Lecture 13

Physiology of the cardiovascular system.

Plan.

1. **Cardiac Output and Its Control**
2. **Laws of hemodynamics.**
3. **Capillary Exchange and Regulation of Interstitial Fluid Volume**
4. **Control of Blood Flow**
5. **Short-Term Regulation of Blood Pressure**
6. **Long-Term Regulation of Blood Pressure**

Cardiac Output and Its Control.

Cardiac output (CO) is the volume of blood pumped by each ventricle per minute (not the total amount of blood pumped by the heart). During any period of time, the volume of blood flowing through the pulmonary circulation is the same as the volume flowing through the systemic circulation. Therefore, the cardiac output from each ventricle normally is the same, although on a beat-to-beat basis, minor variations may occur.

The two determinants of cardiac output are heart rate(beats per minute) and stroke volume(volume of blood pumped per beat or stroke). The average resting heart rate is 70 beats per minute, established by SA node rhythmicity; the average resting stroke volume is 70 ml per beat, producing an average cardiac output of 4900 ml/min, or close to 5 liters/min:

Cardiac output (CO) =| heart rate x stroke volume

| 70 beats/min x 70 ml/beat = | 4900 ml/min = 5 liters/min

During exercise, cardiac output can increase to 20 to 25 liters per minute, and outputs as high as 40 liters per minute have been recorded in trained athletes during heavy endurance-type exercise. The difference between the cardiac output at rest and the maximum volume of blood the heart can pump per minute is called the cardiac reserve.

How can cardiac output vary so tremendously, depending on the demands of the body? You can readily answer this question by thinking about how your own heart pounds rapidly (increased heart rate) and forcefully (increased stroke volume) when you engage in strenuous physical activities (need for increased cardiac output). Thus, regulation of cardiac output depends on the control of both heart rate and stroke volume, topics that we discuss next.

Heart rate is determined primarily by autonomic influences on the SA node. The SA node is normally the pacemaker of the heart because it has the fastest spontaneous rate of depolarization to threshold.

When the SA node reaches threshold, an action potential is initiated that spreads throughout the heart, inducing the heart to contract, or have a “heartbeat.” This happens about 70 times per minute, setting the average heart rate at 70 beats per minute. The heart is innervated by both divisions of the autonomic nervous system, which can modify the rate (as well as the strength) of contraction, even though nervous stimulation is not required to initiate contraction. **The parasympathetic nerve** to the heart, the vagus nerve, primarily supplies the atrium, especially the SA and AV nodes. Parasympathetic innervation of the ventricles is sparse. **The cardiac sympathetic nerves** also supply the atria, including the SA and AV nodes, and richly innervate the ventricles as well.

Both the parasympathetic and sympathetic nervous system bring about their effects on the heart primarily by altering the activity of **the cyclic AMP** second-messenger system in the innervated cardiac cells. Acetylcholine released from the vagus nerve binds to a muscarinic receptor and is coupled to an inhibitory G protein that reduces activity of the cyclic AMP. By contrast, the sympathetic neurotransmitter norepinephrine binds with a 1adrenergic receptor and is coupled to a stimulatory G protein that accelerates the cyclic AMP pathway in the target cells. The cAMP pathway leads to phosphorylation and altered activity of various proteins within cardiac muscle, for example, keeping channels open longer.

Effect of parasympathetic stimulation on the heart.

Parasympathetic stimulation decreases the SA node's rate of spontaneous depolarization, prolonging the time required to drift to threshold. Therefore, the SA node reaches threshold and fires less frequently, decreasing the heart rate.

Parasympathetic stimulation decreases the AV node's excitability, prolonging transmission of impulses to the ventricles even longer than the usual AV nodal delay.

Parasympathetic stimulation of the atrial contractile cells shortens the plateau phase of the action potential by reducing the slow inward current carried by Ca^{2+} . As a result, atrial contraction is weakened.

The parasympathetic system has little effect on ventricular contraction because of the sparseness of parasympathetic innervation to the ventricles.Thus, the heart is more "leisurely" under parasympathetic influence—it beats less rapidly, the time between atrial and ventricular contraction is stretched out, and atrial contraction is weaker. These actions are appropriate, considering that the parasympathetic system controls heart action in quiet, relaxed situations when the body is not demanding enhanced cardiac output.

Effect of sympathetic stimulation on the heart.

In contrast, the sympathetic nervous system, which controls heart action in emergency or exercise situations that require greater blood flow, "revs up" the heart.

The main effect of sympathetic stimulation on the SA node is to speed up depolarization so that threshold is reached more rapidly. This swifter drift to threshold under sympathetic influence permits more frequent action potentials and a correspondingly faster heart rate.

Sympathetic stimulation of the AV node reduces the AV nodal delay by increasing conduction velocity. Similarly, sympathetic stimulation speeds up spread of the action potential throughout the specialized conduction pathway.

In the atrial and ventricular contractile cells, both of which have many sympathetic nerve endings, sympathetic stimulation increases contractile strength so that the heart beats more forcefully and squeezes out more blood. This effect is produced by increasing Ca^{2+} permeability through prolonged opening of the slow Ca^{2+} channels. The resultant enhanced Ca^{2+} influx strengthens contraction by intensifying Ca^{2+} participation in excitation–contraction coupling.

The overall effect of sympathetic stimulation on the heart, therefore, is to improve its effectiveness as a pump by increasing heart rate, decreasing the delay between atrial and ventricular contraction, decreasing conduction time throughout the heart, and increasing the force of contraction.

Control of heart rate.

Thus, as is typical of the autonomic nervous system, parasympathetic and sympathetic effects on heart rate are antagonistic (oppose each other). At any given moment, heart rate is determined largely by the balance between inhibition of the SA node by the vagus nerve and stimulation by the cardiac sympathetic nerves. Under resting conditions, parasympathetic discharge dominates because acetylcholine (the parasympathetic neurotransmitter) suppresses sympathetic activity by inhibiting the release of norepinephrine (the sympathetic neurotransmitter) from neighboring sympathetic nerve endings. If all autonomic nerves to the heart were blocked, the resting heart rate would increase from its average value of 70 beats per minute to about 100 beats per minute, which is the inherent rate of the SA node's spontaneous discharge when not subjected to any nervous influence.

The heart rate can be altered beyond this resting level in either direction by shifting the balance of autonomic nervous stimulation. Heart rate is speeded up by simultaneously increasing sympathetic and decreasing parasympathetic activity; heart rate is slowed by a concurrent rise in parasympathetic activity and decline in sympathetic activity. The relative level of activity in these two autonomic branches to the heart in turn is primarily coordinated by the cardiovascular control center in the brain stem.

Although autonomic innervation is the primary means by which heart rate is regulated, other factors affect it as well. The most important is ***epinephrine***, a hormone secreted into the blood from the adrenal medulla on sympathetic stimulation. Epinephrine acts in a manner similar to

norepinephrine to increase heart rate, thus reinforcing the direct effect that the sympathetic nervous system has on the heart.

Control of stroke volume.

The other component besides heart rate that determines cardiac output is stroke volume, the amount of blood pumped out by each ventricle during each beat. Two types of controls influence stroke volume:

(1) intrinsic control related to the extent of venous return and

(2) extrinsic control related to the extent of sympathetic stimulation of the heart.

Both factors increase stroke volume by increasing the strength of heart contraction. Let us examine each of these mechanisms in detail.

Intrinsic control of stroke volume.

Intrinsic regulation of the heart modifies stroke volume through the normal functional characteristics of cardiac muscle cells. It does not depend on neural or hormonal regulation. According to the **Starling law of the heart**, as the resting length of cardiac muscle cells increases, the force of contraction they produce increases. Past a certain length, however, the force of contraction decreases. This is similar to the length-tension relationship seen in skeletal muscle. Normally, cardiac muscle cells are not stretched past the point at which they can contract with a maximal force.

