Blood Flow and the Control of Blood Pressure

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Since 1900, CVD (cardiovascular disease) has been the No. 1 killer in the United States every year but 1918.

— American Heart Association, Heart Disease and Stroke Statistics

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From Chapter 15 of Human Physiology: An Integrated Approach, Sixth Edition. Dee Unglaub Silverthorn. Copyright © 2013 by Pearson Education, Inc. All rights reserved.
Anthony was sure he was going to be a physician, until the day in physiology laboratory they studied blood types. When the lancet pierced his fingertip and he saw the drop of bright red blood well up, the room started to spin, and then everything went black. He awoke, much embarrassed, to the sight of his classmates and the teacher bending over him.

Anthony suffered an attack of vasovagal syncope (syncope = fainting), a benign and common emotional reaction to blood, hypodermic needles, or other upsetting sights. Normally, homeostatic regulation of the cardiovascular system maintains blood flow, or perfusion, to the heart and brain. In vasovagal syncope, signals from the nervous system cause a sudden decrease in blood pressure, and the individual faints from lack of oxygen to the brain. In this chapter you will learn how the heart and blood vessels work together most of the time to prevent such problems.

A simplified model of the cardiovascular system (Fig. 15.1) illustrates the key points we discuss in this chapter. This model shows the heart as two separate pumps, with the...
right heart pumping blood to the lungs and back to the left heart. The left heart then pumps blood through the rest of the body and back to the right heart.

Blood leaving the left heart enters systemic arteries, shown here as an expandable, elastic region. Pressure produced by contraction of the left ventricle is stored in the elastic walls of arteries and slowly released through elastic recoil. This mechanism maintains a continuous driving pressure for blood flow during ventricular relaxation. For this reason, the arteries are known as the pressure reservoir (reservoir, to retain) of the circulatory system.

Downstream from the arteries, small vessels called arterioles create a high-resistance outlet for arterial blood flow. Arterioles direct distribution of blood flow to individual tissues by selectively constricting and dilating, so they are known as the site of variable resistance. Arteriolar diameter is regulated both by local factors, such as tissue oxygen concentrations, and by the autonomic nervous system and hormones.

When blood flows into the capillaries, their leaky epithelium allows exchange of materials between the plasma, the interstitial fluid, and the cells of the body. At the distal end of the capillaries, blood flows into the venous side of the circulation. The veins act as a volume reservoir from which blood can be sent to the arterial side of the circulation if blood pressure falls too low. From the veins, blood flows back to the right heart.

Total blood flow through any level of the circulation is equal to cardiac output. For example, if cardiac output is 5 L/min, blood flow through all the systemic capillaries is 5 L/min. In the same manner, blood flow through the pulmonary side of the circulation is equal to blood flow through the systemic circulation.

The Blood Vessels

The walls of blood vessels are composed of layers of smooth muscle, elastic connective tissue, and fibrous connective tissue (Fig. 15.2). The inner lining of all blood vessels is a thin layer of endothelium, a type of epithelium. For years, the endothelium was thought to be simply a passive barrier. However, we now know that endothelial cells secrete many paracines and play important roles in the regulation of blood pressure, blood vessel growth, and absorption of materials. Some scientists have even proposed that endothelium be considered a separate physiological organ system.

In most vessels, layers of connective tissue and smooth muscle surround the endothelium. The endothelium and its adjacent elastic connective tissue together make up the intima, usually called simply the intima (intima, innermost). The thickness of the smooth muscle–connective tissue layers surrounding the intima varies in different vessels. The descriptions that follow apply to the vessels of the systemic circulation, although those of the pulmonary circulation are generally similar.

**Blood Vessels Contain Vascular Smooth Muscle**

The smooth muscle of blood vessels is known as vascular smooth muscle. Most blood vessels contain smooth muscle, arranged in either circular or spiral layers. Vasoconstriction narrows the diameter of the vessel lumen, and vasodilation widens it.

In most blood vessels, smooth muscle cells maintain a state of partial contraction at all times, creating the condition known as muscle tone. Contraction of smooth muscle, like that of cardiac muscle, depends on the entry of Ca$^{2+}$ from
the extracellular fluid through Ca^{2+} channels. A variety of chemicals, including neurotransmitters, hormones, and paracrine, influences vascular smooth muscle tone. Many vasoactive paracrine are secreted either by endothelial cells lining blood vessels or by tissues surrounding the vessels.

**Arterioles, along with capillaries and small postcapillary vessels called venules, form the microcirculation.** Regulation of blood flow through the microcirculation is an active area of physiological research.

Some arterioles branch into vessels known as **metarterioles** (meta-, beyond) (Fig. 15.3). True arterioles have a continuous smooth muscle layer, but the wall of a metarteriole is only partially surrounded by smooth muscle. Blood flowing through metarterioles can take one of two paths. If muscle rings called **precapillary sphincters** (sphingein, to hold tight) are relaxed, blood flowing into a metarteriole is directed into adjoining capillary beds (Fig. 15.3b). If the precapillary sphincters constrict, blood flow bypasses capillaries and goes directly to the venous circulation (Fig. 15.3c). In addition, metarterioles allow white blood cells to go directly from the arterial to the venous circulation. Capillaries are barely large enough to let red blood cells through, much less white blood cells, which are twice as large.

**Exchange Takes Place in the Capillaries**

Capillaries are the smallest vessels in the cardiovascular system. They and the postcapillary venules are the site of exchange between the blood and the interstitial fluid. To facilitate
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Angiogenesis Creates New Blood Vessels

One topic of great interest to researchers is angiogenesis (angeion, vessel + gignesthai, to beget), the process by which new blood vessels develop, especially after birth. In children, blood vessel growth is necessary for normal development. In adults, angiogenesis takes place as wounds heal and as the uterine lining grows after menstruation. Angiogenesis also occurs with endurance exercise training, enhancing blood flow to the heart muscle and to skeletal muscles. The growth of malignant tumors is a disease state that requires angiogenesis. As cancer cells invade tissues and multiply, they instruct the host tissue to develop new blood vessels to feed the growing tumor. Without these new vessels, the interior cells of a cancerous mass would be unable to get adequate oxygen and nutrients, and would die.

Blood Flow Converges in the Venules and Veins

Blood flows from the capillaries into small vessels called venules. The very smallest venules are similar to capillaries, with a thin exchange epithelium and little connective tissue (Fig. 15.2). They are distinguished from capillaries by their convergent pattern of flow.

Smooth muscle begins to appear in the walls of larger venules. From venules, blood flows into veins that become larger in diameter as they travel toward the heart. Finally, the largest veins, the venae cavae, empty into the right atrium. To assist venous flow, some veins have internal one-way valves (Fig. 15.4). These valves, like those in the heart, ensure that blood passing the valve cannot flow backward. Once blood reaches the vena cava, there are no valves.

Veins are more numerous than arteries and have a larger diameter. As a result of their large volume, the veins hold more than half of the blood in the circulatory system, making them the volume reservoir of the circulatory system. Veins lie closer to the surface of the body than arteries, forming the bluish blood vessels that you see running just under the skin. Veins have thinner walls than arteries, with less elastic tissue. As a result, they expand easily when they fill with blood.

When you have blood drawn from your arm (venipuncture), the technician uses a tourniquet to exert pressure on the blood vessels. Blood flow into the arm through deep high-pressure arteries is not affected, but pressure exerted by the tourniquet stops outflow through the low-pressure veins. As a result, blood collects in the surface veins, making them stand out against the underlying muscle tissue.

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From studies of normal blood vessels and tumor cells, scientists learned that angiogenesis is controlled by a balance of angiogenic and antiangiogenic cytokines. A number of related growth factors, including vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), promote angiogenesis.
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These growth factors are mitogens, meaning they promote mitosis, or cell division. They are normally produced by smooth muscle cells and pericytes.

Cytokines that inhibit angiogenesis include angiotatin, made from the blood protein plasminogen, and endostatin [stasis, a state of standing still]. Scientists are currently testing these cytokines for treating cancer, to see if they can block angiogenesis and literally starve tumors to death.

In contrast, coronary heart disease, also known as coronary artery disease, is a condition in which blood flow to the myocardium is decreased by fatty deposits that narrow the lumen of the coronary arteries. In some individuals, new blood vessels develop spontaneously and form collateral circulation that supplements flow through the partially blocked artery. Researchers are testing angiogenic cytokines to see if they can duplicate this natural process and induce angiogenesis to replace occluded vessels (occludere, to close up).

**Blood Pressure**

The force that creates blood flow through the cardiovascular system is ventricular contraction. As blood under pressure is ejected from the left ventricle, the aorta and arteries expand to accommodate it (Fig. 15.5a). When the ventricle relaxes and the semilunar valve closes, the elastic arterial walls recoil, propelling the blood forward into smaller arteries and arterioles (Fig. 15.5b). By sustaining the *driving pressure* for blood flow during ventricular relaxation, the arteries keep blood flowing continuously through the blood vessels.

Blood flow obeys the rules of fluid flow. Flow is directly proportional to the pressure gradient between any two points, and inversely proportional to the resistance of the vessels to flow (Tbl. 15.1). Unless otherwise noted, the discussion that follows is restricted to the events that take place in the systemic circuit.

**Blood Pressure Is Highest in Arteries and Lowest in Veins**

Blood pressure is highest in the arteries and decreases continuously as blood flows through the circulatory system (Fig. 15.6). The decrease in pressure occurs because energy is lost as a result of the resistance to flow offered by the vessels. Resistance to blood flow also results from friction between the blood cells.

In the systemic circulation, the highest pressure occurs in the aorta and results from pressure created by the left ventricle. Aortic
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Pressure reaches an average high of 120 mm Hg during ventricular systole (systolic pressure), then falls steadily to a low of 80 mm Hg during ventricular diastole (diastolic pressure). Notice that pressure in the ventricle falls to only a few mm Hg as the ventricle relaxes, but diastolic pressure in the large arteries remains relatively high. The high diastolic pressure in arteries reflects the ability of those vessels to capture and store energy in their elastic walls.

The rapid pressure increase that occurs when the left ventricle pushes blood into the aorta can be felt as a pulse, or pressure wave, transmitted through the fluid-filled arteries. The pressure wave travels about 10 times faster than the blood itself. Even so, a pulse felt in the arm is occurring slightly after the ventricular contraction that created the wave.

The amplitude of the pressure wave decreases over distance because of friction, and the wave finally disappears at the capillaries (Fig. 15.6). Pulse pressure, a measure of the strength of the pressure wave, is defined as systolic pressure minus diastolic pressure:

\[
\text{Pulse pressure} = \text{Systolic pressure} - \text{Diastolic pressure}
\]

For example, in the aorta:

\[
120 \text{ mm Hg} - 80 \text{ mm Hg} = 40 \text{ mm Hg pressure}
\]

By the time blood reaches the veins, pressure has fallen because of friction, and a pressure wave no longer exists. Venous blood flow is steady rather than pulsatile, pushed along by the continuous movement of blood out of the capillaries.

Low-pressure blood in veins below the heart must flow "uphill," or against gravity, to return to the heart. Try holding your arm straight down without moving for several minutes and notice how the veins in the back of your hand begin to stand out as they fill with blood. (This effect may be more evident in older people, whose subcutaneous connective tissue has lost elasticity). Then raise your hand so that gravity assists the venous flow and watch the bulging veins disappear.

Blood return to the heart, known as venous return, is aided by valves, the skeletal muscle pump, and the respiratory pump. When muscles such as those in the calf of the leg contract, they compress the veins, forcing blood upward past the valves. While your hand is hanging down, try clenching and unclenching your fist to see the effect muscle contraction has on distention of the veins.

**Concept Check**

1. Would you expect to find valves in the veins leading from the brain to the heart? Defend your answer.

2. If you checked the pulse in a person's carotid artery and left wrist at the same time, would the pressure waves occur simultaneously? Explain.

