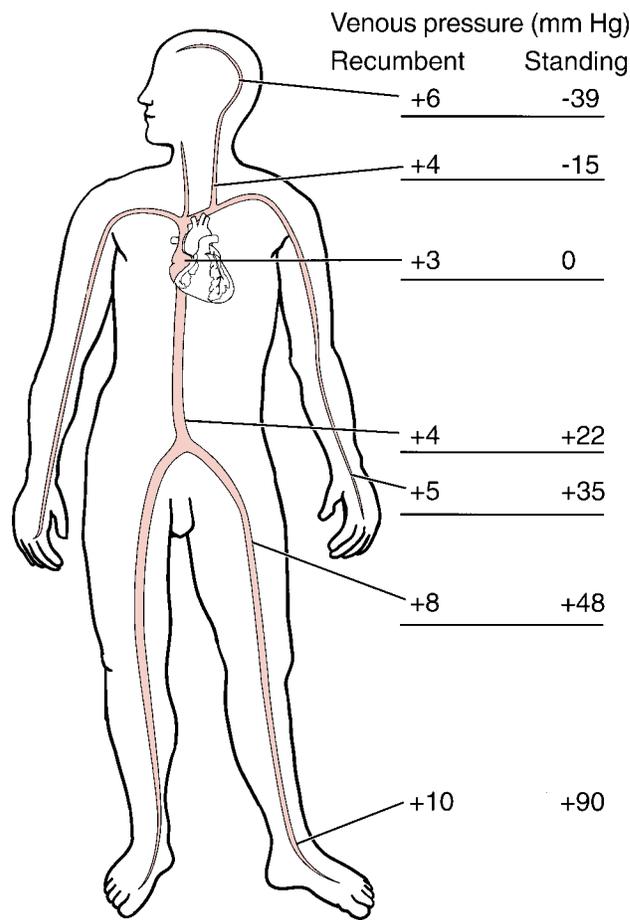


FIGURE 18.7 Venous pressures in the recumbent and standing positions. In this example, standing places a hydrostatic pressure of approximately 80 mm Hg on the feet. Right atrial pressure is lowered because of the reduction in central blood volume. The negative pressures above the heart with standing do not actually occur because once intravascular pressure drops below atmospheric pressure, the veins collapse. These are the pressures that would exist if the veins remained open.

the transmural (distending) pressure because the outside pressure is still zero (atmospheric). Because the veins are highly compliant, such a large increase in transmural pressure is accompanied by an increase in venous volume.

The arteries of the legs undergo exactly the same increases in transmural pressure. However, the increase in their volume is minimal because the compliance of the systemic arterial system is only 1/20th that of the systemic venous system. Standing increases pressure in the arteries and veins of the legs by exactly the same amount, so the added pressure has no influence on the difference in pressure driving blood flow from the arterial to the venous side of the circulation. It only influences the distension of the veins.

Standing Requires a Complex Cardiovascular Response

When a person stands and the veins of the legs are distended, blood that would normally be returned toward the right atrium remains in the legs, filling the expanding veins. For a few seconds after standing, venous return to the heart is lower than cardiac output and, during this time, there is a net shift of blood from the central blood volume to the veins of the legs.

When a 70-kg person stands, central blood volume is quickly reduced by approximately 550 mL. If no compensatory mechanisms existed, this would significantly reduce cardiac end-diastolic volume and cause a more than 60% decrease in stroke volume, cardiac output, and blood pressure; the resulting fall in cerebral blood flow would probably cause a loss of consciousness. If the individual continues to stand quietly for 30 minutes, 20% of plasma volume is lost by net filtration through the capillary walls of the legs. Therefore, quiet standing for half an hour without compensation is the hemodynamic equivalent of losing a

liter of blood. It follows that an adequate cardiovascular response to the changes caused by upright posture—**orthostasis**—is absolutely essential to our lives as bipeds (see Clinical Focus Box 18.1).

The immediate cardiovascular adjustments to upright posture are the baroreceptor- and cardiopulmonary receptor-initiated reflexes, followed by the muscle and respiratory pumps and, later, adjustments in blood volume.

Standing Elicits Baroreceptor and Cardiopulmonary Reflexes

The decreased central blood volume caused by standing includes reduced atrial, ventricular, and pulmonary vessel volumes. These volume reductions unload the cardiopulmonary receptors and elicit a cardiopulmonary reflex. Reduced left ventricular end-diastolic volume decreases stroke volume and pulse pressure as well as cardiac output and mean arterial pressure, leading to decreased firing of aortic arch and carotid baroreceptors. The combined reduction in firing of cardiopulmonary receptors and baroreceptors results in a reflex decrease in parasympathetic nerve activity and an increase in sympathetic nerve activity to the heart.

When a person stands up, the heart rate generally increases by about 10 to 20 beats/min. The increased sympathetic nerve activity to the ventricular myocardium shifts the ventricle to a new function curve and, despite the lowered ventricular filling, stroke volume is decreased to only 50 to 60% of the recumbent value. In the absence of the compensatory increase in sympathetic nerve activity, stroke volume would fall much more. These cardiac adjustments maintain cardiac output at 60 to 80% of the recumbent value. An increase in sympathetic activity also causes arteriolar constriction and increased SVR. The effect of these compensatory changes in heart rate, ventricular con-

CLINICAL FOCUS BOX 18.1

Hypotension

Baroreceptors, volume receptors, chemoreceptors, and pain receptors all help maintain adequate blood pressure during various forms of hemodynamic stress, such as standing and exercise. However, in the presence of certain cardiovascular abnormalities, these mechanisms may fail to regulate blood pressure appropriately; when this occurs, a person may experience transient or sustained **hypotension**. As a practical definition, hypotension exists when symptoms are caused by low blood pressure and, in extreme cases, hypotension may cause weakness, lightheadedness, or even fainting.