The amount of blood in the ventricles at the end of ventricular diastole (end-diastolic volume) determines the degree to which cardiac muscle cells are stretched. Venous return is the amount of blood that returns to the heart, and the degree to which the ventricular walls are stretched at the end of diastole is called **preload**. If venous return increases, the heart fills to a greater volume and stretches the cardiac muscle cells, producing an increased preload. In response to the increased preload, cardiac muscle cells contract with a greater force. The greater force of contraction causes an increased volume of blood to be ejected from the heart, resulting in an increased stroke volume, which increases cardiac output.

As a result of the Starling law of the heart, the amount of blood entering the heart (venous return) is equal to the amount of blood leaving the heart (cardiac output). When venous return increases, preload, force of contraction, stroke volume, and cardiac output increase. Conversely, when venous return decreases, preload, force of contraction, stroke volume, and cardiac output decrease.

The Starling law of the heart has a major influence on cardiac output because venous return is influenced by many conditions. For example, during exercise, blood vessels in skeletal muscles dilate, which increases blood delivery to the muscles. As the blood flows through the muscles and returns to the heart, venous return increases. Increased venous return results in an increased preload, stroke volume, and cardiac output. This is beneficial because an increased cardiac output is needed during exercise to deliver blood to exercising skeletal muscles.

Afterload refers to the pressure against which the ventricles must pump blood. People suffering from hypertension have an increased afterload because they have an elevated aortic pressure during contraction of the ventricles. The heart must do more work to pump blood from the left ventricle into the aorta, which increases the workload on the heart and can eventually lead to heart failure. A reduced afterload decreases the work the heart must do.

People who have a lower blood pressure have a reduced afterload and develop heart failure less often than people who have hypertension. The afterload, however, influences cardiac output less than preload influences it. Aortic blood pressure must increase to more than 170 mm Hg before it hampers the ability of a healthy ventricle to pump blood.

Extrinsic Regulation of stroke volume

Extrinsic regulation of the heart modifies heart rate and stroke volume through neural and hormonal mechanisms. Neural control of the heart results from sympathetic and parasympathetic reflexes, and the major hormonal control comes from epinephrine and norepinephrine secreted from the adrenal medulla.

The heart is autorhythmic with its own inherent heart rate The intrinsic heart rate can be modified by hyperpolarization or depolarization of cardiac muscle cell plasma membranes. Hyperpolarization moves the membrane potential further from threshold, increasing the duration of

the autorhithmic phase of AP and slowing heart rate. Depolarization moves the membrane potential closer to threshold, decreasing the duration of the autorhithmic phase and increasing heart rate.

The parasympathetic division supplies the heart through the vagus nerves, which primarily innervate the SA and AV nodes. The postganglionic neurons of the vagus nerves release acetylcholine, which causes ligand-gated K+ channels to open. Increased movement of K+ out of cardiac muscle cells causes hyperpolarization, and heart rate slows. At rest, the parasympathetic division tonically stimulates the heart and depresses heart rate. Without parasympathetic stimulation, the resting heart rate would be approximately 100 beats/minute.

During exercise, withdrawal of parasympathetic stimulation (removal of the inhibitory effect) contributes to an increase in heart rate.

The sympathetic division supplies the heart through sympathetic nerves, called cardiac nerves, which arise from the inferior cervical and upper thoracic sympathetic chain ganglia. The cardiac nerves innervate the SA node, the AV node, and the myocardium of the atria and ventricles. The postganglionic neurons of cardiac nerves release norepinephrine that binds to membrane-bound receptors, activating G proteins and causing Ca^{2+} channels to open. The movement of Ca^{2+} into cardiac muscle cells causes depolarization, and heart rate speeds up. The movement of Ca^{2+} into cardiac muscle cells also increases their force of contraction. In response to strong sympathetic stimulation, the heart rate can increase to 250 or, occasionally, 300 bpm. Stronger contractions cause the heart to empty to a greater extent by decreasing end- systolic volume, which increases stroke volume .

Epinephrine and norepinephrine released from the adrenal medulla can markedly influence the pumping effectiveness of the heart. Epinephrine has essentially the same effect on cardiac muscle as norepinephrine and, therefore, increases the rate and force of heart contractions. The secretion of epinephrine and norepinephrine from the adrenal medulla is controlled by sympathetic stimulation of the adrenal medulla and occurs in response to increased physical activity, emotional excitement, and stressful conditions.

Laws of hemodynamics.

The function of the circulatory system is to maintain adequate blood flow to all tissues. An adequate blood flow maintains homeostasis by providing nutrients and oxygen to tissues and removing the waste products of metabolism from the tissues. Blood flows through blood vessels primarily as a result of the pressure produced by contractions of the heart's ventricles.

Blood pressure is a measure of the force blood exerts against the blood vessel walls. In arteries, blood pressure values exhibit a cycle dependent on the rhythmic contractions of the heart. When the ventricles contract, blood is forced into the arteries, and the pressure reaches a maximum, called the systolic pressure. When the ventricles relax, blood pressure in the arteries falls to a minimum value, called the diastolic pressure. The standard unit for measuring blood pressure is millimeters of mercury (mm Hg). If the blood pressure is 100 mm Hg, the pressure is great enough to lift a column of mercury 100 mm.

The auscultatory method of determining blood pressure is used under most clinical conditions (figure 18.29). A blood pressure cuff connected to a sphygmomanometer, (instrument for measuring pressure) is placed around the patient's arm, and a stethoscope is placed over the brachial artery. The blood pressure cuff is then inflated until the brachial artery is completely blocked. Because no blood flows through the constricted area, no sounds can be heard through the stethoscope at this point. The pressure in the cuff is then gradually lowered. As soon as the pressure in the cuff declines below the systolic pressure, blood flows through the constricted area each time the left ventricle contracts. The blood flow is turbulent immediately downstream from the constricted area. This turbulence produces vibrations in the blood and surrounding tissues that can be heard through the stethoscope. These sounds are called Korotkoff sounds, and the pressure at which the first Korotkoff sound is heard is **the systolic pressure**.

As the pressure in the blood pressure cuff is lowered still more, the Korotkoff sounds change tone and loudness. When the pressure has dropped until the brachial artery is no longer constricted and blood flow is no longer turbulent, the sound disappears completely.

The pressure at which the Korotkoff sounds disappear is **the diastolic pressure**. The brachial artery remains open during systole and diastole, and continuous, nonturbulent blood flow is reestablished.

The systolic pressure is the maximum pressure produced in the large arteries. It is also a good measure of the maximum pressure within the left ventricle. The diastolic pressure is close to the lowest pressure within the large arteries. During relaxation of the left ventricle, the aortic semilunar valve closes, trapping the blood that was ejected during ventricular contraction in the aorta. The pressure in the ventricles falls to 0 mm Hg during ventricular relaxation. The blood trapped in the elastic arteries is compressed by the recoil of the elastic arteries, however, and the pressure falls more slowly, reaching the diastolic pressure (see figure 17.16).

Blood Flow Through a Blood Vessel

Blood flow through a blood vessel is the volume of blood that passes through the vessel per unit of time. The blood flow in a vessel can be described by the following equation:

$$\text{Flow} = \frac{P_1 - P_2}{R}$$

where $P_1$and P_2 are the pressures in the vessel at points one and two, respectively, and R is the resistance to flow. Blood always flows from an area of higher pressure to an area of lower pressure and, the greater the pressure difference, the greater the rate of flow. For example, the average blood pressure in the aorta (P_1) is greater than the blood pressure in the relaxed right atrium (P_2). Therefore, blood flows from the aorta to tissues and from tissues to the right atrium. If the heart should stop contracting, the pressure in the aorta would become equal to that in the right atrium and blood would no longer flow.