3. Who has the higher pulse pressure, someone with blood pressure of 90/60 or someone with blood pressure of 130/95?
Arterial Blood Pressure Reflects the Driving Pressure for Blood Flow

Arterial blood pressure, or simply “blood pressure,” reflects the driving pressure created by the pumping action of the heart. Because ventricular pressure is difficult to measure, it is customary to assume that arterial blood pressure reflects ventricular pressure. Because arterial pressure is pulsatile, we use a single value—the mean arterial pressure (MAP)—to represent driving pressure. MAP is represented graphically in Fig. 15.6.

Mean arterial pressure is estimated as diastolic pressure plus one-third of pulse pressure:

\[
\text{MAP} = \text{diastolic P} + \frac{1}{3} (\text{systolic P} - \text{diastolic P})
\]

For a person whose systolic pressure is 120 and diastolic pressure is 80:

\[
\text{MAP} = 80 \text{ mm Hg} + \frac{1}{3} (120 - 80 \text{ mm Hg}) = 93 \text{ mm Hg}
\]

Mean arterial pressure is closer to diastolic pressure than to systolic pressure because diastole lasts twice as long as systole.

Abnormally high or low arterial blood pressure can be indicative of a problem in the cardiovascular system. If blood pressure falls too low (hypotension), the driving force for blood flow is unable to overcome opposition by gravity. In this instance, blood flow and oxygen supply to the brain are impaired, and the person may become dizzy or faint.

On the other hand, if blood pressure is chronically elevated (a condition known as hypertension, or high blood pressure), high pressure on the walls of blood vessels may cause weakened areas to rupture and bleed into the tissues. If a rupture occurs in the brain, it is called a cerebral hemorrhage and may cause the loss of neurological function commonly called a stroke. If a weakened area ruptures in a major artery, such as the descending aorta, rapid blood loss into the abdominal cavity causes blood pressure to fall below the critical minimum. Without prompt treatment, rupture of a major artery is fatal.

**Concept Check**

4. The formula given for calculating MAP applies to a typical resting heart rate of 60–80 beats/min. If heart rate increases, would the contribution of systolic pressure to mean arterial pressure decrease or increase, and would MAP decrease or increase?

5. Peter’s systolic pressure is 112 mm Hg, and his diastolic pressure is 68 mm Hg (written 112/68). What is his pulse pressure? His mean arterial pressure?

**RUNNING PROBLEM**

Kurt’s second blood pressure reading is 158/98. Dr. Cortez asks him to take his blood pressure at home daily for two weeks and then return to the doctor’s office. When Kurt comes back with his diary, the story is the same: his blood pressure continues to average 160/100. After running some tests, Dr. Cortez concludes that Kurt is one of approximately 50 million adult Americans with high blood pressure, also called hypertension. If not controlled, hypertension can lead to heart failure, stroke, and kidney failure.

Q1: Why are people with high blood pressure at greater risk for having a hemorrhagic (or bleeding) stroke?

**Blood Pressure Is Estimated by Sphygmomanometry**

We estimate arterial blood pressure in the radial artery of the arm using a sphygmomanometer, an instrument consisting of an inflatable cuff and a pressure gauge (sphygnum, pulse + manometer, an instrument for measuring pressure of a fluid). The cuff encircles the upper arm and is inflated until it exerts pressure higher than the systolic pressure driving arterial blood. When cuff pressure exceeds arterial pressure, blood flow into the lower arm stops (Fig. 15.7a).

Now pressure on the cuff is gradually released. When cuff pressure falls below systolic arterial blood pressure, blood begins to flow again. As blood squeezes through the still-compressed artery, a thumping noise called a Korotkoff sound can be heard with each pressure wave (Fig. 15.7b). Once the cuff pressure no longer compresses the artery, the sounds disappear (Fig. 15.7c).

The pressure at which a Korotkoff sound is first heard represents the highest pressure in the artery and is recorded as the systolic pressure. The point at which the Korotkoff sounds disappear is the lowest pressure in the artery and is recorded as the diastolic pressure. By convention, blood pressure is written as systolic pressure over diastolic pressure.

For years the “average” value for blood pressure has been stated as 120/80. Like many average physiological values, however, these numbers are subject to wide variability, both from one person to another and within a single individual from moment to moment. A systolic pressure that is consistently over 140 mm Hg at rest, or a diastolic pressure that is chronically over 90 mm Hg, is considered a sign of hypertension in an otherwise healthy person.
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Arterial blood pressure is measured with a sphygmomanometer (an inflatable cuff plus a pressure gauge) and a stethoscope. The inflation pressure shown is for a person whose blood pressure is 120/80.

**Cardiac Output and Peripheral Resistance Determine Mean Arterial Pressure**

Mean arterial pressure is the driving force for blood flow, but what determines mean arterial pressure? Arterial pressure is a balance between blood flow into the arteries and blood flow out of the arteries. If flow in exceeds flow out, blood collects in the arteries, and mean arterial pressure increases. If flow out exceeds flow in, mean arterial pressure falls.

Blood flow into the aorta is equal to the cardiac output of the left ventricle. Blood flow out of the arteries is influenced primarily by peripheral resistance, defined as the resistance to flow offered by the arterioles (Fig. 15.8a). Mean arterial pressure (MAP) then is proportional to cardiac output (CO) times resistance (R) of the arterioles:

\[
\text{MAP} \propto \text{CO} \times R_{\text{arterioles}}
\]

Let’s consider how this works. If cardiac output increases, the heart pumps more blood into the arteries per unit time. If resistance to blood flow out of the arteries does not change, flow into the arteries is greater than flow out, blood volume in the arteries increases, and arterial blood pressure increases.

In another example, suppose cardiac output remains unchanged but peripheral resistance increases. Flow into arteries is unchanged, but flow out is decreased. Blood again accumulates in the arteries, and the arterial pressure again increases. Most cases of hypertension are believed to be caused

Furthermore, the guidelines published in the 2003 JNC 7 Report* now recommend that individuals maintain their blood pressure below 120/80. Persons whose systolic pressure is consistently in the range of 120–139 or whose diastolic pressure is in the range of 80–89 are now considered to be prehypertensive and should be counseled on lifestyle modification strategies to reduce their blood pressure.

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by increased peripheral resistance without changes in cardiac output.

Two additional factors can influence arterial blood pressure: the distribution of blood in the systemic circulation and the total blood volume. The relative distribution of blood between the arterial and venous sides of the circulation can be an important factor in maintaining arterial blood pressure.

Arteries are low-volume vessels that usually contain only about 11% of total blood volume at any one time. Veins, in contrast, are high-volume vessels that hold about 60% of the circulating blood volume at any one time.

The veins act as a volume reservoir for the circulatory system, holding blood that can be redistributed to the arteries if needed. If arterial blood pressure falls, increased sympathetic
activity constricts veins, decreasing their holding capacity. Venous return sends blood to the heart, which according to the Frank-Starling law of the heart, pumps all the venous return out to the systemic side of the circulation. Thus, constriction of the veins redistributes blood to the arterial side of the circulation and raises mean arterial pressure.

**Changes in Blood Volume Affect Blood Pressure**

Although the volume of the blood in the circulation is usually relatively constant, changes in blood volume can affect arterial blood pressure (Fig. 15.8b). If blood volume increases, blood pressure increases. When blood volume decreases, blood pressure decreases.

To understand the relationship between blood volume and pressure, think of the circulatory system as an elastic balloon filled with water. If only a small amount of water is in the balloon, little pressure is exerted on the walls, and the balloon is soft and flabby. As more water is added to the balloon, more pressure is exerted on the elastic walls. If you fill a balloon close to the bursting point, you risk popping the balloon. The best way to reduce this pressure is to remove some of the water.

Small increases in blood volume occur throughout the day due to ingestion of food and liquids, but these increases usually do not create long-lasting changes in blood pressure because of homeostatic compensations. Adjustments for increased blood volume are primarily the responsibility of the kidneys. If blood volume increases, the kidneys restore normal volume by excreting excess water in the urine (Fig. 15.9).

Compensation for decreased blood volume is more difficult and requires an integrated response from the kidneys and the cardiovascular system. If blood volume decreases, the kidneys cannot restore the lost fluid. The kidneys can only conserve blood volume and thereby prevent further decreases in blood pressure.

The only way to restore lost fluid volume is through drinking or intravenous infusions. This is an example of mass balance: volume lost to the external environment must be replaced from the external environment. Cardiovascular compensation for decreased blood volume includes vasoconstriction and increased sympathetic stimulation of the heart to increase cardiac output. However, there are limits to the effectiveness of cardiovascular compensation—if fluid loss

**COMPENSATION FOR INCREASED BLOOD VOLUME**

Blood pressure control includes rapid responses from the cardiovascular system and slower responses by the kidneys.
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**CLINICAL FOCUS**

**Shock**

*Shock* is a broad term that refers to generalized, severe circulatory failure. Shock can arise from multiple causes: failure of the heart to maintain normal cardiac output (*cardiogenic shock*), decreased circulating blood volume (*hypovolemic shock*), bacterial toxins (*septic shock*), and miscellaneous causes, such as the massive immune reactions that cause *anaphylactic shock*. No matter what the cause, the results are similar: low cardiac output and falling peripheral blood pressure. When tissue perfusion can no longer keep up with tissue oxygen demand, the cells begin to sustain damage from inadequate oxygen and from the buildup of metabolic wastes. Once this damage occurs, a positive feedback cycle begins. The shock becomes progressively worse until it becomes irreversible, and the patient dies. The management of shock includes administration of oxygen, fluids, and norepinephrine, which stimulates vasoconstriction and increases cardiac output. If the shock arises from a cause that is treatable, such as a bacterial infection, measures must also be taken to remove the precipitating cause.

Figure 15.8b summarizes the four key factors that influence mean arterial blood pressure.

**Resistance in the Arterioles**

Peripheral resistance is one of the two main factors influencing blood pressure. According to Poiseuille’s Law, resistance to blood flow (R) is directly proportional to the length of the tubing through which the fluid flows (L) and to the viscosity (η) of the fluid, and inversely proportional to the fourth power of the tubing radius (r):

\[
R \propto \frac{L \eta}{r^4}
\]

Normally the length of the systemic circulation and the blood’s viscosity are relatively constant. That leaves only the radius of the blood vessels as the primary resistance to blood flow:

\[
R \propto \frac{1}{r^4}
\]

The arterioles are the main site of variable resistance in the systemic circulation and contribute more than 60% of the total resistance to flow in the system. Resistance in arterioles is variable because of the large amounts of smooth muscle in the arteriolar walls. When the smooth muscle contracts or relaxes, the radius of the arterioles changes.

Arteriolar resistance is influenced by both local and systemic control mechanisms:

1. **Local control of arteriolar resistance** matches tissue blood flow to the metabolic needs of the tissue. In the heart and skeletal muscle, these local controls often take precedence over reflex control by the central nervous system.
2. **Sympathetic reflexes** mediated by the CNS maintain mean arterial pressure and govern blood distribution for certain homeostatic needs, such as temperature regulation.
3. **Hormones**—particularly those that regulate salt and water excretion by the kidneys— influence blood pressure by acting directly on the arterioles and by altering autonomic reflex control.

Table 15.2 lists significant chemicals that mediate arteriolar resistance by producing vasoconstriction or vasodilation. In the following sections we look at some factors that influence blood flow at the tissue level.