Hypotension may be due to neurogenic or nonneurogenic factors. Neurogenic causes include autonomic dysfunction or failure, which can occur in association with other central nervous system abnormalities, such as Parkinson's disease, or may be secondary to systemic diseases that can damage the autonomic nerves, such as diabetes or amyloidosis; vasovagal hyperactivity; hypersensitivity of the carotid sinus; and drugs with sympathetic stimulating or blocking properties. Nonneurogenic causes of hypotension

include vasodilation caused by alcohol, vasodilating drugs, or fever; cardiac disease (e.g., cardiomyopathy, valvular disease); or reduced blood volume secondary to hemorrhage, dehydration, or other causes of fluid loss. In many patients, multiple causative factors are involved.

The treatment of symptomatic hypotension is to eliminate the underlying cause whenever possible, which, in some cases, produces satisfactory results. When this approach is not possible, other adjunctive measures may be necessary, especially when the symptoms are disabling. Common treatment modalities include avoidance of factors that can precipitate hypotension (e.g., sudden changes in posture, hot environments, alcohol, certain drugs, large meals), volume expansion (using salt supplements and/or medications with salt-retaining/volume-expanding properties), and mechanical measures (including tight-fitting elastic compression stockings or pantyhose to prevent the blood from pooling in the veins of the legs upon standing). Unfortunately, even when these measures are employed, some patients continue to have severe, debilitating effects from hypotension.

tractility, and SVR is maintenance of mean arterial pressure. In fact, mean arterial pressure may be increased slightly above the recumbent value.

How is increased sympathetic nerve activity maintained if the mean arterial pressure reaches a value near or above that of the recumbent value? In other words, why doesn't the sympathetic nerve activity return to recumbent levels if the mean arterial pressure returns to the recumbent value? There are two reasons. First, although the mean arterial pressure returns to the same level (or even higher), pulse pressure remains reduced because the stroke volume is decreased to 50 to 60% of the recumbent value. As indicated earlier, the firing rate of the baroreceptors depends on both mean arterial and pulse pressures. Reduced pulse pressure means the baroreceptor firing rate is reduced even if the mean arterial pressure is slightly higher. Second, although mean arterial pressure is returned to the recumbent value, central blood volume remains low. Consequently, the cardiopulmonary receptors continue to discharge at a lower rate, leading to increased sympathetic activity. Some investigators believe it is the decreased stretch of the cardiopulmonary receptors that provides the primary steady state afferent information for the reflex cardiovascular response to standing.

The heart and brain do not participate in the arteriolar constriction caused by increased sympathetic nerve activity during standing; therefore, the blood flow and supply of oxygen and nutrients to these two vital organs are maintained.

Muscle and Respiratory Pumps Help Maintain Central Blood Volume

Although standing would appear to be a perfect situation for increased venoconstriction (which could return some of the blood from the legs to the central blood volume), reflex venoconstriction is a relatively minor part of the response

to standing. A more powerful activation of the baroreceptor reflex, as occurs during severe hemorrhage is required to cause significant venoconstriction. However, two other mechanisms return blood from the legs to the central blood volume. The more important mechanism is the **muscle pump** (Fig. 18.8). If the leg muscles periodically contract while an individual is standing, venous return is increased. Muscles swell as they shorten, and this compresses adjacent veins. Because of the venous valves in the limbs, the blood in the compressed veins can flow only toward the heart. The combination of contracting muscle and venous valves provides an effective pump that transiently increases venous return relative to cardiac output. This mechanism shifts blood volume from the legs to the central blood volume, and end-diastolic volume is increased. Even mild exercise, such as walking, returns the central blood volume and stroke volume to recumbent values (Fig. 18.9).

The **respiratory pump** is the other mechanism that acts to enhance venous return and restore central blood volume (Fig. 18.10). Quiet standing for 5 to 10 minutes invariably leads to sighing. This exaggerated respiratory movement lowers intrathoracic pressure more than usually occurs with inspiration. The fall in intrathoracic pressure raises the transmural pressure of the intrathoracic vessels, causing these vessels to expand. Contraction of the diaphragm simultaneously raises intraabdominal pressure, which compresses the abdominal veins. Because the venous valves prevent the backflow of blood into the legs, the raised intraabdominal pressure forces blood toward the intrathoracic vessels (which are expanding because of the lowered intrathoracic pressure). The seesaw action of the respiratory pump tends to displace extrathoracic blood volume toward the chest and raise right atrial pressure and stroke volume. Figure 18.11 provides an overview of the main cardiovascular events associated with a short period of standing.