The flow of blood, resulting from a pressure difference between the two ends of a blood vessel, is opposed by a resistance to flow. As the resistance increases, blood flow decreases; as the resistance decreases, blood flow increases. Factors that affect resistance can be represented as follows:

$$\text{Resistance} = \frac{128vl}{\pi d^4}$$

where v is the viscosity of blood, l is the length of the vessel, and d is the diameter of the vessel. The diameter of a round vessel is the distance from one side of the vessel through the center of the vessel to the opposite side. Both 128 and π are constants and, for practical purposes, the length of the blood vessel is constant. Thus, the diameter of the blood vessel and the viscosity of the blood determine resistance.

When the equation for resistance is combined with the equation for flow, the following relationship, called Poiseuille's law, results:

$$\text{Flow} = \frac{P_1 - P_2}{R} = \frac{\pi (P_1 - P_2) d^4}{128vl}$$

According to Poiseuille's law, a small change in the diameter of a vessel dramatically changes the resistance to flow, and therefore the amount of blood that flows through the vessel, because the diameter is raised to the fourth power. Vasoconstriction decreases the diameter of a vessel, increases the resistance to flow, and decreases the blood flow through the vessel. For example, decreasing the diameter of a vessel by half increases the resistance to flow 16-fold and

decreases flow 16-fold. Vasodilation increases the diameter of a vessel, decreases resistance to fl ow, and increases blood flow through the vessel.

Viscosity is a measure of the resistance of a liquid to flow. A common means for reporting the viscosity of liquids is to consider the viscosity of distilled water as 1 and to compare the viscosity of other liquids with it. Using this procedure, whole blood normally has a viscosity of 3.0–4.5. As the viscosity of a liquid increases, the pressure required to force it to flow increases. It takes 3.0–4.5 times as much pressure to move whole blood through a tube at the same rate as water.

The viscosity of blood is influenced largely by hematocrit, which is the percentage of the total blood volume composed of red blood cells).

Increasing the number of red blood cells or decreasing plasma volume increases hematocrit; decreasing the number of red blood cells or increasing plasma volume decreases viscosity. As the hematocrit changes, the viscosity of blood changes logarithmically. Blood with a hematocrit of 45% has a viscosity about three times that of water, whereas blood with a very high hematocrit of 65% has a viscosity about seven to eight times that of water. Viscosity above its normal range of values increases the workload on the heart; if this workload is great enough, heart failure can result.

Blood Flow Through the Body

The equation for blood flow can be used to describe blood flow through the body. The volume of blood flowing through the body per minute is cardiac output (CO),which is the volume of blood pumped per minute by the left ventricle. Thus, flow (F) in the equation for blood flow is CO. Contractions of the left ventricle maintain a mean arterial pressure (MAP) of 93 mm Hg in the aorta. Blood flows from the aorta to the relaxed right atrium, which has a pressure near 0 mm Hg. Thus, P1 − P2 is MAP −0, or MAP. Because of aortal pressure has a pulsative character, changing from systolic to diastolic pressure, MAP can be calculated using Hickam's formula

$$MAP \cong P_{dias} + \frac{1}{3}\left(P_{sys} - P_{dias}\right)$$

Where P_{dias} - diastolic blood pressure (in mm Hg), P_{syst} -- systolic blood pressure (in mm Hg)

Peripheral resistance (PR) is the sum of all the resistances to blood flow in all of the blood vessels in the body. Thus, R in the flow equation becomes PR.

$$\text{Flow} = \frac{P_1 - P_2}{R} = CO = \frac{\text{MAP}}{PR}$$

Rearranging the terms of the equation, gives:

$$\text{MAP} = CO \times PR$$

Thus, maintaining adequate blood pressure, which is necessary for blood delivery to tissues, depends on CO and PR. Peripheral resistance is maintained and regulated through the sympathetic division of the autonomic nervous system (ANS). Continual sympathetic stimulation of the smooth muscle in the walls of blood vessels keeps them in a state of partial constriction called **vasomotor tone**. Changing the amount of sympathetic stimulation changes vasomotor tone and peripheral resistance. Increased sympathetic stimulation of blood vessel smooth muscle causes vasoconstriction by decreasing blood vessel diameter. Increased vasoconstriction increases vasomotor tone and the resistance to blood flow, which increases peripheral resistance. Conversely, decreased sympathetic stimulation results in vasodilation, decreased vasomotor tone, and decreased peripheral resistance.

Th e aortic pressure fluctuates between a systolic pressure of 120 mm Hg and a diastolic pressure of 80 mm Hg (figure 18.30). MAP is slightly less than the average of systolic and diastolic

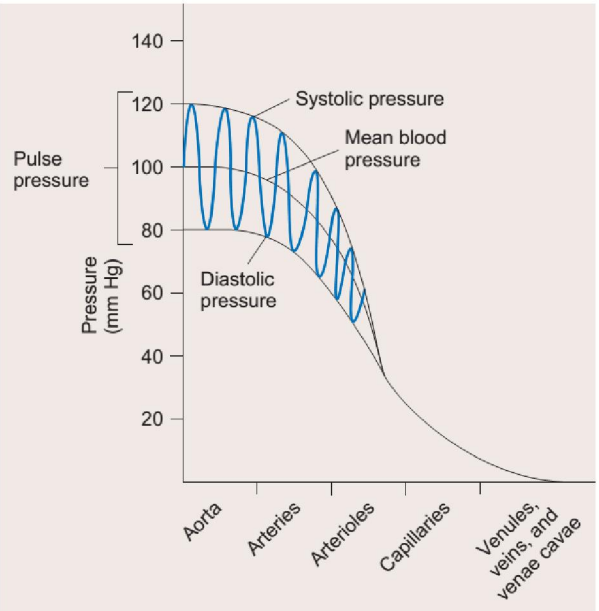


Figure 18.30 Blood Pressure in the Major Blood Vessel Types

pressures because diastole lasts longer than systole. MAP is approximately 70 mm Hg at birth, is slightly less than 100 mm Hg from adolescence to middle age, and reaches 110 mm Hg in healthy older persons, but it can be as high as 130 mm Hg.

Blood pressure falls progressively as blood flows from arteries through the capillaries and veins to about 0 mm Hg by the time blood is returned to the right atrium (see figure 18.30). The greater the resistance to blood flow in a blood vessel, the more rapidly the pressure decreases as blood flows through it. The most rapid decline in blood pressure occurs in the arterioles and then in capillaries because their small diameters increase the resistance to blood flow. In addition, the pressure is damped, in that the difference between the systolic and diastolic pressures is decreased in the small- diameter vessels. By the time blood reaches the capillaries, there is no variation in blood pressure, and only a steady pressure of about 30 mm Hg remains.

Pulse Pressure and Vascular Compliance

Pulse pressure is the difference between the systolic and diastolic pressures. If a person has a systolic pressure of 120 mm Hg and a diastolic pressure of 80 mm Hg, the pulse pressure is 40 mm Hg. Two major factors influence pulse pressure: stroke volume and vascular compliance. When the stroke volume increases, the systolic pressure increases more than the diastolic pressure, causing the pulse pressure to increase.

Vascular compliance is the tendency for blood vessel volume to increase as the blood pressure increases. The more easily the vessel wall stretches the greater is its compliance, whereas the less easily the vessel wall stretches the smaller is its compliance. By analogy, it is easier to blow up a thin-walled (more compliant) balloon than a thick-walled (less compliant) balloon. As vascular compliance decreases, pulse pressure increases.