**Myogenic Autoregulation Automatically Adjusts Blood Flow**

Vascular smooth muscle has the ability to regulate its own state of contraction, a process called *myogenic autoregulation*. In the absence of autoregulation, an increase in blood pressure increases blood flow through an arteriole. However, when smooth muscle fibers in the wall of the arteriole stretch because of increased blood pressure, the arteriole constricts. This vasoconstriction increases the resistance offered by the arteriole, automatically decreasing blood flow through the vessel. With...
### Table 15.2

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Physiological Role</th>
<th>Source</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vasoconstriction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine ((α\text{-receptors}))</td>
<td>Baroreceptor reflex</td>
<td>Sympathetic neurons</td>
<td>Neurotransmitter</td>
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<td>Serotonin</td>
<td>Platelet aggregation, smooth muscle contraction</td>
<td>Neurons, digestive tract, platelets</td>
<td>Paracrine, neurotransmitter</td>
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<tr>
<td>Endothelin</td>
<td>Local control of blood flow</td>
<td>Vascular endothelium</td>
<td>Paracrine</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Increases blood pressure in hemorrhage</td>
<td>Posterior pituitary</td>
<td>Neurohormone</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>Increases blood pressure</td>
<td>Plasma hormone</td>
<td>Hormone</td>
</tr>
<tr>
<td><strong>Vasodilation</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine ((β\text{-receptors}))</td>
<td>Increase blood flow to skeletal muscle, heart, liver</td>
<td>Adrenal medulla</td>
<td>Neurohormone</td>
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<td>Acetylcholine</td>
<td>Erection reflex (indirectly through NO production)</td>
<td>Parasympathetic neurons</td>
<td>Neurotransmitter</td>
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<td>Nitric oxide (NO)</td>
<td>Local control of blood flow</td>
<td>Endothelium</td>
<td>Paracrine</td>
</tr>
<tr>
<td>Bradykinin (via NO)</td>
<td>Increases blood flow</td>
<td>Multiple tissues</td>
<td>Paracrine</td>
</tr>
<tr>
<td>Adenosine</td>
<td>Increases blood flow to match metabolism</td>
<td>Hypoxic cells</td>
<td>Paracrine</td>
</tr>
<tr>
<td>↓\text{O}_2, ↑\text{CO}_2, ↑H^+, ↑K^+</td>
<td>Increase blood flow to match metabolism</td>
<td>Cell metabolism</td>
<td>Paracrine</td>
</tr>
<tr>
<td>Histamine</td>
<td>Increases blood flow</td>
<td>Mast cells</td>
<td>Paracrine</td>
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<td>Natriuretic peptides (example—ANP)</td>
<td>Reduce blood pressure</td>
<td>Atrial myocardium, brain</td>
<td>Hormone, neurotransmitter</td>
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<tr>
<td>Vasoactive intestinal peptide</td>
<td>Digestive secretion, relax smooth muscle</td>
<td>Neurons</td>
<td>Neurotransmitter, neurohormone</td>
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</table>

**Paracrine Mechanisms of Vascular Smooth Muscle Contraction**

This simple and direct response to pressure, arterioles have limited ability to regulate their own blood flow.

How does myogenic autoregulation work at the cellular level? When vascular smooth muscle cells in arterioles are stretched, mechanically gated channels in the muscle membrane open. Cation entry depolarizes the cell. The depolarization opens voltage-gated \( Ca^{2+} \) channels, and \( Ca^{2+} \) flows into the cell down its electrochemical gradient. Calcium entering the cell combines with calmodulin and activates myosin light chain kinase. MLCK in turn increases myosin ATPase activity and crossbridge activity, resulting in contraction.

**Paracrines Alter Vascular Smooth Muscle Contraction**

Local control is an important strategy by which individual tissues regulate their own blood supply. In a tissue, blood flow into individual capillaries can be regulated by the precapillary sphincters described earlier in the chapter. When these small bands of smooth muscle at metarteriole-capillary junctions constrict, they restrict blood flow into the capillaries (see Fig. 15.3). When the sphincters dilate, blood flow into the capillaries increases. This mechanism provides an additional site for local control of blood flow.
Local regulation also takes place by changing arteriolar resistance in a tissue. This is accomplished by paracranes (including the gases O₂, CO₂, and NO) secreted by the vascular endothelium or by cells to which the arterioles are supplying blood (Tbl. 15.2).

The concentrations of many paracrines change as cells become more or less metabolically active. For example, if aerobic metabolism increases, tissue O₂ levels decrease while CO₂ production goes up. Both low O₂ and high CO₂ dilate arterioles. This vasodilation increases blood flow into the tissue, bringing additional O₂ to meet the increased metabolic demand and removing waste CO₂ (Fig. 15.10a). The process in which an increase in blood flow accompanies an increase in metabolic activity is known as active hyperemia (hyper-, above normal + haimia, blood).

If blood flow to a tissue is occluded (occludere, to close up) for a few seconds to a few minutes, O₂ levels fall and metabolic paracrines such as CO₂ and H⁺ accumulate in the interstitial fluid. Local hypoxia (hypo-, low + oxia, oxygen) causes endothelial cells to synthesize the vasodilator nitric oxide. When blood flow to the tissue resumes, the increased concentrations of NO, CO₂, and other paracrines immediately trigger significant vasodilation. As the vasodilators are metabolized or washed away by the restored tissue blood flow, the radius of the arteriole gradually returns to normal. An increase in tissue blood flow following a period of low perfusion (blood flow) is known as reactive hyperemia (Fig. 15.10b).

Nitric oxide is probably best known for its role in the male erection reflex, and drugs used to treat erectile dysfunction prolong NO activity. Decreases in endogenous NO activity are suspected to play a role in other medical conditions, including hypertension and preeclampsia, the elevated blood pressure that sometimes occurs during pregnancy.

Another vasodilator paracrine is the nucleotide adenosine. If oxygen consumption in heart muscle exceeds the rate at which oxygen is supplied by the blood, myocardial hypoxia results. In response to low tissue oxygen, the myocardial cells release adenosine. Adenosine dilates coronary arterioles in an attempt to bring additional blood flow into the muscle.

Not all vasoactive paracrines reflect changes in metabolism. For example, kinins and histamine are potent vaso-dilators that play a role in inflammation. Serotonin (5-HT), previously mentioned as a CNS neurotransmitter, is also a vasoconstricting paracrine released by activated platelets. When damaged blood vessels activate platelets, the subsequent serotonin-mediated vasoconstriction helps slow blood loss.
Serotonin agonists called triptans (for example, sumatriptan) are drugs that bind to 5-HT1 receptors and cause vasoconstriction. These drugs are used to treat migraine headaches, which are caused by inappropriate cerebral vasodilation.

RUNNING PROBLEM

After two months, Kurt returns to the doctor’s office for a checkup. He has lost five pounds and is walking at least a mile daily, but his blood pressure has not changed. “I swear, I’m trying to do better,” says Kurt, “but it’s difficult.” Because lifestyle changes and the diuretic have not lowered Kurt’s blood pressure, Dr. Cortez adds an antihypertensive drug. “This drug, called an ACE inhibitor, blocks production of a chemical called angiotensin II, a powerful vasoconstrictor. This medication should bring your blood pressure back to a normal value.”

Q3: Why would blocking the action of a vasoconstrictor lower blood pressure?

The Sympathetic Branch Controls Most Vascular Smooth Muscle

Smooth muscle contraction in arterioles is regulated by neural and hormonal signals in addition to locally produced paracines. Among the hormones with significant vasoactive properties are atrial natriuretic peptide and angiotensin II (ANG II). These hormones also have significant effects on the kidney’s excretion of ions and water.

Most systemic arterioles are innervated by sympathetic neurons. A notable exception is arterioles involved in the erection reflex of the penis and clitoris. They are controlled indirectly by parasympathetic innervation. Acetylcholine from parasympathetic neurons causes paracrine release of nitric oxide, resulting in vasodilation.

Tonic discharge of norepinephrine from sympathetic neurons helps maintain myogenic tone of arterioles (Fig. 15.11a). Norepinephrine binding to α-receptors on vascular smooth muscle causes vasoconstriction. If sympathetic release of norepinephrine decreases, the arterioles dilate. If sympathetic stimulation increases, the arterioles constrict.

Epinephrine from the adrenal medulla travels through the blood and also binds with α-receptors, reinforcing vasoconstriction. However, α-receptors have a lower affinity for epinephrine and do not respond as strongly to it as they do to norepinephrine. In addition, epinephrine binds to β2-receptors, found on vascular smooth muscle of heart, liver, and skeletal muscle arterioles. These receptors are not innervated and therefore respond primarily to circulating epinephrine. Activation of vascular β2-receptors by epinephrine causes vasodilation.

One way to remember which tissues’ arterioles have β2-receptors is to think of a fight-or-flight response to a stressful event. This response includes a generalized increase in sympathetic activity, along with the release of epinephrine. Blood vessels that have β2-receptors respond to epinephrine by vasodilating. Such β2-mediated vasodilation enhances blood flow to the heart, skeletal muscles, and liver, tissues that are active during the fight-or-flight response. (The liver produces glucose for muscle contraction.) During fight or flight, increased sympathetic activity at arteriolar α-receptors causes vasoconstriction. The increase in resistance diverts blood from nonessential organs, such as the gastrointestinal tract, to the skeletal muscles, liver, and heart.

The map in Fig. 15.11b summarizes the many factors that influence blood flow in the body. The pressure to drive blood flow is created by the pumping heart and captured by the arterial pressure reservoir, as reflected by the mean arterial pressure. Flow through the body as a whole is equal to the cardiac output, but flow to individual tissues can be altered by selectively changing resistance in a tissue’s arterioles. In the next section we consider the relationship between blood flow and arteriolar resistance.

The extracellular fluid concentration of K+ increases in exercising skeletal muscles. What effect does this increase in K+ have on blood flow in the muscles?

Resistance to blood flow is determined primarily by which? (a) blood viscosity, (b) blood volume, (c) cardiac output, (d) blood vessel diameter, or (e) blood pressure gradient (∆P)

**Concept Check**

6. Resistance to blood flow is determined primarily by which? (a) blood viscosity, (b) blood volume, (c) cardiac output, (d) blood vessel diameter, or (e) blood pressure gradient (∆P)

7. The extracellular fluid concentration of K+ increases in exercising skeletal muscles. What effect does this increase in K+ have on blood flow in the muscles?
Blood Flow and the Control of Blood Pressure

**RESISTANCE AND FLOW**

(a) Tonic control of arteriolar diameter

Arteriole diameter is controlled by tonic release of norepinephrine.

![Diagram of norepinephrine release onto α receptors](image)

Electrical signals from neuron

Time

Moderate signal rate results in a blood vessel of intermediate diameter.

Change in signal rate

↑ Norepinephrine release onto α receptors

Time

As the signal rate increases, the blood vessel constricts.

↓ Norepinephrine release onto α receptors

Time

As the signal rate decreases, the blood vessel dilates.

(b) Factors influencing peripheral blood flow

<table>
<thead>
<tr>
<th>Pressure gradient</th>
<th>Resistance to flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (MAP) minus Right atrial pressure (=0)</td>
<td>Poiseulle’s Law</td>
</tr>
<tr>
<td>Blood volume</td>
<td>Radius⁴</td>
</tr>
<tr>
<td>Arterio-venous distribution</td>
<td>1/viscosity</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>1/length</td>
</tr>
<tr>
<td>Flow into arteries</td>
<td>Reflex control</td>
</tr>
<tr>
<td>Flow out of arteries</td>
<td>Local control</td>
</tr>
<tr>
<td>Heart rate</td>
<td>?</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>?</td>
</tr>
</tbody>
</table>

Intrinsic Modulated Passive (Frank-Starling law) Modulated

---

Fill in the autonomic control and local control mechanisms for cardiac output and resistance, represented by ? in the map.
Distribution of Blood to the Tissues

The nervous system’s ability to selectively alter blood flow to organs is an important aspect of cardiovascular regulation. The distribution of systemic blood varies according to the metabolic needs of individual organs and is governed by a combination of local control mechanisms and homeostatic reflexes. For example, skeletal muscles at rest receive about 20% of cardiac output. During exercise, when the muscles use more oxygen and nutrients, they receive as much as 85%.

Blood flow to individual organs is set to some degree by the number and size of arteries feeding the organ. Figure 15.12 shows how blood is distributed to various organs when the body is at rest. Usually, more than two-thirds of the cardiac output is routed to the digestive tract, liver, muscles, and kidneys.