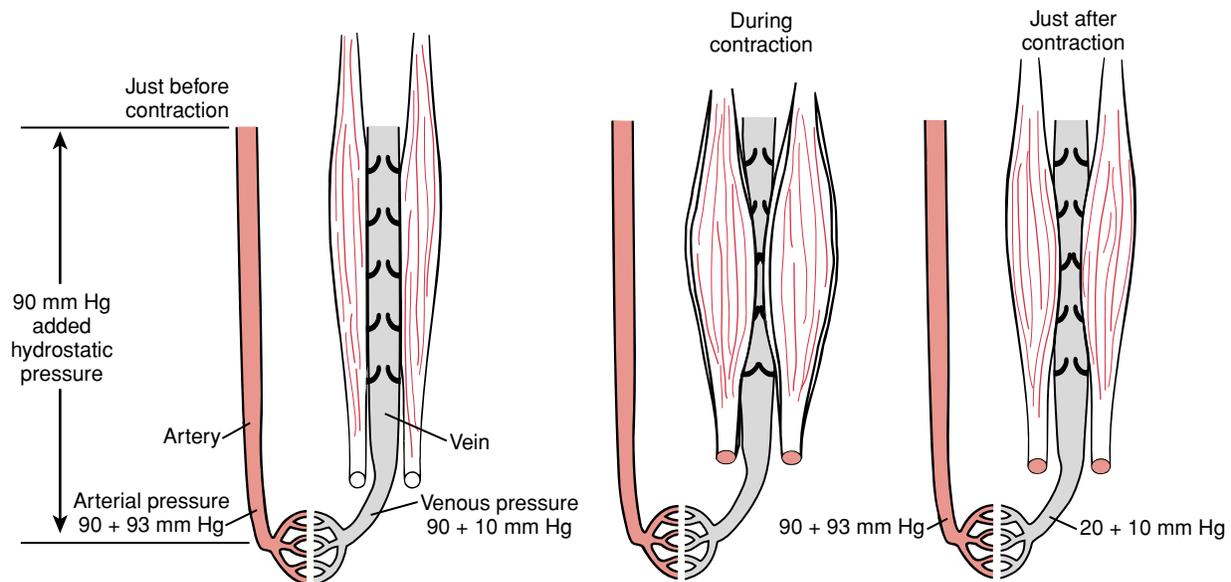


FIGURE 18.8 Muscle pump. This mechanism increases venous return and decreases venous volume. The valves (which are closed after contraction) break up the hydro-

static column of blood, lowering venous (and capillary) hydrostatic pressure.

blood above the capillaries of the legs and feet raises capillary hydrostatic pressure and filtration. During a period of 30 minutes, a 10% loss of blood volume into the interstitial space can occur. This loss, coupled with the 550 mL displaced by redistribution from the central blood volume into the legs, causes central blood volume to fall to a level so low that reflex sympathetic nerve activity cannot maintain cardiac output and mean arterial pressure. Diminished cerebral blood flow and a loss of consciousness (fainting) result.

Arteriolar constriction due to the increased reflex sympathetic nerve activity tends to reduce capillary hydrostatic pressure. However, this alone does not bring capillary hydrostatic pressure back to normal because it does not affect the hydrostatic pressure exerted on the capillaries from the venous side. The muscle pump is the most important factor counteracting increased capillary hydrostatic pressure. The alternate compression and filling of the veins as the muscle pump works means the venous valves are closed most of the time. When the valves are closed, the hydrostatic column of blood in the leg veins at any point is only as high as the distance to the next valve.

The myogenic response of arterioles to increased transmural pressure also acts to oppose filtration. As discussed earlier, raising the transmural pressure stretches vascular smooth muscle and stimulates it to contract. This is especially true for the myocytes of precapillary arterioles. The elevated transmural pressure associated with standing causes a myogenic response and decreases the number of open capillaries. With fewer open capillaries, the filtration rate for a given capillary hydrostatic pressure imbalance is less.

In addition to the factors cited above, other safety factors against edema are important for preventing excessive

translocation of plasma volume into the interstitial space (see Chapter 16). These factors, together with neural and myogenic responses and the muscle and respiratory pumps, play a significant role during the seconds and minutes following standing (Fig. 18.12). The combination of all of these factors minimizes net capillary filtration, making it possible to remain standing for long periods.

Long-Term Responses Defend Venous Return During Prolonged Upright Posture

In addition to the relatively short-term cardiovascular responses, there are equally important long-term adjustments to orthostasis. These are observed in patients confined to bed (or astronauts not subject to the force of gravity). In people who are bedridden, intermittent upright posture does not shift the distribution of blood volume from the thorax to the legs. During the course of a day, average central blood volume (and pressure) is greater than in a person who is periodically standing up in the presence of gravity. The average increase in central blood volume caused by ex-

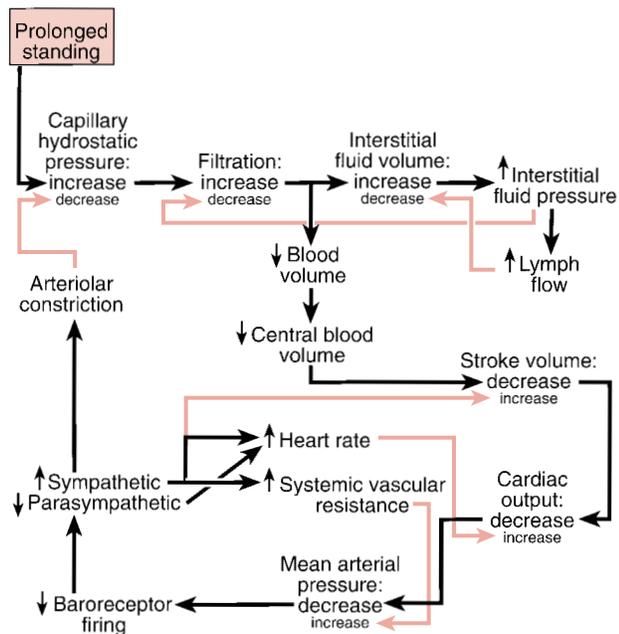


FIGURE 18.12 Effects of prolonged standing. With prolonged standing, capillary filtration reduces venous return. Without the compensatory events that result in the changes shown in small type, prolonged standing would inevitably lead to fainting.