Arteriosclerosis in older people results in less elastic arteries, which decreases compliance. The decreased compliance causes the pressure in the aorta to rise more rapidly and to a greater degree during systole. Thus, for a given stroke volume, systolic pressure and pulse pressure are higher. Arteriosclerosis increases the amount of work performed by the heart because the left ventricle must produce a greater pressure to eject the same amount of blood into a less elastic artery. In severe cases, the increased workload on the heart leads to heart failure.

Ejection of blood from the left ventricle into the aorta produces a **pulse**, or pressure wave, which travels rapidly along the arteries. The rate of transmission of the pulse wave is much more rapid than the flow of blood. A pulse wave takes approximately 0.1 sec to travel from the aorta to the radial artery, whereas a drop of blood takes approximately 8 sec to make the same journey.

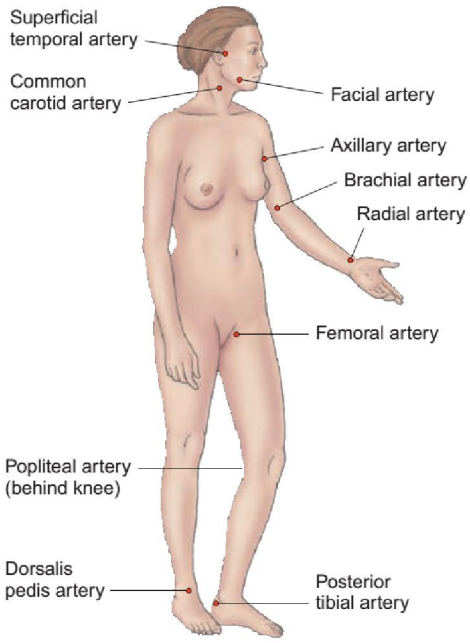


Figure 18.31 Major Points at Which the Pulse Can Be Monitored

A pulse can be felt at locations where large arteries are close to the surface of the body (figure 18.31). It is helpful to know the major locations where the pulse can be detected because monitoring the pulse is important clinically. Heart rate, heart rhythm, and other characteristics can be determined by feeling the pulse. For example, a weak pulse usually indicates a decreased stroke volume or increased constriction of the arteries.

Blood Pressure and the Effect of Gravity

Hydrostatic pressure is the pressure, or weight, produced by a column of fluid due to the effects of gravity. When a person is standing, the blood pressure in a blood vessel in the foot results from the pressure generated by contraction of the heart plus the hydrostatic pressure produced by the "column" of blood above the foot. The hydrostatic pressure at the foot adds approximately 90 mm Hg to the pressures recorded in figure 18.30. Blood pressure is approximately 0 mm Hg in the relaxed right atrium, and it averages approximately 100 mm Hg in the aorta. In the foot, pressure in a vein is approximately 90 mm Hg and in an artery is approximately 190 mm Hg.

When a person changes position from lying down to standing, the blood pressure in the veins of the lower limbs increases. The compliance of veins is approximately 24 times greater than the compliance of arteries because of the structure of their walls. The increased blood pressure causes the distensible (compliant) veins to expand, but has little effect on the arteries. Venous return decreases because less blood is returning to the heart as the veins are filling with blood. As venous return decreases, cardiac output and blood pressure decrease, and there is inadequate delivery of blood to the brain.

Homeostasis of the brain is disrupted and dizziness or fainting can occur, unless negative feedback mechanisms, such as the baroreceptor reflex, compensate and cause blood pressure to increase.

Capillary Exchange and Regulation of Interstitial Fluid Volume

There are approximately 10 billion capillaries in the body. The heart and blood vessels all maintain blood flow through those capillaries and support capillary exchange, which is the movement of substances between capillaries and the interstitial fluids of tissues.

Capillary exchange is the process by which cells receive everything they need to survive and to eliminate metabolic waste products. If blood flow through capillaries is not adequate to maintain capillary exchange, cells cannot survive.

Substances leave the blood and enter the interstitial fluid of tissues by passing through or between the endothelial cells of capillaries.

1. **Passage through endothelial cells.** Substances can pass through endothelial cells by crossing their plasma membranes. There are four ways that substances pass through plasma membranes: diffusion, osmosis, mediated transport, and vesicular transport. For example, in vesicular transport, endothelial cells take in substances from the blood by pinocytosis. The vesicles formed cross the cell and release their contents into the interstitial fluid by exocytosis. Some endothelial cells are penetrated bylarge pores, called **fenestrae**, through which substances can pass through the cells.

2. **Passage between endothelial cells**. In a typical capillary, there are

intercellular spaces approximately 6–7 nm wide between cells through which substances can pass. Lipid-soluble molecules cross capillary walls by diffusing through the plasma membranes of the endothelial cells of the capillaries. Examples include oxygen, carbon dioxide, steroid hormones, and fatty acids.

The permeability of capillaries to water-soluble substances, such as glucose and amino acids, varies tremendously. In a typical capillary the space between endothelial cells allows the passage of most substances, except for proteins. In the kidneys, there are many fenestrae, which also allow the passage of most substances, except for proteins.

The numerous fenestrae allow large amounts of substances to move rapidly from the blood into kidney tubules, where urine is produced. In the liver, the spaces between the endothelial cells are large enough to allow proteins to pass through them. The capillaries in the brain forming the blood–brain barrier have tight junctions between cells, and few molecules pass between them. In these capillaries, mediated transport processes move water-soluble substances across the capillary walls.

Diffusion, osmosis, and filtration are the primary means by which most substances cross capillary walls. Nutrients, oxygen, and hormones diffuse from a higher concentration in capillaries to a lower concentration in the interstitial fluid. Waste products, including carbon dioxide, diffuse from a higher concentration in the interstitial fluid to a lower concentration in the capillaries.

Osmosis is the movement of water across a selectively permeable membrane. The capillary wall acts as a selectively permeable membrane that prevents proteins from moving from the capillary into the interstitial fluid but allows water to move across the wall of the capillary. There is a higher concentration of proteins in the blood than in the interstitial fluid. Consequently, water moves from the less concentrated interstitial fluid, which has fewer proteins but more water molecules, into the more concentrated blood, which has more proteins but fewer water molecules. Materials dissolved or suspended in the water that can pass through the capillary wall accompany the water into the blood.

Filtration is the movement of fluid through a partition containing small holes. The fluid movement results from the pressure or weight of the fluid pushing against the partition, and the fluid moves from the side of the partition with the greater pressure to the side with the lower pressure. The fluid and substances small enough to pass through the holes move through the partition, but substances larger than the holes do not pass through it. For example, in a car, oil but not dirt particles passes through an oil filter. In capillaries, blood pressure moves fluid through the spaces between endothelial cells or through fenestrae.