Variations in blood flow to individual tissues are possible because the arterioles in the body are arranged in parallel. In other words, all arterioles receive blood at the same time from the aorta (see Fig. 15.1). Total blood flow through all the arterioles of the body always equals the cardiac output.

However, the flow through individual arterioles depends on their resistance (R). The higher the resistance in an arteriole, the lower the blood flow through it. If an arteriole constricts and resistance increases, blood flow through that arteriole decreases (Fig. 15.13):

\[ \text{Flow}_{\text{arteriole}} \propto \frac{1}{R_{\text{arteriole}}} \]

In other words, blood is diverted from high-resistance arterioles to lower-resistance arterioles. You might say that blood traveling through the arterioles takes the path of least resistance. We will return to this subject after we look at the control mechanisms that govern blood flow and blood pressure.

Regulation of Cardiovascular Function

The central nervous system coordinates the reflex control of blood pressure and distribution of blood to the tissues. The main integrating center is in the medulla oblongata. Because of the complexity of the neural networks involved in cardiovascular control, we will simplify this discussion and refer to this medullary network as the cardiovascular control center (CVCC).

DISTRIBUTION OF BLOOD IN THE BODY AT REST

Blood flow to the major organs is represented in three ways: as a percentage of total flow, as volume per 100 grams of tissue per minute, and as an absolute rate of flow (in L/min).

**Fig. 15.12**

What is the rate of blood flow through the lungs?

The primary function of the cardiovascular control center is to ensure adequate blood flow to the brain and heart by maintaining sufficient mean arterial pressure. However, the CVCC also receives input from other parts of the brain, and it has the ability to alter function in a few organs or tissues while leaving
are lowering rate of the Blood Flow and the Control of Blood Pressure (b) When vessel B constricts, resistance of B increases and flow through B decreases. Flow diverted from B is divided among the lower-resistance vessels A, C, and D.

**FIGURE QUESTION**

You are monitoring blood pressure in the artery at the point indicated by A. What happens to blood pressure when vessel B suddenly constricts?

others unaffected. For example, thermoregulatory centers in the hypothalamus communicate with the CVCC to alter blood flow to the skin. Brain-gut communication following a meal increases blood flow to the intestinal tract. Reflex control of blood flow to selected tissues changes mean arterial pressure, so the CVCC is constantly monitoring and adjusting its output as required to maintain homeostasis.

### The Baroreceptor Reflex Controls Blood Pressure

The primary reflex pathway for homeostatic control of mean arterial blood pressure is the baroreceptor reflex. The components of the reflex are illustrated in Figure 15.14a. Stretch-sensitive mechanoreceptors known as baroreceptors are located in the walls of the carotid arteries and aorta, where they can monitor the pressure of blood flowing to the brain (carotid baroreceptors) and to the body (aortic baroreceptors).

The carotid and aortic baroreceptors are tonically active stretch receptors that fire action potentials continuously at normal blood pressures. When increased blood pressure in the arteries stretches the baroreceptor membrane, the firing rate of the receptor increases. If blood pressure falls, the firing rate of the receptor decreases.

If blood pressure changes, the frequency of action potentials traveling from the baroreceptors to the medullary cardiovascular control center changes. The CVCC integrates the sensory input and initiates an appropriate response. The response of the baroreceptor reflex is quite rapid: changes in cardiac output and peripheral resistance occur within two heartbeats of the stimulus.

Output signals from the cardiovascular control center are carried by both sympathetic and parasympathetic autonomic neurons. Peripheral resistance is under tonic sympathetic control, with increased sympathetic discharge causing vasoconstriction.

Heart function is regulated by antagonistic control. Increased sympathetic activity increases heart rate at the SA node, shortens conduction time through the AV node, and enhances the force of myocardial contraction. Increased parasympathetic activity slows heart rate but has only a small effect on ventricular contraction.

The baroreceptor reflex in response to increased blood pressure is mapped in Fig. 15.14b. Baroreceptors increase their firing rate as blood pressure increases, activating the medullary cardiovascular control center. In response, the cardiovascular control center increases parasympathetic activity and decreases sympathetic activity to slow down the heart and dilate arterioles.

When heart rate falls, cardiac output falls. In the vasculature, decreased sympathetic activity causes dilation of arterioles, lowering their resistance and allowing more blood to flow out of the arteries. Because mean arterial pressure is directly proportional to cardiac output and peripheral resistance (MAP $\propto CO \times R$), the combination of reduced cardiac output and decreased peripheral resistance lowers the mean arterial blood pressure.

It is important to remember that the baroreceptor reflex is functioning all the time, not just with dramatic disturbances in blood pressure, and that it is not an all-or-none response. A change in blood pressure can result in a change in both cardiac output and peripheral resistance or a change in only one of the two variables. Let’s look at an example.

For this example, we will use the schematic diagram in Figure 15.15, which combines the concepts introduced in Figures 15.8 and 15.13. In this model there are four sets of variable resistance arterioles (A–D) whose diameters can be independently controlled by local or reflex control mechanisms. Baroreceptors in the arteries monitor mean arterial pressure and communicate with the medullary cardiovascular control center.
Cardiovascular Control

The intrinsic rate of the heartbeat is modulated by sympathetic and parasympathetic neurons. Blood vessel diameter is under tonic control by the sympathetic division.

(a) CNS control of the heart and blood vessels

(b) The baroreceptor reflex

This map shows the reflex response to an increase in mean arterial pressure.

FIGURE QUESTION
Name the neurotransmitters and receptors for each of the target tissues.

KEY
- Stimulus
- Sensor
- Afferent pathway
- Integrating center
- Output signal
- Target
- Tissue response
- Systemic response
Orthostatic Hypotension Triggers the Baroreceptor Reflex

The baroreceptor reflex functions every morning when you get out of bed. When you are lying flat, gravitational forces are distributed evenly up and down the length of your body, and blood is distributed evenly throughout the circulation. When you stand up, gravity causes blood to pool in the lower extremities. This pooling creates an instantaneous decrease in venous return. As a result, less blood is in the ventricles at the beginning of the next contraction. Cardiac output falls from 5 L/min to 3 L/min, causing arterial blood pressure to decrease. This decrease in blood pressure upon standing is known as orthostatic hypotension [orthos, upright + statikos, to stand].

Orthostatic hypotension normally triggers the baroreceptor reflex. The combination of increased cardiac output and increased peripheral resistance increases mean arterial pressure and brings it back up to normal within two heartbeats. The skeletal muscle pump also contributes to the recovery by enhancing venous return when abdominal and leg muscles contract to maintain an upright position.

The baroreceptor reflex is not always effective, however. For example, during extended bed rest or in the zero-gravity conditions of space flights, blood from the lower extremities is distributed evenly throughout the body rather than pooled in the lower extremities. This even distribution raises arterial pressure, triggering the kidneys to excrete what is perceived as excess fluid. Over the course of three days, excretion of water leads to a 12% decrease in blood volume.

When the person finally gets out of bed or returns to earth, gravity again causes blood to pool in the legs. Orthostatic hypotension occurs, and the baroreceptors attempt to compensate. In this instance, however, the cardiovascular system is unable to restore normal pressure because of the loss of blood volume. As a result, the individual may become dizzy or even faint from reduced delivery of oxygen to the brain.

Concept Check

11. Baroreceptors have stretch-sensitive ion channels in their cell membrane. Increased pressure stretches the receptor membrane, opens the channels, and initiates action potentials. What ion probably flows through these channels and in which direction (into or out of the cell)?

12. Use the map in Fig. 15.14b to map the reflex response to orthostatic hypotension.
Other Systems Influence Cardiovascular Function

Cardiovascular function can be modulated by input from peripheral receptors other than the baroreceptors. For example, arterial chemoreceptors activated by low blood oxygen levels increase cardiac output. The cardiovascular control center also has reciprocal communication with centers in the medulla that control breathing.

The integration of function between the respiratory and circulatory systems is adaptive. If tissues require more oxygen, it is supplied by the cardiovascular system working in tandem with the respiratory system. Consequently, increases in breathing rate are usually accompanied by increases in cardiac output.

Blood pressure is also subject to modulation by higher brain centers, such as the hypothalamus and cerebral cortex. The hypothalamus mediates vascular responses involved in body temperature regulation and for the fight-or-flight response. Learned and emotional responses may originate in the cerebral cortex and be expressed by cardiovascular responses such as blushing and fainting.

One such reflex is vasovagal syncope, which may be triggered in some people by the sight of blood or a hypodermic needle. (Recall Anthony's experience at the beginning of this chapter.) In this pathway, increased parasympathetic activity and decreased sympathetic activity slow heart rate and cause widespread vasodilation. Cardiac output and peripheral resistance both decrease, triggering a precipitous drop in blood pressure. With insufficient blood to the brain, the individual faints.

Regulation of blood pressure in the cardiovascular system is closely tied to regulation of body fluid balance by the kidneys. Certain hormones secreted from the heart act on the kidneys, while hormones secreted from the kidneys act on the heart and blood vessels. Together, the heart and kidneys play a major role in maintaining homeostasis of body fluids, an excellent example of the integration of organ system function.

Concept Check

13. In the movie Jurassic Park, Dr. Ian Malcolm must flee from the T. rex. Draw a reflex map showing the cardiovascular response to his flight-or-flight situation. Remember that flight-or-flight causes epinephrine secretion as well as output from the cardiovascular control center. (Hints: What is the stimulus? Fear is integrated in the limbic system.)

Exchange at the Capillaries

The transport of materials around the body is only part of the function of the cardiovascular system. Once blood reaches the capillaries, the plasma and the cells exchange materials across the thin capillary walls. Most cells are located within 0.1 mm of the nearest capillary, and diffusion over this short distance proceeds rapidly.

The capillary density in any given tissue is directly related to the metabolic activity of the tissue's cells. Tissues with a higher metabolic rate require more oxygen and nutrients. Those tissues have more capillaries per unit area. Subcutaneous tissue and cartilage have the lowest capillary density. Muscles and glands have the highest. By one estimate, the adult human body has about 50,000 miles of capillaries, with a total exchange surface area of more than 6300 m², nearly the surface area of two football fields.

Capillaries have the thinnest walls of all the blood vessels, composed of a single layer of flattened endothelial cells supported on a basal lamina (Fig. 15.2). The diameter of a capillary is barely larger than that of a red blood cell, forcing the RBCs to pass through in single file. Cell junctions between the endothelial cells vary from tissue to tissue and help determine the "leakiness" of the capillary.

The most common capillaries are continuous capillaries, whose endothelial cells are joined to one another with leaky junctions (Fig. 15.16a). These capillaries are found in muscle, connective tissue, and neural tissue. The continuous capillaries of the brain have evolved to form the blood-brain barrier, with tight junctions that protect neural tissue from toxins that may be present in the bloodstream.

Fenestrated capillaries (fenestra, window) have large pores (fenestrae) that allow high volumes of fluid to pass rapidly between the plasma and interstitial fluid (Fig. 15.16b). These capillaries are found primarily in the kidney and the intestine, where they are associated with absorptive transporting epithelia.

Three tissues—the bone marrow, the liver, and the spleen—do not have typical capillaries. Instead they have modified vessels called sinusoids that are as much as five times wider than a capillary. The sinusoidal endothelium has fenestrations, and there may be gaps between the cells as well. Sinusoids are found in locations where blood cells and plasma proteins need to cross the endothelium to enter the blood. In the liver, the sinusoidal endothelium lacks a basal lamina, which allows even more free exchange between plasma and interstitial fluid.

Velocity of Blood Flow Is Lowest in the Capillaries

The rate at which blood flows through the capillaries plays a role in the efficiency of exchange between the blood and the interstitial fluid. At a constant flow rate, velocity of flow is higher in a smaller diameter tube than in a larger one. From this, you might conclude that blood moves very rapidly through the capillaries because they are the smallest blood vessels. However, the primary determinant for velocity is not the diameter of an individual capillary but the total cross-sectional area of all the capillaries.
Blood Flow and the Control of Blood Pressure

What is total cross-sectional area? Imagine circles representing cross sections of all the capillaries placed edge to edge, and you have it. For the capillaries, those circles would cover an area much larger than the total cross-sectional areas of all the arteries and veins combined. Therefore, because total cross-sectional area of the capillaries is so large, the velocity of flow through them is low.