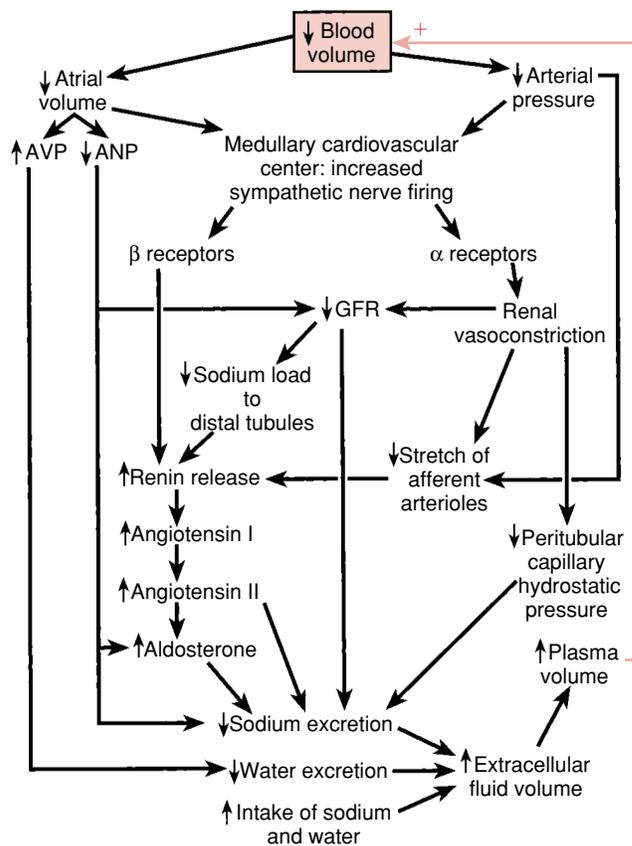


FIGURE 18.13 Regulation of blood volume. Blood loss influences sodium and water excretion by the kidney via several pathways. All these pathways, combined with an increased intake of salt and water, restore the extracellular fluid volume and, eventually, blood volume. These responses occur later than those shown in Figures 18.10, 18.11, and 18.12. The pathways responsible for stimulating an increased intake of salt and water are not shown. AVP, arginine vasopressin; ANP, atrial natriuretic peptide; GFR, glomerular filtration rate.

tended bed rest results in reduced activity of all of the pathways that increase blood volume in response to standing. The reduction in total blood volume begins during the first day and is quantitatively significant after a few days. At this point, standing becomes difficult because blood volume is not adequate to sustain a normal blood pressure. Looking at it another way, maintaining an erect posture in the earth's gravitational field results in increased blood volume. This increase, proportioned between the extrathoracic and intrathoracic vessels, augments stroke volume during standing. If blood volume is not maintained by intermittent erect posture, standing becomes extremely difficult or impossible because of **orthostatic hypotension**—diminished blood pressure associated with standing.

The long-term regulation of blood volume is driven by changes in plasma volume accomplished by sympathetic nervous system effects on the kidneys; hormonal changes, including RAAS, AVP, and ANP; and alterations in pressure diuresis. Figure 18.13 depicts several components of plasma volume regulation by showing their response to a moderate (approximately 10%) blood loss, which is easily compensated for in healthy individuals.

Plasma is a part of the extracellular compartment and is subject to the factors that regulate the size of that space. The osmotically important electrolytes of the extracellular fluid are the sodium ion and its main partner, the chloride ion. The control of extracellular fluid volume is determined by the balance between the intake and excretion of sodium and water. This topic is discussed in depth in Chapter 24. Sodium excretion is much more closely regulated than sodium intake. Excretion of sodium is determined by the glomerular filtration rate, the plasma concentrations of aldosterone and ANP, and a variety of other factors, including angiotensin II.

Glomerular filtration rate is determined by glomerular capillary pressure, which is dependent on precapillary (afferent arteriolar) and postcapillary (efferent arteriolar) resistance and arterial pressure. Decreased mean arterial pressure and/or afferent arteriolar constriction tends to result in lowered glomerular capillary pressure, less filtration of fluid, and lower sodium excretion. Changes in glomerular capillary pressure are primarily the result of changes in sympathetic nerve activity and plasma angiotensin II and ANP concentrations.

Aldosterone acts on the distal nephron to cause increased reabsorption of sodium and, thereby, decrease its excretion. Aldosterone released from the adrenal cortex is increased by (among other things) angiotensin II. Water intake is determined by thirst and the availability of water.

The excretion of water is strongly influenced by AVP. Increased plasma osmolality, sensed by the hypothalamus, results in both thirst and increased AVP release. Thirst and AVP release are also increased by decreased stretch of baroreceptors and cardiopulmonary receptors.

Consider how these physiological variables are altered by an upright posture to produce an increase in the extracellular fluid volume. Renal arteriolar vasoconstriction associated with increased sympathetic nerve activity produced by standing reduces the glomerular filtration rate. This results in a decrease in filtered sodium and tends to decrease sodium excretion. The increased sympathetic nerve activity to the kidney also triggers the release of renin, which increases circulating angiotensin II and, in turn, aldosterone release. The decrease in central blood volume associated with standing reduces cardiopulmonary stretch receptor activity, causing an increased release of AVP from the posterior pituitary. Therefore, both sodium and water are retained and thirst is increased. Regulation of the precise quantities of water and sodium that are excreted maintains the correct osmolality of the plasma.

The distribution of extracellular fluid between plasma and interstitial compartments is determined by the balance of hydrostatic and colloid osmotic forces across the capillary wall. Retention of sodium and water tends to dilute plasma proteins, decreasing plasma colloid osmotic pressure and favoring the filtration of fluid from the plasma into the interstitial fluid. However, as increased synthesis of plasma proteins by the liver occurs, a portion of the retained sodium and water contributes to an increase in plasma volume.