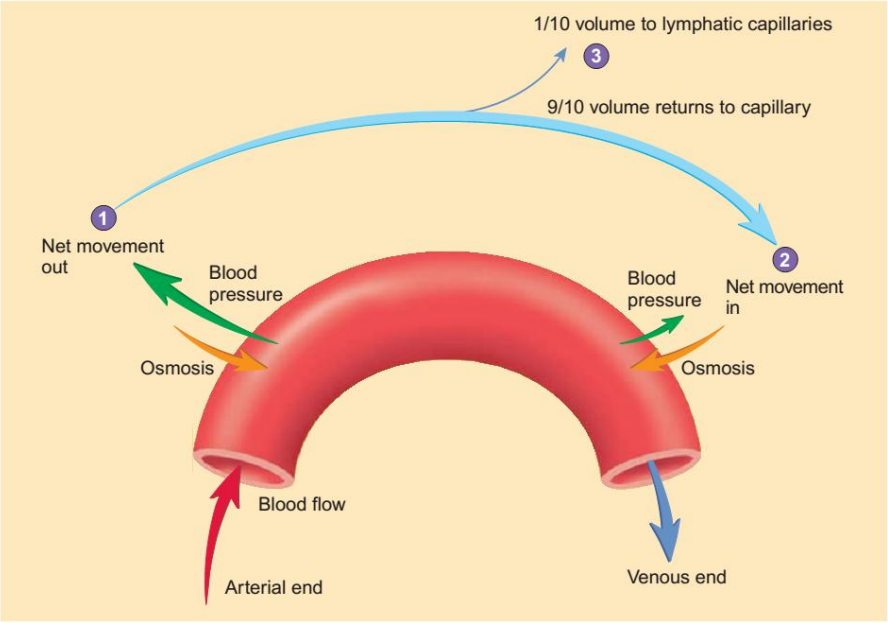
Blood pressure forces fluid out of capillaries and osmosis moves fluid into them. The balance between these two forces determines whether or not fluid leaves or enters capillaries. At the arterial end of the capillary, the movement of fluid out of the capillary caused by blood pressure is greater than the movement of fluid into the capillary as a result of osmosis (figure 18.32; note the size of the arrows representing fluid movement caused by blood pressure and osmosis).

Consequently, there is a net movement of fluid out of the capillary. At the venous end of the capillary, blood pressure is lower than at the arterial end because of the resistance to blood flow through the capillary. Consequently, the movement of fluid into the capillary caused by osmosis is greater than the movement of fluid out of the capillary resulting from blood pressure, and there is a net movement of fluid into the capillary (see figure 18.32). Approximately nine-tenths of the fluid that leaves the capillary at the arterial end reenters the capillary at its venous end. The remaining one-tenth of the fluid enters the lymphatic capillaries and is eventually returned to the blood.

1. At the arterial end of the capillary, the movement of fluid out of the capillary due to blood pressure is greater than the movement of fluid into the capillary due to osmosis (*green arrow* is larger than *orange arrow*).

2. At the venous end of the capillary, the movement of fluid into the capillary due to osmosis is greater than the movement of fluid out of the capillary due to blood pressure (*orange arrow* is larger than *green arrow*).

3. Approximately nine-tenths of the fluid (*blue arrow*) that leaves the capillary at its arterial end reenters the capillary at its venous end. About one-tenth of the fluid passes into the lymphatic capillaries.



Process Figure 18.32 Fluid Exchange Across the Walls of Capillaries AP R

Control of Blood Flow

Blood flow is highly controlled and matched closely to the metabolic needs of tissues. Mechanisms that control blood flow to and through tissues are classified as

(1) local control and

(2) nervous and hormonal control.

Local Control

Blood flow at the tissue level is regulated by arterioles and precapillary sphincters. The arterioles control the amount of blood reaching the capillary beds, and the precapillary sphincters control the flow of blood through capillaries (see figure 18.4). The arterioles and the precapillary sphincters are regulated by local control. The arterioles are also regulated by nervous and hormonal control.

Local control is the response of vascular smooth muscle to changes in tissue gases, nutrients, and waste products levels; it does not involve the nervous system or hormones. Arterioles vasodilate and precapillary sphincters relax when oxygen levels decrease or, to a lesser degree, when glucose, amino acids, fatty acids, and other nutrients decrease. An increase in carbon dioxide and lactic acid or a decrease in pH also causes arterioles to vasodilate and precapillary sphincters to relax. For example, during exercise, the metabolic needs of skeletal muscle increase dramatically, and the by-products of metabolism are produced at a more rapid rate. Local control increases blood flow to match the metabolic needs of the tissue. Conversely, when metabolic needs are low, the vasoconstriction of arterioles and contraction of precapillary sphincters reduce blood flow.

The long-term regulation of blood flow through tissues is matched closely to the metabolic requirements of the tissue. If the metabolic activity of a tissue increases and remains elevated for an extended period, the diameter and the number of capillaries in the tissue increase, and local blood flow increases. The increased density of capillaries in the well-trained skeletal muscles of athletes, compared with that in poorly trained skeletal muscles, is an example.

Nervous and Hormonal Control

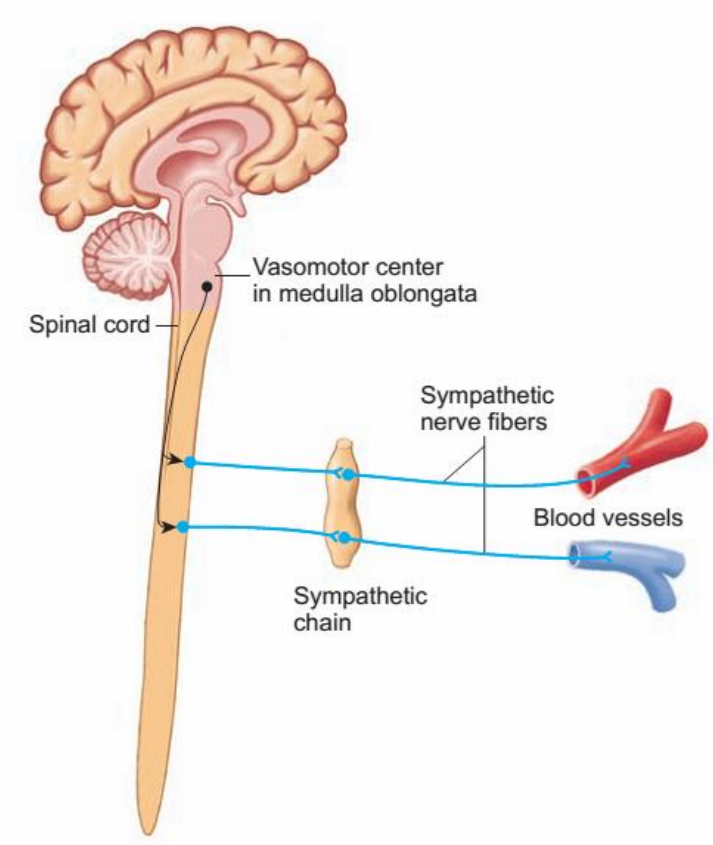


Figure 18.33 Nervous Regulation of Blood Vessels

Blood flow through arterioles, arteries, and v eins is regulated by nervous and hormonal mechanisms. An area of the lower pons and upper medulla oblongata, called the vasomotor center, continually transmits a low frequency of action potentials through sympathetic fibers to the smooth

muscle of blood vessels, except for the precapillary sphincters. As a consequence, the peripheral blood vessels, especially the arterioles, are continually in a partially constricted state, a condition called **vasomotor tone**. Increased sympathetic stimulation of a blood vessel causes vasoconstriction, and decreased stimulation causes vasodilation.

Areas throughout the pons, midbrain, and diencephalon can stimulate or inhibit the vasomotor center. For example, the hypothalamus can exert either strong excitatory or inhibitory effects on the vasomotor center. Increased body temperature detected by temperature receptors in the hypothalamus causes vasodilation of blood vessels in the skin. The cerebral cortex also can either excite or inhibit the vasomotor center. For example, action potentials that originate in the cerebral cortex during periods of emotional excitement activate hypothalamic centers, which in turn increase vasomotor tone.

The neurotransmitter for the sympathetic fibers is norepinephrine, which binds to α-adrenergic receptors on blood vessel smooth muscle cells to cause vasoconstriction. Sympathetic action potentials also cause the release of epinephrine and norepinephrine into the blood from the adrenal medulla. These hormones are transported in the blood to all parts of the body. In most blood vessels, they bind to α-adrenergic receptors and cause vasoconstriction. In skeletal and cardiac muscle, epinephrine causes vasodilation. There are large numbers of β-adrenergic receptors in addition to α-adrenergic receptors in skeletal and cardiac muscle. Epinephrine binding to β-adrenergic receptors promotes vasodilation. The overall effect is vasodilation because the effect of activating the large number of β-adrenergic receptors outweighs the effect of activating the α-adrenergic receptors.