Figure 15.17 compares cross-sectional areas of different parts of the systemic circulation with the velocity of blood flow in each part. The fastest flow is in the relatively small-diameter arterial system. The slowest flow is in the capillaries and venules, which collectively have the largest cross-sectional area. The low velocity of flow through capillaries is a useful characteristic that allows enough time for diffusion to go to equilibrium.

Most Capillary Exchange Takes Place by Diffusion and Transcytosis

Exchange between the plasma and interstitial fluid takes place either by movement between endothelial cells (the paracellular pathway) or by movement through the cells (endothelial transport). Smaller dissolved solutes and gases move by diffusion between or through the cells, depending on their lipid solubility. Larger solutes and proteins move mostly by vesicular transport.

The diffusion rate for dissolved solutes is determined primarily by the concentration gradient between the plasma and the interstitial fluid. Oxygen and carbon dioxide diffuse freely across the thin endothelium. Their plasma concentrations reach equilibrium with the interstitial fluid and cells by the time blood reaches the venous end of the capillary. In capillaries with leaky cell junctions, most small dissolved solutes can diffuse freely between the cells or through the fenestrae.

In continuous capillaries, blood cells and most plasma proteins are unable to pass through the junctions between endothelial cells. However, we know that proteins do move from plasma to interstitial fluid and vice versa. In most capillaries, larger molecules (including selected proteins) are transported across the endothelium by transcytosis. The endothelial cell surface appears dotted with numerous caveolae and noncoated pits that become vesicles for transcytosis. It appears that in some capillaries, chains of vesicles fuse to create open channels that extend across the endothelial cell (Fig. 15.16).

Capillary Filtration and Absorption Take Place by Bulk Flow

A third form of capillary exchange is bulk flow into and out of the capillary. Bulk flow refers to the mass movement of fluid as the result of hydrostatic or osmotic pressure gradients. If the direction of bulk flow is into the capillary, the fluid movement is called absorption. If the direction of flow is out of the capillary,
Blood Flow and the Control of Blood Pressure

The fluid movement is known as filtration. Capillary filtration is caused by hydrostatic pressure that forces fluid out of the capillary through leaky cell junctions. As an analogy, think of garden “soaker” hoses whose perforated walls allow water to ooze out.

Most capillaries show a transition from net filtration at the arterial end to net absorption at the venous end. There are some exceptions to this rule, though. Capillaries in part of the kidney filter fluid along their entire length, for instance, and some capillaries in the intestine are only absorptive, picking up digested nutrients that have been transported into the interstitial fluid from the lumen of the intestine.

Two forces regulate bulk flow in the capillaries. One is hydrostatic pressure, the lateral pressure component of blood flow that pushes fluid out through the capillary pores, and the other is osmotic pressure. These forces are sometimes called Starling forces, after the English physiologist E. H. Starling, who first described them (the same Starling as in the Frank-Starling law of the heart).

Osmotic pressure is determined by solute concentration of a compartment. The main solute difference between plasma and interstitial fluid is due to proteins, which are present in the plasma but mostly absent from interstitial fluid. The osmotic pressure created by the presence of these proteins is known as colloid osmotic pressure (\(\pi\)), also called oncotic pressure.

Colloid osmotic pressure is not equivalent to the total osmotic pressure in a capillary. It is simply a measure of the osmotic pressure created by proteins. Because the capillary endothelium is freely permeable to ions and other solutes in the plasma and interstitial fluid, these other solutes do not contribute to the osmotic gradient.

Colloid osmotic pressure is higher in the plasma (\(\pi_{\text{cap}} = 25\) mm Hg) than in the interstitial fluid (\(\pi_{\text{if}} = 0\) mm Hg). Therefore, the osmotic gradient favors water movement by osmosis from the interstitial fluid into the plasma, represented by the red arrows in Figure 15.18b. For the purposes of our discussion, colloid osmotic pressure is constant along the length of the capillary, at \(\pi = 25\) mm Hg.

Capillary hydrostatic pressure (\(P_{\text{H}}\)), by contrast, decreases along the length of the capillary as energy is lost to friction. Average values for capillary hydrostatic pressure, shown in Fig. 15.18b, are 32 mm Hg at the arterial end of a capillary and 15 mm Hg at the venous end. The hydrostatic pressure of the interstitial fluid (\(P_{\text{if}}\)) is very low, and so we consider it to be essentially zero. This means that water movement due to hydrostatic pressure is directed out of the capillary, as denoted by the blue arrows in Fig. 15.18b, with the pressure gradient decreasing from the arterial end to the venous end.

If we assume that the interstitial hydrostatic and colloid osmotic pressures are zero, as discussed above, then the net pressure driving fluid flow across the capillary is determined by the difference between the hydrostatic pressure (\(P_{\text{H}}\)) and the colloid osmotic pressure (\(\pi\)):

\[
\text{Net pressure} = P_{\text{H}} - \pi
\]

A positive value for the net pressure indicates net filtration and a negative value indicates net absorption.

Using the hydrostatic and oncotic pressure values given in Fig. 15.18b, we can calculate the following values at the arterial end of a capillary:

\[
\text{Net pressure} = P_{\text{H}} (32\ \text{mm Hg}) - \pi (25\ \text{mm Hg}) = 7\ \text{mm Hg}
\]

At the arterial end, \(P_{\text{H}}\) is greater than \(\pi\), so the net pressure is 7 mm Hg of filtration pressure.

At the venous end, where capillary hydrostatic pressure is less:

\[
\text{Net pressure}_{\text{venous end}} = (15\ \text{mm Hg} - 25\ \text{mm Hg}) = -10\ \text{mm Hg}
\]

At the venous end, \(\pi\) is greater than \(P_{\text{H}}\), the net pressure is -10 mm Hg, favoring absorption. (A negative net pressure indicates absorption.)
Fluid movement down the length of a capillary is shown in Fig. 15.18b. There is net filtration at the arterial end and net absorption at the venous end. If the point at which filtration equals absorption occurred in the middle of the capillary, there would be no net movement of fluid. All volume that was filtered at the arterial end would be absorbed at the venous end. However, filtration is usually greater than absorption, resulting in bulk flow of fluid out of the capillary into the interstitial space.

By most estimates, that bulk flow amounts to about 3 liters per day, which is the equivalent of the entire plasma volume! If this filtered fluid could not be returned to the plasma, the blood would turn into a sludge of blood cells and proteins. Restoring fluid lost from the capillaries to the circulatory system is one of the functions of the lymphatic system, which we discuss next.
Blood Flow and the Control of Blood Pressure

The Lymphatic System

The vessels of the lymphatic system interact with three other physiological systems: the cardiovascular system, the digestive system, and the immune system. Functions of the lymphatic system include (1) returning fluid and proteins filtered out of the capillaries to the circulatory system, (2) picking up fat absorbed at the small intestine and transferring it to the circulatory system, and (3) serving as a filter to help capture and destroy foreign pathogens. In this discussion we focus on the role of the lymphatic system in fluid transport.

The lymphatic system allows the one-way movement of interstitial fluid from the tissues into the circulation. Blind-end lymph vessels (lymph capillaries) lie close to all blood capillaries except those in the kidney and central nervous system (Fig. 15.18a). The smallest lymph vessels are composed of a single layer of flattened endothelium that is even thinner than the capillary endothelium.

The walls of these tiny lymph vessels are anchored to the surrounding connective tissue by fibers that hold the thin-walled vessels open. Large gaps between cells allow fluid, interstitial proteins, and particulate matter such as bacteria to be swept into the lymph vessels, also called lymphatics, by bulk flow. Once inside the lymphatics, this clear fluid is called simply lymph.

Lymph vessels in the tissues join one another to form larger lymphatic vessels that progressively increase in size (Fig. 15.19). These vessels have a system of semilunar valves, similar to valves in the venous circulation. The largest lymph ducts empty into the venous circulation just under the clavicles, where the left and right subclavian veins join the internal jugular veins. At intervals along the way, vessels enter lymph nodes, bean-shaped nodules of tissue with a fibrous outer capsule and an internal collection of immunologically active cells, including lymphocytes and macrophages.

The lymphatic system has no single pump like the heart. Lymph flow depends primarily on waves of contraction of smooth muscle in the walls of the larger lymph vessels. Flow is aided by contractile fibers in the endothelial cells, by the one-way valves, and by external compression created by skeletal muscles.

The skeletal muscle pump plays a significant role in lymph flow, as you know if you have ever injured a wrist or ankle. An immobilized limb frequently swells from the accumulation of fluid in the interstitial space, a condition known as edema (oedema, swelling). Patients with edema in an injured limb are told to elevate the limb above the level of the heart so that gravity can assist lymph flow back to the blood.

An important reason for returning filtered fluid to the circulation is the recycling of plasma proteins. The body must maintain a low protein concentration in the interstitial fluid because colloid osmotic pressure is the only significant force that opposes capillary hydrostatic pressure. If proteins move from the plasma to the interstitial fluid, the osmotic pressure gradient that opposes filtration decreases. With less opposition to capillary hydrostatic pressure, additional fluid moves into the interstitial space.

Inflammation is an example of a situation in which the balance of colloid osmotic and hydrostatic pressures is disrupted. Histamine released in the inflammatory response makes capillary walls leakier and allows proteins to escape from the plasma into the interstitial fluid. The local swelling that accompanies a region of inflammation is an example of edema caused by redistribution of proteins from the plasma to the interstitial fluid.
malnutrition or liver failure. The liver is the main site for plasma protein synthesis.

3. An increase in interstitial proteins. As discussed earlier, excessive leakage of proteins out of the blood decreases the colloid osmotic pressure gradient and increases net capillary filtration.

On occasion, changes in the balance between filtration and absorption help the body maintain homeostasis. For example, if arterial blood pressure falls, capillary hydrostatic pressure also decreases. This change increases fluid absorption. If blood pressure falls low enough, there is net absorption in the capillaries rather than net filtration. This passive mechanism helps maintain blood volume in situations in which blood pressure is very low, such as hemorrhage or severe dehydration.

## Edema Results from Alterations in Capillary Exchange

Edema is a sign that normal exchange between the circulatory system and the lymphatics has been disrupted. Edema usually arises from one of two causes: (1) inadequate drainage of lymph or (2) blood capillary filtration that greatly exceeds capillary absorption.

Inadequate lymph drainage occurs with obstruction of the lymphatic system, particularly at the lymph nodes. Parasites, cancer, or fibrotic tissue growth caused by therapeutic radiation can block the movement of lymph through the system. For example, *elephantiasis* is a chronic condition marked by gross enlargement of the legs and lower appendages when parasites block the lymph vessels. Lymph drainage may also be impaired if lymph nodes are removed during surgery, a common procedure in the diagnosis and treatment of cancer.

Factors that disrupt the normal balance between capillary filtration and absorption include:

1. An increase in capillary hydrostatic pressure. Increased hydrostatic pressure is usually indicative of elevated venous pressure. An increase in arterial pressure is generally not noticeable at the capillaries because of autoregulation of pressure in the arterioles.

   One common cause of increased venous pressure is *heart failure*, a condition in which one ventricle loses pumping power and can no longer pump all the blood sent to it by the other ventricle. For example, if the right ventricle begins to fail but the left ventricle maintains its cardiac output, blood accumulates in the systemic circulation. Blood pressure rises first in the right atrium, then in the veins and capillaries draining into the right side of the heart. When capillary hydrostatic pressure increases, filtration greatly exceeds absorption, leading to edema.