Finally, the increase in plasma volume (in the absence of any change in total red cell volume) decreases hematocrit, which stimulates erythropoietin release and erythropoiesis. This helps total red blood cell volume keep pace with plasma volume.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. A person has cold, painful fingertips because of excessively constricted blood vessels in the skin. Which of the following alterations in autonomic function is most likely to be involved?
 - (A) Low concentration of circulating epinephrine
 - (B) High sensitivity of arterioles to norepinephrine
 - (C) High sensitivity of arterioles to nitric oxide
 - (D) Low parasympathetic nerve activity
 - (E) Arterioles insensitive to epinephrine
2. In the presence of a drug that blocks all effects of norepinephrine and epinephrine on the heart, the autonomic nervous system can
 - (A) Raise the heart rate above its intrinsic rate
 - (B) Lower the heart rate below its intrinsic rate
 - (C) Raise and lower the heart rate above and below its intrinsic rate
 - (D) Neither raise nor lower the heart rate from its intrinsic rate
3. The cold pressor response is initiated by stimulation of
 - (A) Baroreceptors
 - (B) Cardiopulmonary receptors
 - (C) Hypothalamic receptors
 - (D) Pain receptors
 - (E) Chemoreceptors

(continued)

4. Which of the following occurs when acetylcholine binds to muscarinic receptors?
 (A) Heart rate slows
 (B) Cardiac conduction velocity rises
 (C) Norepinephrine release from sympathetic nerve terminals is enhanced
 (D) Nitric oxide release from endothelial cells is inhibited
 (E) Blood vessels of the external genitalia constrict
5. Carotid baroreceptors
 (A) Are important in the rapid, short-term regulation of arterial blood pressure
 (B) Do not fire until a pressure of approximately 100 mm Hg is reached
 (C) Adapt over 1 to 2 weeks to the prevailing mean arterial pressure
 (D) Stretch reflexively decreases cerebral blood flow
 (E) Reflexively decrease coronary blood flow when blood pressure falls
6. Which of the following is true with respect to peripheral chemoreceptors?
 (A) Activation is important in inhibiting the diving response
 (B) Activity is increased by increased pH
 (C) They are located in the medulla oblongata, but not the hypothalamus
 (D) Activation is important in the cardiovascular response to hemorrhagic hypotension
 (E) Activity is increased by lowering of the oxygen content, but not the PO_2 , of arterial blood
7. Parasympathetic stimulation of the heart accompanied by a withdrawal of sympathetic tone to most of the blood vessels of the body is characteristic of
 (A) The fight-or-flight response
 (B) Vasovagal syncope
 (C) Exercise
 (D) The diving response
 (E) The cold pressor response
8. A patient suffers a severe hemorrhage resulting in a lowered mean arterial pressure. Which of the following would be elevated *above normal* levels?
 (A) Splanchnic blood flow
 (B) Cardiopulmonary receptor activity
 (C) Right ventricular end-diastolic volume
 (D) Heart rate
 (E) Carotid baroreceptor activity
9. A person stands up. Compared with the recumbent position, 1 minute after standing, the
 (A) Skin blood flow increases
 (B) Volume of blood in leg veins increases
 (C) Cardiac preload increases
 (D) Cardiac contractility decreases
 (E) Brain blood flow decreases
10. Pressure diuresis lowers arterial pressure because it
 (A) Lowers renal release of renin
 (B) Lowers systemic vascular resistance
 (C) Lowers blood volume
 (D) Causes renal vasodilation
 (E) Increases baroreceptor firing
11. Central blood volume is decreased by
 (A) The muscle pump
 (B) The respiratory pump
 (C) Increased excretion of salt and water

- (D) Lying down
 (E) Living in a space station

SUGGESTED READING

- Champléau MW. Arterial baroreflexes. In: Izzo JL, Black HR, eds. *Hypertension Primer*. Baltimore: Lippincott Williams & Wilkins, 1999.
- Dampney RA. Functional organization of central pathways regulating the cardiovascular system. *Physiol Rev* 1994;74:323–364.
- Hainsworth R, Mark AL, eds. *Cardiovascular Reflex Control in Health and Disease*. London: WB Saunders, 1993.
- Katz AM. *Physiology of the Heart*. 3rd Ed. New York: Lippincott Williams & Wilkins, 2001.
- Mohanty PK. Cardiopulmonary baroreflexes. In: Izzo JL, Black HR, eds. *Hypertension Primer*. Baltimore: Lippincott Williams & Wilkins, 1999.
- Reis DJ. Functional neuroanatomy of central vasomotor control centers. In: Izzo JL, Black HR, eds. *Hypertension Primer*. Baltimore: Lippincott Williams & Wilkins, 1999.
- Rowell LB. *Human Cardiovascular Control*. New York: Oxford University Press, 1993.
- Waldrop TG, Eldridge FL, Iwamoto GA, Mitchell JH. Central neural control of respiration and circulation during exercise. In: Rowell LB, Shepherd JT, eds. *Handbook of Physiology, Section 12. Exercise: Regulation and integration of multiple systems*. New York: Oxford University Press, 1996.

CASE STUDIES FOR PART IV ● ● ●

CASE STUDY FOR CHAPTER 11

Chronic Granulomatous Disease of Childhood

An 18-month-old boy, with a high fever and cough and with a history of frequent infections, was brought to the emergency department by his father. A blood examination shows elevated numbers of neutrophils, but no other defects. A blood culture for bacteria is positive. The physician sent a sample of the boy's blood to a laboratory to test the ability of the patient's neutrophils to produce hydrogen peroxide. The ability of this patient's neutrophils to generate hydrogen peroxide is found to be completely absent.

Questions

1. What cellular defect may have led to the complete absence of hydrogen peroxide generation in this patient's neutrophils?
2. How might this disease be treated using hematotherapy?

Answers to Case Study Questions for Chapter 11

1. The disease, chronic granulomatous disease of childhood, results from a congenital lack of the superoxide-forming enzyme NADPH oxidase in this patient's neutrophils. The lack of this enzyme results in deficient hydrogen peroxide generation by these cells when they ingest or phagocytose bacteria, resulting in a compromised capacity to combat recurrent, life-threatening bacterial infections.
2. Normal neutrophil stem cells grown in culture may be infused to supplement the patient's own defective neutrophils. In addition, researchers are now trying to genetically reverse the defect in cultures of a patient's stem cells for subsequent therapeutic infusion.

Reference

Baehner RL. Chronic granulomatous disease of childhood: Clinical, pathological, biochemical, molecular, and genetic aspects of the disease. *Pediatr Pathol* 1990;10:143–153.