Regulation of Mean Arterial Pressure.

Blood flow to all areas of the body depends on the maintenance of an adequate pressure in the arteries. As long as arterial blood pressure is adequate, local control of blood flow through tissues is appropriately matched to their metabolic needs. If blood pressure is too low, the metabolic needs of tissues are not met. If blood pressure is too high, blood vessels and the heart can be damaged.

Blood flow through the circulatory system is determined by the cardiac output (CO),which is equal to the heart rate (HR) times the stroke volume (SV), and peripheral resistance (PR),which is the resistance to blood flow in all the blood vessels:

$MAP = CO \times PR$ or $MAP = HR \times SV \times PR$

This equation expresses the effect of heart rate, stroke volume, and peripheral resistance on blood pressure. An increase in any one of them results in an increase in blood pressure. Conversely, a decrease in any one of them produces a decrease in blood pressure. The mechanisms that control blood pressure do so by changing peripheral resistance, heart rate, or stroke volume. Regulatory mechanisms that control blood volume also affect blood pressure because stroke volume depends on the amount of blood entering the heart. For example, an increase in blood volume increases venous return, which increases stroke volume. Two major types of control systems operate to achieve these responses:

(1) those that respond in the short term and (2)
(2) those that respond in the long term.

The regulatory mechanisms that control pressure on a short-term basis respond quickly but begin to lose their capacity to regulate blood pressure a few hours to a few days after blood pressure is maintained at higher or lower values. This occurs because sensory receptors adapt to the altered pressures. The long-term regulation of blood pressure is controlled primarily by mechanisms that influence kidney function, and those mechanisms do not adapt rapidly to altered blood pressures.

Short-Term Regulation of Blood Pressure

The short-term, rapidly acting mechanisms controlling blood pressure are the baroreceptor reflexes, the adrenal medullary mechanism, and chemoreceptor reflexes. Some of these reflex mechanisms operate on a minute-to-minute basis and help regulate blood pressure within a narrow range of values. Some of them respond primarily to emergency situations.

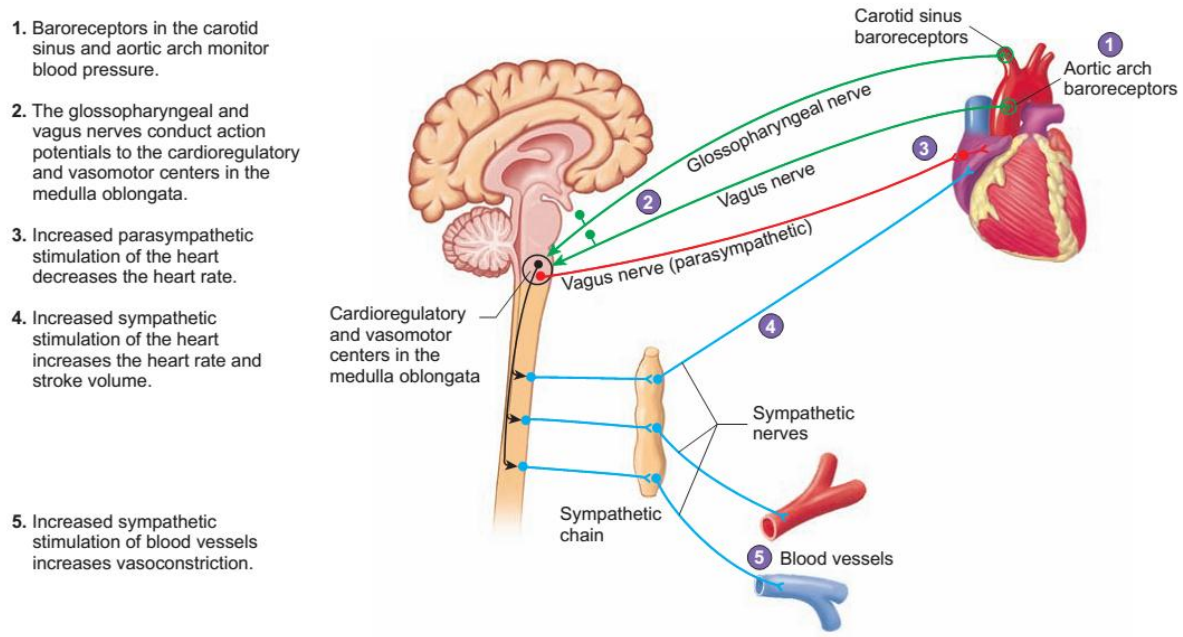
Baroreceptor Reflexes.

Baroreceptor reflexes help regulate blood pressure by modifying heart rate and stroke volume. In addition, they regulate blood pressure by changing peripheral resistance. Baroreceptors

are sensory receptors that respond to stretch in arteries caused by increased blood pressure. They are scattered along the walls of most of the large arteries of the neck and thorax, and there are many in the carotid sinus at the base of the internal carotid artery and in the walls of the aortic arch (figure 18.34). Action potentials are transmitted from the baroreceptors to the medulla oblongata along sensory nerve fibers in cranial nerves.

A sudden increase in blood pressure stretches the artery walls and increases action potential frequency in the baroreceptors. The increased action potential frequency delivered to the vasomotor and cardioregulatory centers in the medulla oblongata causes responses that lower the blood pressure. One major response is vasodilation, resulting in decreased vasomotor tone and peripheral resistance. Other responses, controlled by the cardioregulatory center, are an increase in the parasympathetic stimulation of the heart, which decreases the heart rate, and a decrease in sympathetic stimulation of the heart, which reduces the stroke volume. The decreased heart rate, stroke volume, and peripheral resistance lower the blood pressure toward its normal value.

A sudden decrease in blood pressure results in a decreased action potential frequency in the baroreceptors. The decreased action potential frequency delivered to the vasomotor and cardioregulatory centers in the medulla oblongata produces responses that raise blood pressure. Vasoconstriction increases vasomotor tone and peripheral resistance. Increased sympathetic stimulation of the heart increases the heart rate and stroke volume. The increased peripheral resistance, heart rate, and stroke volume raise the blood pressure toward its normal value.



Process Figure 18.34 Baroreceptor Reflex Control of Blood Pressure APR

The baroreceptor reflexes regulate blood pressure on a moment-to-moment basis. When a person rises rapidly from a sitting or lying position to a standing position, hydrostatic pressure in the lower limbs increases, resulting in decreased venous return, cardiac output, and blood pressure. This reduction in blood pressure can be so great that blood flow to the brain is reduced enough to cause dizziness or even loss of consciousness. The falling blood pressure activates the baroreceptor reflexes, which reestablish normal blood pressure within a few seconds. In a healthy person, there may be no awareness that blood pressure has dropped momentarily.

The baroreceptor reflexes do not change the average blood pressure in the long run. The baroreceptors adapt within 1–3 days to any new sustained blood pressure to which they are exposed. If the blood pressure is elevated for more than a few days, the baroreceptors adapt to the elevated pressure and the baroreceptor reflexes do not reduce the blood pressure to its original value. This adaptation is common in people who have hypertension.

Adrenal Medullary Mechanism

Stimuli that result in increased sympathetic stimulation of the heart and blood vessels also cause increased stimulation of the adrenal medulla. The adrenal medulla responds by releasing

epinephrine and norepinephrine into the blood (figure 18.35). The main effect of epinephrine and norepinephrine is to increase heart rate and stroke volume. Epinephrine causes vasodilation in skeletal muscle and cardiac muscle and vasoconstriction in the skin and kidneys. Norepinephrine increases vasoconstriction everywhere. The overall effect of epinephrine is to decrease peripheral resistance slightly, whereas norepinephrine increases peripheral resistance.