2. A decrease in plasma protein concentration. Plasma protein concentrations may decrease as a result of severe
Cardiovascular Disease

Disorders of the heart and blood vessels, such as heart attacks and strokes, play a role in more than half of all deaths in the United States. The American Heart Association predicted that by 2030 over 40% of the U.S. population will have cardiovascular disease. The direct medical costs for these people are expected to triple, to more than $800 billion. The prevalence of cardiovascular disease is reflected in the tremendous amount of research being done worldwide. The scientific investigations range from large-scale clinical studies that track cardiovascular disease in thousands of people, such as the Framingham (Massachusetts) Heart Study, to experiments at the cellular and molecular levels.

Much of the research at the cellular and molecular levels is designed to expand our understanding of both normal and abnormal function in the heart and blood vessels. Scientists are studying a virtual alphabet soup of transporters and regulators. Some of these molecules, such as adenosine, endothelin, vascular endothelial growth factor (VEGF), phospholamban, and nitric oxide, you have studied here.

As we increase our knowledge of cardiovascular function, we also begin to understand the actions of drugs that have been used for centuries. A classic example is the cardiac glycoside *digitalis*, whose mechanism of action was explained when scientists discovered the role of Na⁺-K⁺-ATPase. It is a sobering thought to realize that for many therapeutic drugs, we know what they do without fully understanding how they do it.

Risk Factors Include Smoking and Obesity

Conducting and interpreting research on humans is a complicated endeavor in part because of the difficulty of designing well-controlled experiments. The economic and social importance of cardiovascular disease (CVD) makes it the focus of many studies each year as researchers try to improve treatments and prediction algorithms. (An algorithm is a set of rules or a sequence of steps used to solve a problem.) We can predict the likelihood that a person will develop cardiovascular disease during his or her lifetime by examining the various risk factors that the person possesses. The list of risk factors described here is the result of following the medical histories of thousands of people for many years in studies such as the Framingham Heart Study. As more data become available, additional risk factors may be added.

Risk factors are generally divided into those over which the person has no control and those that can be controlled. Medical intervention is aimed at reducing risk from the controllable factors. The risk factors that cannot be controlled include sex, age, and a family history of early cardiovascular disease. As noted earlier in the chapter, *coronary heart disease* (CHD) is a form of cardiovascular disease in which the coronary arteries become blocked by cholesterol deposits and blood clots. Up until middle age, men have a 3–4 times higher risk of developing CHD than do women. After age 55, when most women have entered menopause, the death rate from CHD equalsizes in men and women. In general, the risk of coronary heart disease increases as people age. Heredity also plays an important role. If a person has one or more close relatives with this condition, his or her risk is elevated.

Risk factors that can be controlled include cigarette smoking, obesity, sedentary lifestyle, and untreated hypertension. In the United States, smoking-related illnesses are the primary preventable cause of death, followed by conditions related to overweight and obesity. Physical inactivity and obesity have been steadily increasing in the United States since 1991, and currently nearly 70% of U.S. adults are either overweight or obese.

Two risk factors for cardiovascular disease—diabetes mellitus and elevated blood lipids—have both an uncontrollable genetic component and a modifiable lifestyle component. Diabetes mellitus is a metabolic disorder that puts a person at risk for developing coronary heart disease by contributing to the development of *atherosclerosis* (“hardening of the arteries”), in which fatty deposits form inside arterial blood vessels. Elevated serum cholesterol and triglycerides also lead to atherosclerosis. The increasing prevalence of these risk factors has created an epidemic in the United States, with one in
every 3.4 deaths in 2009 attributed to all forms of cardiovascular disease.

**Atherosclerosis Is an Inflammatory Process**

Coronary heart disease accounts for the majority of cardiovascular disease deaths and is the single largest killer of Americans, both men and women. Let’s look at the underlying cause of this disease: atherosclerosis.

The role of elevated blood cholesterol in the development of atherosclerosis is well established. Cholesterol, like other lipids, is not very soluble in aqueous solutions, such as the plasma. Therefore, when cholesterol in the diet is absorbed from the digestive tract, it combines with lipoproteins to make it more soluble. Clinicians generally are concerned with two of these: high-density lipoprotein-cholesterol (HDL-C) complexes and low-density lipoprotein-cholesterol (LDL-C) complexes. HDL-C is the more desirable form of blood cholesterol because high levels of HDL are associated with lower risk of heart attacks. (Memory aid: “H” in HDL stands for “healthy.”)

LDL-C is sometimes called “bad” cholesterol because elevated plasma LDL-C levels are associated with coronary heart disease. (Remember this by associating “L” with “lethal.”) Normal levels of LDL-C are not bad, however, because LDL is necessary for cholesterol transport into cells. LDL-C’s binding site—a protein called apoB—combines with an LDL receptor found in clathrin-coated pits on the cell membrane, and the receptor-LDL-C complex is brought into the cell by endocytosis. The LDL receptor recycles to the cell membrane, and the endosome fuses with a lysosome. LDL-C’s proteins are digested to amino acids, and the freed cholesterol is used to make cell membranes or steroid hormones.

Although LDL is needed for cellular uptake of cholesterol, excess levels of plasma LDL-C lead to atherosclerosis. Endothelial cells lining the arteries transport LDL-C into the extracellular space so that it accumulates just under the intima. There, white blood cells called macrophages ingest cholesterol and other lipids to become lipid-filled foam cells. Cytokines released by the macrophages promote smooth muscle cell division. This early-stage lesion (laesio, injury) is called a fatty streak.

As the condition progresses, the lipid core grows, and smooth muscle cells reproduce, forming bulging plaques that protrude into the lumen of the artery. In the advanced stages of atherosclerosis, the plaques develop hard, calcified regions and fibrous collagen caps. The mechanism by which calcium carbonate is deposited is still being investigated.

Scientists once believed that the occlusion (blockage) of coronary blood vessels by large plaques that triggered blood clots was the primary cause of heart attacks, but that model has been revised. The new model indicates that blood clot formation on plaques is more dependent on the structure of a plaque than on its size. Atherosclerosis is now considered to be an inflammatory process in which macrophages release enzymes that convert stable plaques to vulnerable plaques.

**EMERGING CONCEPTS**

**Inflammatory Markers for Cardiovascular Disease**

In clinical studies, it is sometimes difficult to determine whether a factor that has a positive correlation with a disease function in a cause-effect relationship or represents a simple association. For example, two factors associated with higher incidence of heart disease are C-reactive protein and homocysteine. C-reactive protein (CRP) is a molecule involved in the body’s response to inflammation. In one study, women who had elevated CRP levels were more than twice as likely to have a serious cardiovascular problem as women with low CRP. Does this finding mean that CRP is causing cardiovascular disease? Or could it simply be a marker that can be used clinically to predict who is more likely to develop cardiovascular complications, such as a heart attack or stroke?

Similarly, elevated homocysteine levels are associated with an increased incidence of CVD. Homocysteine is an amino acid that takes part in a complicated metabolic pathway that also requires folic acid and vitamin B₁₂ as cofactors. Should physicians routinely measure homocysteine along with cholesterol? Currently there is little clinical evidence to show that reducing either CRP or homocysteine decreases a person’s risk of developing CVD. If these two markers are not indicators for modifiable risk factors, should a patient’s insurance be asked to pay for the tests used to detect them?
**Hypertension Represents a Failure of Homeostasis**

One controllable risk factor for cardiovascular disease is hypertension—chronically elevated blood pressure, with systolic pressures greater than 130–140 mm Hg or diastolic pressures greater than 80–90 mm Hg. Hypertension is a common disease in the United States and is one of the most common reasons for visits to physicians and for the use of prescription drugs. High blood pressure is associated with increasing risk of CVD: the risk doubles for each 20/10 mm Hg increase in blood pressure over a baseline value of 115/75 (Fig. 15.22).

More than 90% of all patients with hypertension are considered to have essential (or primary) hypertension, with no clear-cut cause other than heredity. Cardiac output is usually normal in these people, and their elevated blood pressure appears to be associated with increased peripheral resistance. Some investigators have speculated that the increased resistance may be due to a lack of nitric
Despite the increasing amount of work that the ventricle must perform as blood pressure increases, the cardiac muscle of the left ventricle responds to chronic high systemic resistance in the same way that skeletal muscle responds to a weight-lifting routine. The heart muscle hypertrophies, increasing the size and strength of the muscle fibers.

However, if resistance remains high over time, the heart muscle cannot meet the work load and begins to fail: cardiac output by the left ventricle decreases. If cardiac output of the right heart remains normal while the output from the left side decreases, fluid collects in the lungs, creating pulmonary edema. At this point, a detrimental positive feedback loop begins. Oxygen exchange in the lungs diminishes because of the pulmonary edema, leading to less oxygen in the blood. Lack of oxygen for aerobic metabolism further weakens the heart, and its pumping effectiveness diminishes even more. Unless treated, this condition, known as congestive heart failure, eventually leads to death.

Many of the treatments for hypertension have their basis in the cardiovascular physiology you have learned. For example, calcium entry into vascular smooth muscle and cardiac muscle can be decreased by a class of drugs known as calcium channel blockers. These drugs bind to Ca\(^{2+}\) channel proteins, making it less likely that the channels will open in response to depolarization. With less Ca\(^{2+}\) entry, vascular smooth muscle dilates, while in the heart the depolarization rate of the SA node and the force of contraction decrease.

Vascular smooth muscle is more sensitive than cardiac muscle to certain classes of calcium channel blockers, and it is possible to get vasodilation at drug doses that are low enough to have no effect on heart rate. Other tissues with Ca\(^{2+}\) channels, such as neurons, are only minimally affected by calcium channel blockers because their Ca\(^{2+}\) channels are of a different subtype.

Other drugs used to treat hypertension include diuretics, which decrease blood volume, and beta-blocking drugs that target \(\beta_1\)-receptors and decrease catecholamine stimulation of cardiac output. Two other groups of antihypertensive drugs, the ACE inhibitors and the angiotensin receptor blockers, act by decreasing the activity of angiotensin, a powerful vasoconstrictor substance. In the future, we may be seeing new treatments for hypertension that are based on other aspects of the molecular physiology of the heart and blood vessels.

**RUNNING PROBLEM CONCLUSION**

**Essential Hypertension**

Kurt remained on the calcium channel blocker and diuretic, and after several months his cough went away and his blood pressure stabilized at 130/85—a significant improvement. Kurt’s new diet also brought his total blood cholesterol down below 200 mg/dL plasma. By improving two of his controllable risk factors, Kurt decreased his...
RUNNING PROBLEM CONCLUSION (continued)

1. Why are people with high blood pressure at greater risk for having a hemorrhagic (or bleeding) stroke?

- High blood pressure exerts force on the walls of the blood vessels.
- If an area of blood vessel wall is weakened or damaged, high blood pressure may cause that area to rupture, allowing blood to leak out of the vessel into the surrounding tissues.

2. What is the rationale for reducing salt intake and taking a diuretic to control hypertension?

- Salt causes water retention. Diuretics increase renal fluid excretion.
- Blood pressure increases if the circulating blood volume increases. By restricting salt in the diet, a person can decrease retention of fluid in the extracellular compartment, which includes the plasma. Diuretics also help decrease blood volume.

3. Why would blocking the action of a vasoconstrictor lower blood pressure?

- Blood pressure is determined by cardiac output and peripheral resistance.
- Resistance is inversely proportional to the radius of the blood vessels. Therefore, if blood vessels dilate as a result of blocking a vasoconstrictor, resistance and blood pressure decrease.

4. How do calcium channel blockers lower blood pressure?

- Calcium entry from the extracellular fluid plays an important role in both smooth muscle and cardiac muscle contraction.
- Blocking Ca\(^{2+}\) entry through Ca\(^{2+}\) channels decreases the force of cardiac contraction and decreases the contractility of vascular smooth muscle. Both of these effects lower blood pressure.

chances of having a heart attack. To learn more about hypertension and some of the therapies currently used to treat it, visit the web site of the American Heart Association (www.americanheart.org). Now check your understanding of this running problem by comparing your answers with the information in the summary table.