CASE STUDY FOR CHAPTER 12

Congestive Heart Failure (Arteriovenous Fistula)

A 29-year-old man presented to his physician with fatigue, shortness of breath, and progressive ankle edema. These signs and symptoms had been worsening slowly for 3 months. His medical history included a motor vehicle accident 4 months ago, during which he sustained a deep puncture wound to the right thigh. The wound was closed with skin sutures on the day of the accident and had healed, although the area around the injury remained tender.

On physical examination, his resting blood pressure is 90/60 mm Hg and his heart rate is 122 beats/min. He appears ill and has shortness of breath at rest. Bilateral lung crackles are present. Pitting edema is evident in both legs, but is worse on the right. His pulses are intact, but the amplitude of the right femoral pulse is increased. A continuous bruit is present over the scar from his previous puncture injury. The superficial veins in the right thigh are prominent and appear distended.

Questions

1. What is the cause of the femoral bruit?
2. Why does the patient have fatigue, shortness of breath, leg edema, lung crackles, and an elevated heart rate?

Answers to Case Study Questions for Chapter 12

1. The patient has an arteriovenous (A-V) fistula caused by his previous puncture injury. During the injury, both the artery and the adjacent vein in the thigh were severed; the vessels healed but, during the healing process, a direct connection formed between the artery and the adjacent vein. The velocity of flow from the artery to the vein is very high; it produces turbulence and a bruit.
2. A large A-V fistula, such as this one, allows a substantial amount of the cardiac output to be shunted directly from the arterial system to the venous system, without passing through the resistance vessels. The lowered systemic vascular resistance leads to a lower arterial pressure. Compensatory mechanisms increase heart rate and cardiac output. However, continuous delivery of a high cardiac output for months causes the heart muscle to fail. As the heart muscle fails, the output of the heart cannot be maintained. This results in the accumulation of fluid in the lungs, causing crackles and shortness of breath, and in the legs, where it appears as pitting edema. Because so much blood is shunted directly to the venous circulation, there is reduced availability of arterial blood for many tissues, including skeletal muscle, thereby, causing fatigue.

References

Schneider M, Creutzig A, Alexander K. Untreated arteriovenous fistula after World War II trauma. *Vasa* 1996;25:174–179.
Wang KT, Hou CJ, Hsieh JJ, et al. Late development of renal arteriovenous fistula following gunshot trauma—a case report. *Angiology* 1998;49:415–418.

CASE STUDY FOR CHAPTER 13

Atrial Fibrillation

A 58-year-old woman arrived in the emergency department complaining of sudden onset of palpitations, light-headedness, and shortness of breath. These symptoms began approximately 2 hours previously. On examination, her blood pressure is 95/70 mm Hg, and the heart rate is 140 beats/min. An ECG demonstrates atrial fibrillation. The physical examination is otherwise unremarkable.

Questions

1. Explain why the patient has these symptoms.
2. Explain how medications could be useful in this setting.
3. While in the emergency department, the patient's symptoms worsened. What immediate action could be taken to stabilize or treat the patient?

Answers to Case Study Questions for Chapter 13

1. During atrial fibrillation, the AV node is incessantly stimulated. Depending upon the conduction velocity and refractory period of the node, the ventricular rate may be from 100 to more than 200 beats/min. When the ventricular rate is extremely rapid, there is little opportunity for ventricular filling to occur; despite the high heart rate, cardiac output falls in this setting (see Chapter 14). This leads to hypotension and associated symptoms such as light-headedness and shortness of breath.
2. Drugs that can slow down conduction through the AV node are useful in treating atrial fibrillation. These included digitalis, beta blockers, and calcium entry blockers. By slowing AV nodal conduction, these drugs reduce the rate of excitation of the ventricles. At a slower ventricular rate, there is more time for filling, and the output of the heart is increased.
3. Atrial fibrillation can be terminated by electrical cardioversion. In this procedure, a strong electrical current is passed through the heart to momentarily depolarize the entire heart. As repolarization occurs, a normal, coordinated rhythm is reestablished.

Reference

Shen W-K, Holmes DR Jr, Packer DL. Cardiac arrhythmias. In: Giuliani ER, Nishimura RA, Holmes DR Jr, eds. *Mayo Clinic Practice of Cardiology*. 3rd Ed. St. Louis: CV Mosby, 1996;727–747.

CASE STUDY FOR CHAPTER 14

Left Ventricular Hypertrophy (Aortic Stenosis)

A 72-year-old woman presented to her physician with a complaint of poor exercise tolerance and dyspnea on exertion. Cardiac auscultation reveals a fourth heart sound and a loud systolic murmur heard best at the base of the heart. The murmur radiates into the region of the carotid artery. The carotid pulses are reduced in amplitude and feel “dampened.” The ECG indicates left ventricular hypertrophy.

Questions

1. Why does the patient have a murmur?
2. Why has left ventricular hypertrophy developed?
3. How should this condition be managed?

Answers to Case Study Questions for Chapter 14

1. The aortic valve of this patient has become narrowed and calcified (aortic stenosis). Because blood must squeeze through the narrowed orifice, flow velocity increases and the blood flow becomes turbulent. This turbulence creates a murmur during cardiac systole (when blood is ejected through the valve).
2. To eject blood through the narrowed aortic valve, the ventricle must develop higher pressure during systole. In response to a sustained increase in afterload, hypertrophy of the muscle of the left ventricle occurs.
3. When symptoms develop and left ventricular enlargement is present, aortic stenosis is best treated with surgery. The valve can be replaced with a prosthetic valve.

Reference

Rahimtoola SH. Aortic stenosis. In: Fuster V, Alexander RW, O'Rourke FA, eds. *Hurst's the Heart*. 10th Ed. New York: McGraw-Hill, 2001.