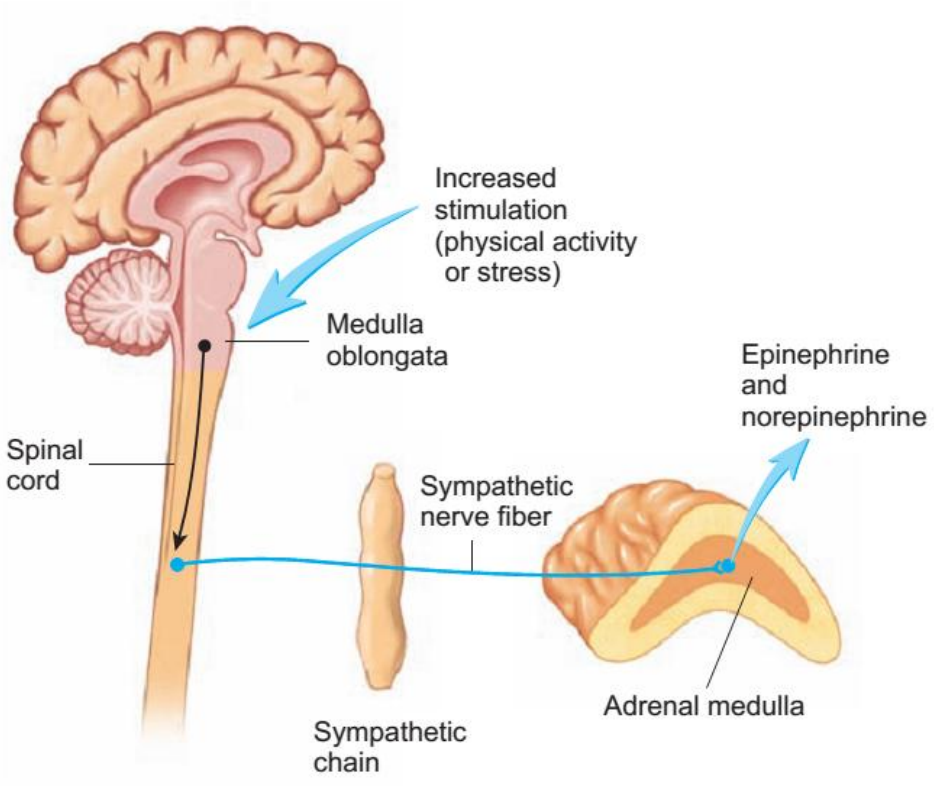


Figure 18.35 Adrenal Medullary Mechanism

Chemoreceptor Reflexes

The chemoreceptor reflexes help maintain homeostasis when oxygen tension in the blood decreases or when carbon dioxide and H^+ concentrations increase. (figure 18.36). Chemoreceptors are sensory receptors responding to chemicals, such as oxygen, carbon dioxide, and pH. Peripheral chemoreceptors are found in the carotid bodies, structures located near the carotid sinuses, and in the aortic bodies, located near the aortic arch. Central chemoreceptors are in the medulla oblongata.

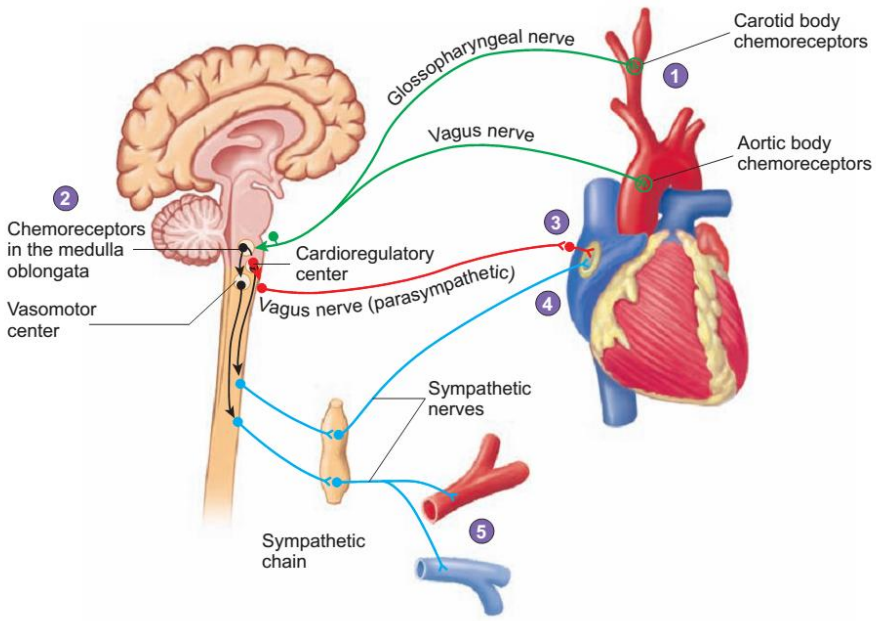
The peripheral chemoreceptors are most sensitive to oxygen. They act under emergency conditions and do not regulate the cardiovascular system under resting conditions. For example, when blood pressure drops significantly, blood oxygen levels decrease because of inadequate circulation of blood through the lungs. The peripheral chemoreceptors stimulate the vasomotor center, resulting in vasoconstriction that maintains or increases blood pressure.

The central chemoreceptors are most sensitive to changes in carbon dioxide and pH. They also act under emergency conditions or unusual conditions. For example, when blood pressure drops significantly, blood carbon dioxide levels increase because of inadequate circulation of blood through the lungs. The central chemoreceptors stimulate the vasomotor center, resulting in vasoconstriction that maintains or increases blood pressure. Heart rate and force of contraction also increase. This response is called the CNS ischemic response. It is activated only when blood pressure is very low and is a last-ditch effort to maintain blood pressure. If the vasomotor center fails because of inadequate delivery of blood, vasomotor tone decreases, blood pressure drops, and death results.

The peripheral and central chemoreceptor reflexes are more important in the regulation of respiration than in the regulation of the cardiovascular system. Low oxygen, increased carbon dioxide, and decreased pH can stimulate increased rate and depth of respiration. The increased

respiratory activity stimulates reflexes that cause heart rate and stroke volume to increase. Thus, there is a match between respiratory and circulatory activities.

1. Chemoreceptors in the carotid and aortic bodies monitor blood O_2, CO_2, and pH.
2. Chemoreceptors in the medulla oblongata monitor blood CO_2 and pH.
3. Decreased blood O_2, increased CO_2, and decreased pH decrease parasympathetic stimulation of the heart, which increases the heart rate.
4. Decreased blood O_2, increased CO_2, and decreased pH increase sympathetic stimulation of the heart, which increases the heart rate and force of contraction.
5. Decreased blood O_2, increased CO_2, and decreased pH increase sympathetic stimulation of blood vessels, which increases vasoconstriction.



Process Figure 18.36 Chemoreceptor Reflex Control of Blood Pressure

Long-Term Regulation of Blood Pressure

The regulation of blood volume and concentration by the kidneys and the movement of fluid across the wall of blood vessels play a central role in the long-term regulation of blood pressure. Some of the long-term regulatory mechanisms begin to respond in minutes, but they continue to function for hours, days, or longer. They adjust the blood pressure precisely and keep it within a narrow range of values for years. The major regulatory mechanisms are the reninangiotensin-aldosterone mechanism, ADH (vasopressin) mechanism, atrial natriuretic mechanism, and fluid shift mechanism.