<table>
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Chapter Summary

Blood flow through the cardiovascular system is an excellent example of mass flow in the body. Cardiac contraction creates high pressure in the ventricles, and this pressure drives blood through the vessels of the systemic and pulmonary circuits, speeding up cell-to-cell communication. Resistance to flow is regulated by local and reflex control mechanisms that act on arteriolar smooth muscle and help match tissue perfusion to tissue needs. The homeostatic baroreceptor reflex monitors arterial pressure to ensure adequate perfusion of the brain and heart. Capillary exchange of material between the plasma and interstitial fluid compartments uses several transport mechanisms, including diffusion, transcytosis, and bulk flow.

1. Homeostatic regulation of the cardiovascular system is aimed at maintaining adequate blood flow to the brain and heart.
2. Total blood flow at any level of the circulation is equal to the cardiac output.
The Blood Vessels

3. Blood vessels are composed of layers of smooth muscle, elastic and fibrous connective tissue, and endothelium. (Fig. 15.2)
4. Vascular smooth muscle maintains a state of muscle tone.
5. The walls of the aorta and major arteries are both stiff and springy. This property allows them to absorb energy and release it through elastic recoil.
6. Metarterioles regulate blood flow through capillaries and allow white blood cells to go directly from arterioles to the venous circulation. Blood flow into individual capillaries can be regulated by precapillary sphincters. (Fig. 15.3)
7. Capillaries and postcapillary venules are the site of exchange between blood and interstitial fluid.
8. Veins hold more than half of the blood in the circulatory system. Veins have thinner walls with less elastic tissue than arteries, so veins expand easily when they fill with blood.
9. Angiogenesis is the process by which new blood vessels grow and develop, especially after birth.

Blood Pressure

10. The ventricles create high pressure that is the driving force for blood flow. The aorta and arteries act as a pressure reservoir during ventricular relaxation. (Fig. 15.5)
11. Blood pressure is highest in the arteries and decreases as blood flows through the circulatory system. At rest, desirable systolic pressure is 120 mm Hg or less, and desirable diastolic pressure is 80 mm Hg or less. (Fig. 15.6)
12. Pressure created by the ventricles can be felt as a pulse in the arteries. Pulse pressure equals systolic pressure minus diastolic pressure.
13. Blood flow against gravity in the veins is assisted by one-way valves and by the respiratory and skeletal muscle pumps. (Fig. 15.4)
14. Arterial blood pressure is indicative of the driving pressure for blood flow. Mean arterial pressure (MAP) is defined as diastolic pressure + 1/3 (systolic pressure – diastolic pressure).
15. Arterial blood pressure is usually measured with a sphygmomanometer. Blood squeezing through a compressed brachial artery makes Korotkoff sounds. (Fig. 15.7)
16. Arterial pressure is a balance between cardiac output and the resistance to blood flow offered by the arterioles (peripheral resistance). (Fig. 15.8)
17. If blood volume increases, blood pressure increases. If blood volume decreases, blood pressure decreases. (Fig. 15.9)
18. Venous blood volume can be shifted to the arteries if arterial blood pressure falls. (Fig. 15.1)

Resistance in the Arterioles

19. The arterioles are the main site of variable resistance in the systemic circulation. A small change in the radius of an arteriole creates a large change in resistance: \( R \propto \frac{1}{r^4} \).
20. Arterioles regulate their own blood flow through myogenic autoregulation. Vasodilation increases the resistance offered by an arteriole and decreases the blood flow through the arteriole.
21. Arteriolar resistance is influenced by local control mechanisms that match tissue blood flow to the metabolic needs of the tissue. Vasodilator paracrine include nitric oxide, \( H^+ \), \( K^+ \), \( CO_2 \), prostaglandins, adenosine, and histamine. Low \( O_2 \) causes vasodilation. Endothelins are powerful vasoconstrictors. (Tbl. 15.2)
22. Active hyperemia is a process in which increased blood flow accompanies increased metabolic activity. Reactive hyperemia is an increase in tissue blood flow following a period of low perfusion. (Fig. 15.10)
23. Most systemic arterioles are under tonic sympathetic control. Noradrenaline causes vasoconstriction. Decreased sympathetic stimulation causes vasodilation.
24. Epinephrine binds to arteriolar \( \alpha \)-receptors and causes vasoconstriction. Epinephrine on \( \beta_2 \)-receptors, found in the arterioles of the heart, liver, and skeletal muscle, causes vasodilation.

Distribution of Blood to the Tissues

25. Changing the resistance of the arterioles affects mean arterial pressure and alters blood flow through the arteriole. (Fig. 15.15)
26. The flow through individual arterioles depends on their resistance. The higher the resistance in an arteriole, the lower the blood flow in that arteriole: \( \text{Flow}_{\text{arteriole}} \propto \frac{1}{R_{\text{arteriole}}} \).

Regulation of Cardiovascular Function

27. The reflex control of blood pressure resides in the medulla oblongata. Baroreceptors in the carotid artery and the aorta monitor arterial blood pressure and trigger the baroreceptor reflex. (Fig. 15.14)
28. Efferent output from the medullary cardiovascular control center goes to the heart and arterioles. Increased sympathetic activity increases heart rate and force of contraction. Increased parasympathetic activity slows heart rate. Increased sympathetic discharge at the arterioles causes vasoconstriction. There is no significant parasympathetic control of arterioles.
29. Cardiovascular function can be modulated by input from higher brain centers and from the respiratory control center of the medulla.
30. The baroreceptor reflex functions each time a person stands up. The decrease in blood pressure upon standing is known as orthostatic hypotension.

Exchange at the Capillaries

31. Exchange of materials between the blood and the interstitial fluid occurs primarily by diffusion.
32. Continuous capillaries have leaky junctions between cells but also transport material using transcytosis. Continuous capillaries with tight junctions form the blood-brain barrier. (Fig. 15.16)

33. Fenestrated capillaries have pores that allow large volumes of fluid to pass rapidly. (Fig. 15.16)

34. The velocity of blood flow through the capillaries is slow, allowing diffusion to go to equilibrium. (Fig. 15.17)

35. The mass movement of fluid between the blood and the interstitial fluid is bulk flow. Fluid movement is called filtration if the direction of flow is out of the capillary and absorption if the flow is directed into the capillary. (Fig. 15.18)

36. The osmotic pressure difference between plasma and interstitial fluid due to the presence of plasma proteins is the colloid osmotic pressure.

The Lymphatic System

37. About 3 liters of fluid filter out of the capillaries each day. The lymphatic system returns this fluid to the circulatory system. (Fig. 15.19)

Questions

Level One  Reviewing Facts and Terms

1. The first priority of blood pressure homeostasis is to maintain adequate perfusion to which two organs?

2. Match the types of systemic blood vessels with the terms that describe them. Each vessel type may have more than one match, and matching items may be used more than once.

| (a) arterioles | 1. store pressure generated by the heart |
| (b) arteries    | 2. have walls that are both stiff and elastic |
| (c) capillaries | 3. carry low-oxygen blood |
| (d) veins       | 4. have thin walls of exchange epithelium |
| (e) venules     | 5. act as a volume reservoir |
|                | 6. their diameter can be altered by neural input |
|                | 7. blood flow slowest through these vessels |
|                | 8. have lowest blood pressure |
|                | 9. are the main site of variable resistance |

3. List the four tissue components of blood vessel walls, in order from inner lining to outer covering. Briefly describe the importance of each tissue.

4. Blood flow to individual tissues is regulated by selective vasoconstriction and vasodilation of which vessels?

5. Aortic pressure reaches a typical high value of ________ (give both numeric value and units) during ________, or contraction of the heart. As the heart relaxes during the event called ________, aortic pressure declines to a typical low value of ________. This blood pressure reading would be written as ________/______.

6. The rapid pressure increase that occurs when the left ventricle pushes blood into the aorta can be felt as a pressure wave, or ________. What is the equation used to calculate the strength of this pressure wave?

7. List the factors that aid venous return to the heart.

8. What is hypertension, and why is it a threat to a person’s health?

9. When measuring a person’s blood pressure, at what point in the procedure are you likely to hear Korotkoff sounds?

10. List three paracines that cause vasodilation. What is the source of each one? In addition to paracines, list two other ways to control smooth muscle contraction in arterioles.

11. What is hyperemia? How does active hyperemia differ from reactive hyperemia?

12. Most systemic arterioles are innervated by the ________ branch of the nervous system. Increased sympathetic input will have what effect on arteriole diameter?

13. Match each event in the left column with all appropriate neurotransmitter(s) and receptor(s) from the list on the right.

   - (a) vasoconstriction of intestinal arterioles
   - (b) vasodilation of coronary arterioles
   - (c) increased heart rate
   - (d) decreased heart rate
   - (e) vasoconstriction of coronary arterioles

   - 1. norepinephrine
   - 2. epinephrine
   - 3. acetylcholine
   - 4. β₁-receptor
   - 5. α-receptor
   - 6. β₂-receptor
   - 7. nicotinic receptor
   - 8. muscarinic receptor

14. Which organs receive more than two-thirds of the cardiac output at rest? Which organs have the highest flow of blood on a per unit weight basis?

15. By looking at the density of capillaries in a tissue, you can make assumptions about what property of the tissue? Which tissue has the lowest capillary density? Which tissue has the highest?

16. What type of transport is used to move each of the following substances across the capillary endothelium?

   - (a) oxygen
   - (b) proteins
   - (c) glucose
   - (d) water

Cardiovascular Disease

40. Cardiovascular disease is the leading cause of death in the United States. Risk factors predict the likelihood that a person will develop cardiovascular disease during her or his lifetime.

41. Atherosclerosis is an inflammatory condition in which fatty deposits called plaques develop in arteries. If plaques are unstable, they may block the arteries by triggering blood clots. (Fig. 15.21)

42. Hypertension is a significant risk factor for the development of cardiovascular disease. (Fig. 15.22)
17. With which three physiological systems do the vessels of the lymphatic system interact?

18. Define edema. List some ways in which it can arise.

19. Define the following terms and explain their significance to cardiovascular physiology.
   (a) perfusion
   (b) colloid osmotic pressure
   (c) vasoconstriction
   (d) angiogenesis
   (e) metarterioles
   (f) pericytes

20. The two major lipoprotein carriers of cholesterol are ______ and ______. Which type is bad when present in the body in elevated amounts?

Level Two Reviewing Concepts

21. Concept map: Map all the following factors that influence mean arterial pressure. You may add terms.

   - aorta
   - arteriole
   - baroreceptor
   - blood volume
   - cardiac output
   - carotid artery
   - contractility
   - heart rate
   - medulla oblongata
   - parasympathetic neuron
   - peripheral resistance
   - SA node
   - sensory neuron
   - stroke volume
   - sympathetic neuron
   - vein
   - venous return
   - ventricle

22. Compare and contrast the following sets of terms:
   (a) lymphatic capillaries and systemic capillaries
   (b) roles of the sympathetic and parasympathetic branches in blood pressure control
   (c) lymph and blood
   (d) continuous capillaries and fenestrated capillaries
   (e) hydrostatic pressure and colloid osmotic pressure in systemic capillaries

23. Calcium channel blockers prevent Ca\(^{2+}\) movement through Ca\(^{2+}\) channels. Explain two ways this action lowers blood pressure. Why are neurons and other cells unaffected by these drugs?

24. Define myogenic autoregulation. What mechanisms have been proposed to explain it?

25. Left ventricular failure may be accompanied by edema, shortness of breath, and increased venous pressure. Explain how these signs and symptoms develop.

Level Three Problem Solving

26. Robert is a 52-year-old nonsmoker. He weighs 180 lbs and stands 5’9” tall, and his blood pressure averaged 145/95 on three successive visits to his doctor’s office. His father, grandfather, and uncle all had heart attacks in their early 50s, and his mother died of a stroke at the age of 71.
   (a) Identify Robert’s risk factors for coronary heart disease.
   (b) Does Robert have hypertension? Explain.
   (c) Robert’s doctor prescribes a drug called a beta blocker. Explain the mechanism by which a beta-receptor-blocking drug may help lower blood pressure.