CASE STUDY FOR CHAPTER 15

Pulmonary Embolism

A 68-year-old man receiving chemotherapy for colon cancer experienced the sudden onset of chest discomfort and shortness of breath. His blood pressure is 100/75 mm Hg and his heart rate is 105 beats/min. The physical examination is unremarkable except for swelling and tenderness in the left leg, which began about 3 days earlier. The ECG shows no changes suggestive of cardiac ischemia.

Questions

1. How are the patient's chest discomfort, shortness of breath, arterial hypotension, tachycardia, and left leg symptoms explained?
2. Is right ventricular pressure likely to be increased or decreased? Why?
3. Would intravenous infusion of additional fluids (such as blood or plasma) help the patient's arterial blood pressure?

Answers to Case Study Questions for Chapter 15

1. The patient's symptoms are caused by pulmonary embolism. In this condition, a piece of blood clot located in a peripheral vein (in this case, a leg vein) breaks off and is carried through the right heart to a pulmonary artery where it lodges. Patients with certain medical problems, including cancer, have altered clotting mechanisms and are at risk of forming these clots. When this occurs, blood flow from the pulmonary artery to the left heart is obstructed (i.e., pulmonary vascular resistance increases), resulting in elevated pulmonary arterial pressure. The sudden rise in pressure causes distension of the artery, which may contribute to the sensation of chest discomfort. Increased pulmonary arterial pressure (pulmonary hypertension) leads to right heart failure. Because left atrial (and left ventricular) filling is reduced (as a result of lack of blood flow from the lungs), left-side cardiac output also falls. The fall in cardiac output causes a reflex increase in heart rate. The result is a combination of right- and left-side heart failure, producing the signs and symptoms seen in this patient.
2. The right ventricular pressure is likely to be increased because the blood clot in the pulmonary artery acts as a form of obstruction that raises the pulmonary artery resistance.
3. The problem here is increased afterload of the right ventricle caused by partial obstruction of the outflow tract. Because of this obstructed outflow, the diastolic volume of the right ventricle is already high. It is unlikely that infusing additional fluids into the veins will improve cardiac output because the extra filling of the right ventricle is unlikely to increase the force of contraction.

Reference

Brownell WH, Anderson FA Jr. Pulmonary embolism. In: Gloviczki P, Yao JST, eds. *Handbook of Venous Disorders: Guidelines of the American Venous Forum*. London: Chapman & Hall, 1996;274.

CASE STUDY FOR CHAPTER 16

Diabetic Microvascular Disease

A 48-year-old man went for a vision examination because his eyesight had been blurry for the past several months. His optometrist referred him to his family physician after seeing a few areas of dense clumps of capillaries over the retinas of both eyes.

The family physician finds fasting blood plasma glucose of 297 mg/dL. The man states he has had periods of

tingling and numbness in his toes for a few weeks, which he attributes to gaining over 35 kg during the past 3 years.

Questions

1. Why were capillaries overgrowing the retina? Is this ever a normal finding?
2. Why does an elevated plasma glucose concentration during fasting indicate serious diabetes mellitus? Why does a large weight gain potentially lead to diabetes mellitus?
3. How might odd sensations in the feet be related to diabetes mellitus and microvascular disease?
4. What are the immediate and long-term treatments for minimizing further microvascular disease?

Answers to Case Study Questions for Chapter 16

1. The formation of clumps of capillaries over the retina is usually diagnostic for microvascular complications of diabetes mellitus and is rarely seen in other diseases. The capillaries probably overgrow the retina because they are attempting to replace capillaries that die off as a consequence of the disease.
2. A moderate elevation of blood glucose concentration after a carbohydrate meal can happen, but it should not exceed 140 to 150 mg/dL. Such a high blood glucose represents a major loss in the regulation of glucose metabolism. The patient is seriously overweight and is likely insulin-resistant. He has ample insulin but the cellular response to insulin is inadequate. The suppressed insulin response develops after repeated and sustained high insulin concentrations associated with excessive carbohydrate intake.
3. The peripheral sensory nerves of the body are nourished by microscopic blood vessels, and the loss of even a few vessels can alter the physiology of a nerve. An altered sensory nerve may fire too frequently, causing odd sensations, or not fire at all, causing numbness. Neuropathy or nerve impairment of the lower body is one of the most common problems in diabetes mellitus.
4. Even though this patient would likely have a high insulin concentration, additional insulin is required to stimulate the cells to take up glucose. However, pharmacological treatment could gradually be decreased or discontinued with a major change in diet, amount of body fat, and exercise level. Loss of body fat is associated with a progressive improvement in glucose metabolism. Exercise improves the ability of skeletal muscle cells to take up and burn glucose without the presence of insulin or at reduced insulin concentration.

Reference

Dahl-Jorgensen K. Diabetic microangiopathy. *Acta Paediatr Suppl* 1998;425:31–34.

CASE STUDY FOR CHAPTER 17

Coronary Artery Disease

A 57-year-old man experienced several months of vague pains in his left chest and shoulder when climbing stairs. During a touch football game at a family picnic, he had much more intense pain and had to rest. After about 45 minutes of intermittent pain, his family brought him to the emergency department.

His heart rate is 105 beats/min, his blood pressure is 105/85 mm Hg, and his hands and feet are cool to touch and somewhat bluish. He is sweating and is short of breath. An electrocardiogram indicates an elevated ST segment, which was most noticeable in leads V4 to V6. The attending cardiologist administers streptokinase intravenously.

One hour later, the ST segment abnormality is less noticeable. The heart rate is 87 beats/min, the arterial blood pressure is 120/85 mm Hg, and the patient's hands and feet are pink and warm. The patient is alert, not sweating, and does not complain of chest pain or shortness of breath.

During a 4-day stay in the hospital, percutaneous angioplasty was performed to open several partially blocked coronary arteries. The patient is told to take half of an adult aspirin pill every day and is given a prescription of a statin drug to lower blood lipids. In addition, he is assigned to a cardiac rehabilitation program designed to teach proper dietary habits and improve exercise performance and, together, to lower gradually body fat.