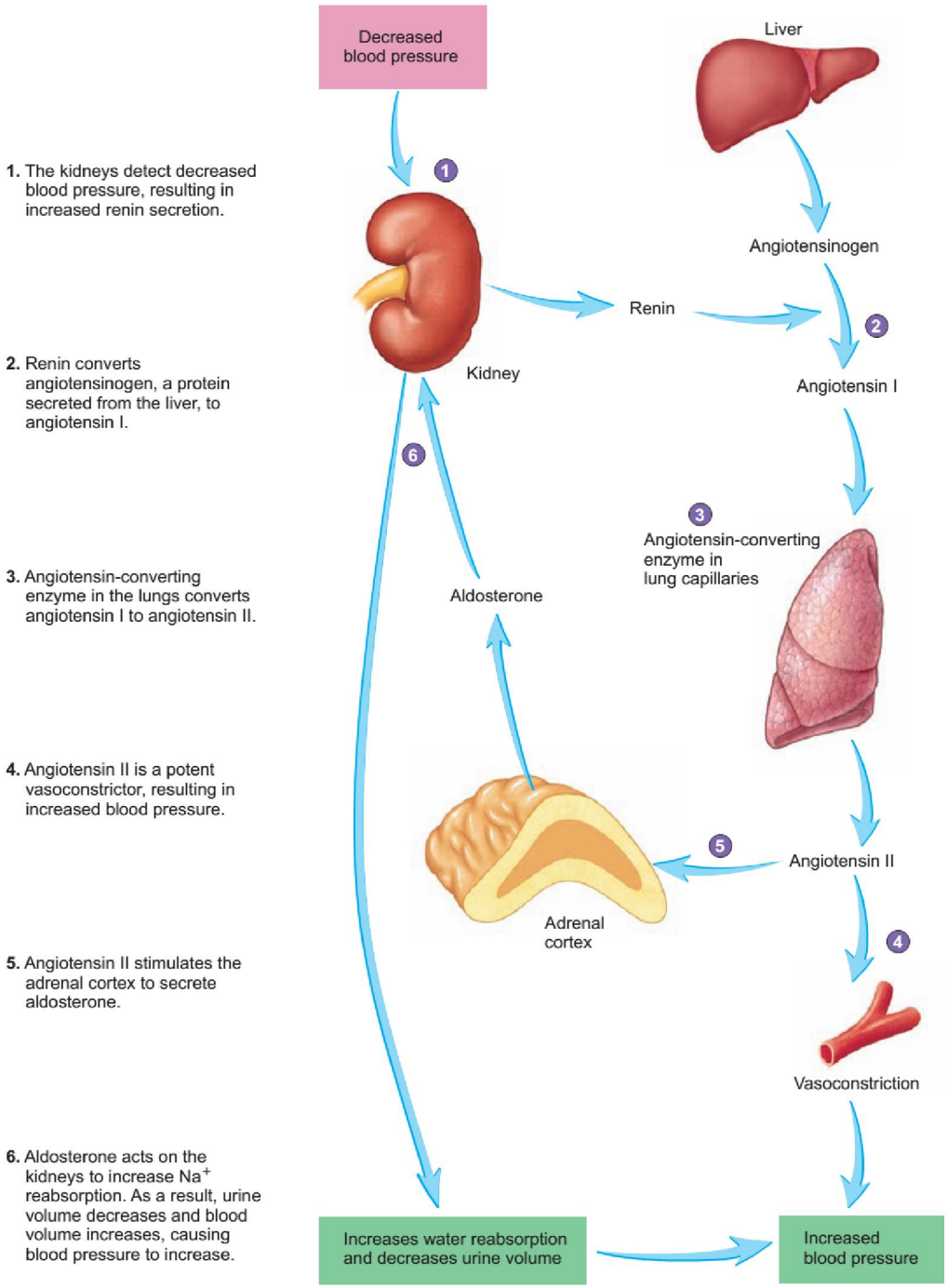
Renin-Angiotensin-Aldosterone Mechanism

The renin-angiotensin-aldosterone mechanismhelps regulate blood pressure by changing peripheral resistance and blood volume. In response to reduced blood flow, the kidneys release an enzyme called rennin into the circulatory system (figure 18.37). Renin acts on the blood protein angiotensinogen to produce angiotensin I. Another enzyme, called angiotensinconverting enzyme, found in large amounts in organs such as the lungs, acts on angiotensin I to convert it to its most active form, called angiotensin II. Angiotensin II is a potent vasoconstrictor substance. Thus, in response to a reduced blood pressure, the release of renin by the kidney increases peripheral resistance, which causes blood pressure to increase toward its normal value.

Angiotensin II also acts on the adrenal cortex to increase the secretion of aldosterone. Aldo sterone acts on the kidneys, causing them to conserve Na^+ and water. As a result, the volume of water lost from the blood into the urine is reduced. The decrease in urine volume results in less fluid loss from the body, which maintains blood volume (see figure 18.37). An adequate blood volume is essential for the maintenance of normal venous return to the heart and therefore for the maintenance of blood pressure.

ADH (Vasopressin) Mechanism.

The ADH (vasopressin) mechanism works in harmony with the renin-angiotensin-aldosterone mechanism in response to changes in blood pressure (figure 18.38). Baroreceptors are sensitive to changes in blood pressure, and decreases in blood pressure detected by the baroreceptors result in the release of antidiuretic hormone (ADH), or vasopressin, from the posterior pituitary. Blood pressure must decrease substantially before this mechanism is activated. For example, extensive burns decrease blood volume and blood pressure because of plasma loss at the burn site. Neurons of the hypothalamus are sensitive to changes in the solute concentration of the plasma. Even small increases in the plasma concentration of solutes directly stimulate hypothalamic neurons that increase ADH secretion. Increases in the concentration of the plasma, such as during dehydration, stimulate ADH secretion. ADH acts directly on blood vessels to cause



Process Figure 18.37 Renin-Angiotensin-Aldosterone Mechanism

vasoconstriction, although it is not as potent as other vasoconstrictor agents. Within minutes after a rapid and substantial decline in blood pressure, ADH is released in sufficient quantities to help

reestablish normal blood pressure. ADH also decreases the rate of urine production by the kidneys, thereby helping maintain blood volume and blood pressure.

Atrial Natriuretic Mechanism.

A polypeptide called atrial natriuretic hormone is released from cells in the atria of the heart. A major stimulus for its release is increased venous return, which stretches atrial cardiac muscle cells. Atrial natriuretic hormone acts on the kidneys to increase the rate of urine production and Na^+ loss in the urine. It also dilates arteries and veins. Loss of water and Na^+ in the urine causes the blood volume to decrease, which decreases venous return, and vasodilation results in a decrease in peripheral resistance. These effects cause a decrease in blood pressure.

The renin-angiotensin-aldosterone, ADH (vasopressin), and atrial natriuretic mechanisms work simultaneously to help regulate blood pressure by controlling urine production by the kidneys. If blood pressure drops below 50 mm Hg, the volume of urine produced by the kidneys is reduced to nearly zero. If blood pressure is increased to 200 mm Hg, the urine volume produced is approximately six to eight times greater than normal. The hormonal mechanisms that regulate blood pressure in the long term are summarized in figure 18.39.

Fluid Shift Mechanism

The fluid shift mechanism begins to act within a few minutes but requires hours to achieve its full functional capacity. It plays a very important role when dehydration develops over several hours, or when a large volume of saline is administered over several hours. The fluid shift mechanism occurs in response to small changes in pressures across capillary walls. As blood pressure increases, some fluid is forced from the capillaries into the interstitial spaces. The movement of fluid into the interstitial spaces helps prevent the development of high blood pressure. As blood pressure falls, interstitial fluid moves into capillaries, which resists a further decline in blood pressure. The fluid shift mechanism is a powerful method through which blood pressure is maintained because the interstitial volume acts as a reservoir, and it is in equilibrium with the large volume of intercellular fluid.