27. The following figure is a schematic representation of the systemic circulation. Use it to help answer the following questions. (CO = cardiac output, MAP = mean arterial pressure).
   (a) If resistance in vessels 1 and 2 increases because of the presence of local paracines but cardiac output is unchanged, what happens to MAP? What happens to flow through vessels 1 and 2? Through vessels 3 and 4?
   (b) Homeostatic compensation occurs within seconds. Draw a reflex map to explain the compensation (stimulus, receptor, and so on).
   (c) When vessel 1 constricts, what happens to the filtration pressure in the capillaries downstream from that arteriole?

28. The following graphs are recordings of contractions in an isolated frog heart. The intact frog heart is innervated by sympathetic neurons that increase heart rate and by parasympathetic neurons that decrease heart rate. Based on these four graphs, what conclusion can you draw about the mechanism of action of atropine? (Atropine does not cross the cell membrane.)

29. Draw a reflex map that explains Anthony’s vasovagal syncope at the sight of blood. Include all the steps of the reflex, and explain whether autonomic pathways are being stimulated or inhibited.

30. A physiologist placed a section of excised arteriole in a perfusion chamber containing saline. When the oxygen content of the saline perfusing (flowing through) the arteriole was reduced, the arteriole
dilated. In a follow-up experiment, she used an isolated piece of arteriolar smooth muscle that had been stripped away from the other layers of the arteriole wall. When the oxygen content of the saline was reduced as in the first experiment, the isolated muscle showed no response. What do these two experiments suggest about how low oxygen exerts local control over arterioles?

31. In advanced atherosclerosis, calcified plaques cause the normally elastic aorta and arteries to become stiff and noncompliant.
(a) What effect does this change in the aorta have on afterload?
(b) If cardiac output remains unchanged, what happens to peripheral resistance and mean arterial pressure?

32. During fetal development, most blood in the pulmonary artery bypasses the lungs and goes into the aorta by way of a channel called the ductus arteriosus. Normally this fetal bypass channel closes during the first day after birth, but each year about 4000 babies in the United States maintain a patent (open) ductus arteriosus and require surgery to close the channel.
(a) Use this information to draw an anatomical diagram showing blood flow in an infant with a patent ductus arteriosus.
(b) In the fetus, why does most blood bypass the lungs?
(c) If the systemic side of the circulatory system is longer than the pulmonary side, which circuit has the greater resistance?
(d) If flow is equal in the pulmonary and systemic circulations, which side of the heart must generate more pressure to overcome resistance?
(e) Use your answer to (d) to figure out which way blood will flow through a patent ductus arteriosus.

**Level Four Quantitative Problems**

33. Using the appropriate equation, mathematically explain what happens to blood flow if the diameter of a blood vessel increases from 2 mm to 4 mm.

34. Duplicate the calculations that led William Harvey to believe that blood circulated in a closed loop:
(a) Take your resting pulse.
(b) Assume that your heart at rest pumps 70 mL/beat, and that 1 mL of blood weighs one gram. Calculate how long it would take your heart to pump your weight in blood. (2.2 pounds = 1 kilogram)

35. Calculate the mean arterial pressure (MAP) and pulse pressure for a person with a blood pressure of 115/73.

36. According to the Fick principle, the oxygen consumption rate of an organ is equal to the blood flow through that organ times the amount of oxygen extracted from the blood as it flows through the organ:

\[ \text{Oxygen consumption rate} = \text{blood flow} \times (\text{arterial oxygen content} - \text{venous oxygen content}) \]

(mL O₂ consumed/min) = (mL blood/min × mL O₂/mL blood)

A woman has a total body oxygen consumption rate of 250 mL/min. The oxygen content of blood in her aorta is 200 mL O₂/L blood, the oxygen content of her pulmonary artery blood is 160 mL O₂/L blood. What is her cardiac output?

37. Beau has an average daily heart rate of 75 beats per minute. If his net capillary filtration rate is 3.24 L/day, how much fluid filters from his capillary with each beat of his heart?

---

**Answers**

**Answers to Concept Check Questions**

1. Veins from the brain do not require valves because blood flow is aided by gravity.
2. The carotid wave would arrive slightly ahead of the wrist wave because the distance from heart to carotid artery is shorter.
3. Pressure of 130/95 has the higher pulse pressure (35 mm Hg).
4. If heart rate increases, the relative time spent in diastole decreases. In that case, the contribution of systolic pressure to mean arterial pressure increases, and MAP increases.
5. Pulse pressure is 112 − 68 = 44 mm Hg. MAP is 68 + 1/3 (44) = 82.7 mm Hg.
6. (d)
7. Extracellular K⁺ dilates arterioles, which increases blood flow (see Tbl. 15.2).
8. Epinephrine binding to myocardial β₁-receptors increases heart rate and force of contraction. Epinephrine binding to β₂-receptors on heart arterioles causes vasodilation.
9. α-Receptors have lower affinity for epinephrine than β₂-receptors, so the β₂-receptors dominate and arterioles dilate.
10. (a) The kidney has the highest blood flow per unit weight. (b) The heart has the lowest total blood flow.
11. The most likely ion is Na⁺ moving into the receptor cell.
12. This map should look exactly like Fig. 15.14b except that the directions of the arrows is reversed.
13. Stimulus: sight, sound, and smell of the T. rex. Receptors: eyes, ears, and nose. Integrating center: cerebral cortex, with descending pathways through the limbic system. Divergent pathways go to the cardiovascular control center, which increases sympathetic output to heart and arterioles. A second descending spinal pathway goes to the adrenal medulla, which releases epinephrine. Epinephrine on β₂-receptors of liver, heart, and skeletal muscle arterioles causes vasodilation of those arterioles. Norepinephrine onto α-receptors in other arterioles causes vasoconstriction. Both catecholamines increase heart rate and force of contraction.
Blood Flow and the Control of Blood Pressure

14. Loss of plasma proteins will decrease colloid osmotic pressure. As a result, hydrostatic pressure will have a greater effect in the filtration-absorption balance, and filtration will increase.

15. Using osmotic pressure rather than osmolarity allows a direct comparison between absorption pressure and filtration pressure, both of which are expressed in mm Hg.

16. If the left ventricle fails, blood backs up into the left atrium and pulmonary veins, and then into lung capillaries. Edema in the lungs is known as pulmonary edema.

17. Low-protein diets result in a low concentration of plasma proteins. Capillary absorption is reduced while filtration remains constant, resulting in edema and ascites.

Fig. 15.1: The pumps are arranged in series (one after the other).
Fig. 15.8: 1. Flow decreases and MAP increases. 2. Volume and MAP decrease. 3. Venous volume decreases, arterial volume increases, and MAP increases.

Answers to Review Questions

Level One  Reviewing Facts and Terms
1. brain and heart
2. (a) 6; 9; (b) 1; 2; (c) 4; 7; (d) 3; 5; 6; 8; (e) 3; 4
3. endothelium (capillary exchange and paracrine secretion); elastic tissue (recoil); smooth muscle (contraction); fibrous connective tissue (resistance to stretch).
4. arterioles
5. 120 mm Hg; systolic; diastole; 80 mm Hg; 120/80
6. pulse. Pulse pressure = systolic pressure — diastolic pressure
7. One-way valves in the veins, skeletal muscle pump, and low pressure in the thorax during breathing
8. Elevated blood pressure can cause a weakened blood vessel to rupture and bleed.
9. Korotkoff sounds occur when cuff pressure is lower than systolic pressure but higher than diastolic pressure.
10. See Table 15.2. Sympathetic neurons (α-receptors) vasoconstrict, and epinephrine on β2-receptors in certain organs vasodilates.
11. A region of increased blood flow. Active—increased blood flow is in response to an increase in metabolism. Reactive—increase in flow follows a period of decreased blood flow.
13. (a) 1, 5; (b) 2, 6; (c) 1, 2, 4; (d) 3, 8; (e) none of the above
14. Digestive tract, liver, kidneys, and skeletal muscles. Kidneys have the highest flow on a per unit weight basis.
15. Capillary density is proportional to the tissue’s metabolic rate. Cartilage—lowest; muscles and glands—highest.
16. (a) diffusion (b) diffusion or transcytosis (c) facilitated diffusion (d) osmosis
17. immune, circulatory, and digestive systems
18. Edema is excess fluid in the interstitial space. Causes include lower capillary oncotic pressure due to decreased plasma proteins or blockage of the lymphatic vessels by a tumor or other pathology.

Level Two  Reviewing Concepts
21. Use Figure 15.8 as the starting point.
22. (a) Pores of lymphatic capillaries are larger. Lymphatic capillaries have contractile fibers to help fluid flow; systemic capillaries depend on systemic blood pressure for flow. (b) Sympathetic division raises blood pressure by increasing cardiac output and causing vasoconstriction. Parasympathetic division can decrease heart rate. (c) Lymph fluid is similar to blood plasma minus most plasma proteins. Blood also has nearly half its volume occupied by blood cells.
23. Preventing $\text{Ca}^{2+}$ entry decreases ability of cardiac and smooth muscles to contract. Decreasing $\text{Ca}^{2+}$ entry into autorhythmic cells decreases heart rate. Neurons and other cells are unaffected because they have types of calcium channels not affected by the drugs.
24. The ability of vascular smooth muscle to regulate its own contraction. Probably results from $\text{Ca}^{2+}$ influx when the muscle is stretched.
25. Left ventricular failure causes blood to pool in the lungs, increasing pulmonary capillary hydrostatic pressure. This may cause pulmonary edema and shortness of breath when oxygen has trouble diffusing into the body. Blood backing up into the systemic circulation increases venous pressure.

Level Three  Problem Solving
26. (a) Uncontrollable: male, middle-aged, family history of cardiovascular disease on both sides of his family. Controllable: elevated blood pressure.
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(b) Yes, because blood pressure >140 or diastolic pressure >90 on several occasions. It would be useful to confirm that this was not “white coat hypertension” by having him take his blood pressure for a week or so at locations away from the doctor’s office, such as at a drug store. (c) Beta blockers block $\beta_1$-receptors in the heart, thus lowering cardiac output and MAP.

27. (a) MAP increases, flow through vessels 1 and 2 decreases, flow through 3 and 4 increases. (b) Pressure increase $\rightarrow$ arterial baroreceptor $\rightarrow$ cardiovascular control center $\rightarrow$ arteriolar vasodilation and decreased CO $\rightarrow$ decreased pressure (c) decreases

28. sight of blood $\rightarrow$ cerebral cortex $\rightarrow$ CVCC in the medulla oblongata $\rightarrow$ increased parasympathetic and decreased sympathetic output $\rightarrow$ decreased heart rate and vasodilation $\rightarrow$ decreased blood pressure

29. Cells (endothelium) in the intact wall detect changes in oxygen and communicate these changes to the smooth muscle.

30. Atropine is an ACh antagonist, possibly by binding to an ACh receptor.

31. (a) increases (b) resistance increases and pressure increases

32. (a) Draw a connection from pulmonary artery to aorta. You can see a remnant of the closed ductus as a small ligament connecting the aorta and pulmonary artery. (b) The lungs are not functioning. (c) Systemic (d) Left side (e) From the aorta into the pulmonary artery

Level Four Quantitative Problems

33. increases 16-fold

34. Answers will vary. For a 50-kg individual with a resting pulse of 70 bpm, she will pump her weight in blood in about 10 minutes.

35. $MAP = 87\ mm\ Hg$; $pulse\ pressure = 42\ mm\ Hg$

36. $250\ mL\ oxygen/min = CO \times (200 - 160\ mL\ oxygen/L\ blood)$. $CO = 6.25\ L/min$

37. $75\ beats/min \times 1440\ min/day = 108,000\ beats/day$. $3240\ mL\ filtered/day \times day/108,000\ beats = 0.03\ mL/beat$. 

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