Questions

1. How did the left chest and shoulder pain during stair climbing predict some abnormality of coronary artery function?
2. Why was a 45-minute delay before going for medical intervention after intense pain started inappropriate for the man's health?
3. How does the lower than normal arterial pressure, smaller than normal arterial pulse pressure, and decreased blood flow to the hands and feet indicate impairment of the contractile function of the heart?
4. How did the streptokinase improve performance of the heart?
5. How is aspirin useful to protect the coronary vasculature from occlusions by blood clots?
6. How might lowering the low-density lipoproteins and raising the high-density lipoproteins with a combination of diet, exercise, and statin therapy lessen the chance of a second heart attack?

Answers to Case Study Questions for Chapter 17

1. The exercise of stair climbing imposed a substantial demand on the heart to pump blood, thereby, requiring more oxygen for the heart cells. Partially occluded arteries did not provide sufficient blood flow to provide the needed oxygen and hypoxia resulted. Coronary artery problems leading to mild hypoxia of the heart muscle typically cause a referred pain to the left chest and shoulder area. In some persons, the pain extends into the left arm and hand, as well as neck and jaw.
2. There is a major risk that cardiac hypoxia will initiate abnormal electrical activity in the heart. The results can range from mild disturbances of conduction to rapidly lethal ventricular fibrillation. In addition, the longer cardiac cells are without adequate blood flow, the more damage is done to the cells. The sooner oxygenation is restored, the less repair is needed in the heart tissue.
3. When the contractile ability of the heart is compromised, the typical result is a reduced stroke volume, which would explain the decreased pulse pressure. If cardiac output decreases, in spite of an increased heart rate, then arterial pressure tends to fall. The decreased blood flow to the hands and feet indicates that the sympathetic nervous system has been activated to constrict peripheral blood vessels, preserving the arterial pressure as much as possible in the presence of reduced cardiac function.
4. Streptokinase is a bacterial product that activates plasminogen, which leads to clot dissolution. Blood flow and oxygen supply to the downstream muscle will then be restored. If the muscle cells are not seriously injured, they will show prompt recovery of contractile function to restore the stroke volume and cardiac output.
5. Aspirin blocks the cyclooxygenase enzymes in all cells. With aspirin present, platelets are far less likely to be activated,

limiting clot formation in areas of vessels with damaged endothelial cells. The production of prostaglandins by platelets is part of the clotting process. Also, thromboxane released by activated platelets will cause constriction of coronary arteries and arterioles, lowering blood flow in an already flow-deprived state.

6. Although regression of plaques is not dramatic when low-density lipoproteins are reduced, continued growth of the plaque is decreased and, in some cases, virtually stopped. This lowers the probability of a plaque rupturing and starting the formation of a new clot that will occlude the artery. In addition, lowering the LDL concentration will limit the formation of new plaques and, thereby, reduces the risk of vessel occlusion.

Reference

Lilly LS. Pathophysiology of Heart Disease. Baltimore: Williams & Wilkins, 1998.

CASE STUDY FOR CHAPTER 18

Hypertension

During a routine health assessment, a 52-year-old man was found to have a blood pressure of 180/95 mm Hg. He reported no significant health problems except "my blood pressure has always been a little high."

The physical examination, including an evaluation of the heart, eyes (including the blood vessels of the retina), and the peripheral pulses, is entirely normal. The resting heart rate is 87 beats/min.

Questions

1. How do changes in cardiac output or systemic vascular resistance affect arterial blood pressure?
2. Why did the physician examine the heart, eyes, and peripheral pulses?
3. Explain how drugs might lower the blood pressure by affecting β_1 -adrenergic receptors, α_1 -adrenergic receptors, intravascular fluid volume, the renin-angiotensin-aldosterone system, and intracellular calcium ion levels.

Answers to Case Study Questions for Chapter 18

1. Anything that increases cardiac output or SVR can cause an increase in arterial blood pressure. When this increase is sustained and significant, it is referred to as hypertension.
2. Chronic hypertension can damage many organs and tissues, some of which may be detected by physical examination. The heart can undergo left ventricular hypertrophy as a result of increased afterload. The blood vessels of the eye can become thickened and sclerotic. Because hypertension can contribute to atherosclerosis, the peripheral pulses may become diminished. Other organs, such as the kidneys, may also be damaged by hypertension, but these abnormalities require specific laboratory testing to evaluate and usually cannot be assessed by physical examination.
3. β_1 -Adrenergic blockers reduce heart rate and contractility of the heart and lower cardiac output and blood pressure. They also block ability of the sympathetic nervous system to stimulate the release of renin. Drugs that block α_1 -adrenergic receptors reduce peripheral vasoconstriction and thus lower SVR. Drugs that reduce intravascular fluid volume (diuretics such as furosemide or hydrochlorothiazide) reduce preload and, thereby, lower cardiac output and arterial pressure. Drugs that interfere with the RAAS (e.g., by blocking the effect of angiotensin-converting enzyme or by directly blocking the actions of angiotensin II) reduce blood pressure by preventing the vasoconstriction and sodium retention that would otherwise occur when the RAAS is acti-

vated. Calcium blockers diminish cardiac contractility (a determinant of cardiac output) and vascular smooth muscle contraction (a determinant of SVR). These drugs work by decreasing the cytosolic concentration of calcium ion by blocking either its entry or its release into the cytosol of cardiac or smooth muscle cells.

References

- Izzo JL, Black HR, eds. Hypertension Primer. Baltimore: Lippincott Williams & Wilkins, 1999.
- Vidt DG. Hypertension. In: Young JR, Olin JW, Bartholomew JR, eds. Peripheral Vascular Diseases. 2nd Ed. St. Louis: CV Mosby, 1996;189.
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