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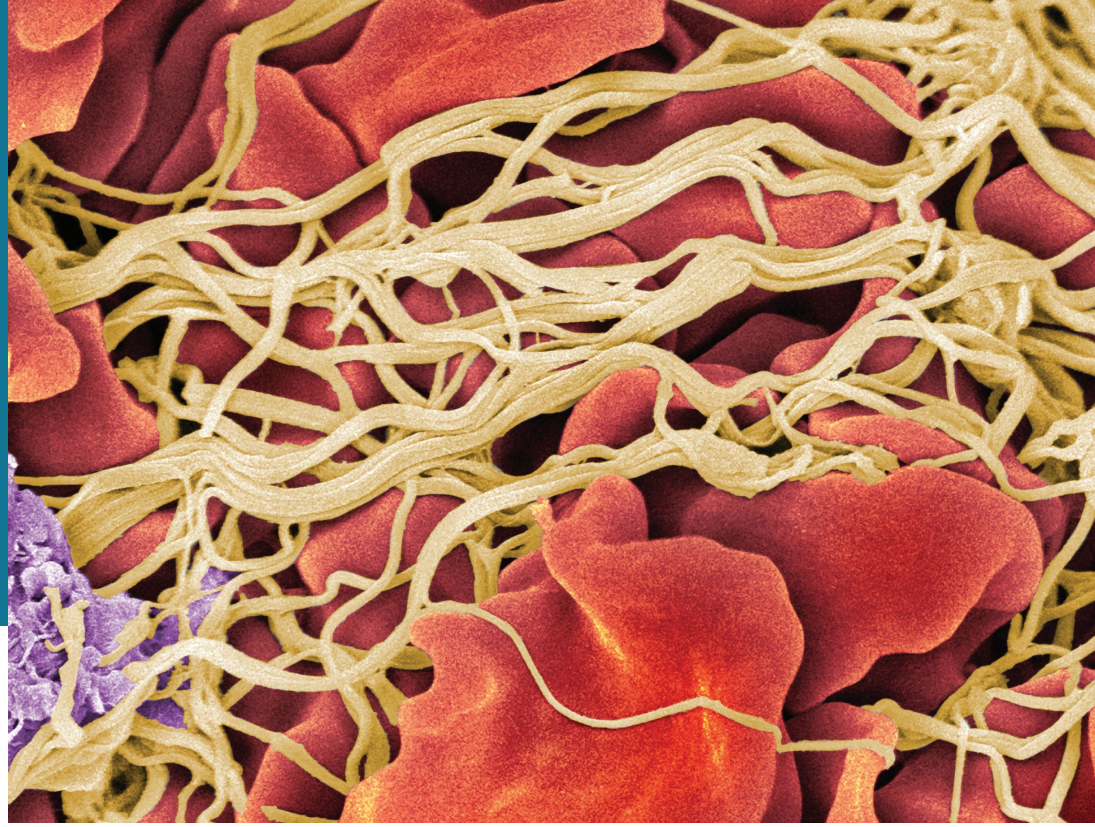


Photo: Colorized scanning electron micrograph of a blood clot. The red discs are red blood cells, the purple particles are platelets, and the yellow strands are fibrin. ©Steve Gschmeissner/Science Source

Learn to Predict

Frankie didn't have time to be sick. So at first she attributed her extreme tiredness to the stress of being a 40-year-old single mother of two teenagers while working full-time and attending school part-time. However, when she started experiencing significant abdominal pain, she consulted her doctor, who ordered several tests. The results indicated a low red blood cell (RBC) count with microcytic RBCs, a high reticulocyte count, low hemoglobin and hematocrit levels, and evidence of hemoglobin in her feces. **After reading this chapter and recalling what you learned about the endocrine system in chapters 17 and 18, explain Frankie's symptoms and test results.**

Cardiovascular System

BLOOD

Historically, many cultures around the world, both ancient and modern, have believed in the magical qualities of blood. Some societies consider blood the "essence of life" because the uncontrolled loss of it can result in death. Blood has also been thought to define character and emotions. For example, people from prominent families are sometimes described as "bluebloods," whereas criminals are said to have "bad blood." Common expressions allege that anger causes the blood to "boil" and that fear results in blood "curdling." The scientific study of blood reveals characteristics as fascinating as any of these fantasies. Blood performs many functions essential to life and can often reveal much about our health.

Blood is one component of the **cardiovascular system,** which also consists of the heart and the blood vessels. The cardiovascular system connects the various tissues of the body. The heart pumps blood through a network of blood vessels extending throughout the body. This network of blood vessels is often referred to as the *circulatory system*. As it flows through the circulatory system, the blood delivers nutrients and picks up waste products at the body tissues. This chapter focuses on the blood, whereas chapters 20 and 21 discuss the heart and the blood vessels, respectively.

19.1 Functions of Blood

LEARNING OUTCOME

After reading this section, you should be able to

A. **List and explain the ways blood helps maintain homeostasis in the body.**

The blood acts as a transport fluid carrying many substances to various parts of the body. By acting this way, blood is vital for maintaining homeostasis throughout the body. Blood helps maintain homeostasis in several ways:

1. *Transport of gases, nutrients, and waste products*. Oxygen enters the blood in the lungs and is carried to the cells. Carbon dioxide, produced by the cells, is carried in the blood to the lungs, where it is exhaled. The blood transports ingested nutrients, ions, and water from the digestive tract to the cells, and the blood transports the cells' waste products to the kidneys for elimination.
2. *Transport of processed molecules*. Many substances are produced in one part of the body and transported in the blood to another part, where they are modified. For example, the precursor to vitamin D is produced in the skin (see chapter 5) and transported by the blood to the liver and then to the kidneys for processing into active vitamin D. The blood then transports active vitamin D to the small intestine, where it promotes the uptake of calcium. Another example involves lactate produced by skeletal muscles during anaerobic respiration (see chapter 9). The blood carries lactate to the liver, where it is converted into glucose.
3. *Transport of regulatory molecules*. Regulatory molecules include chemical messengers, such as hormones, that regulate the activities of many physiological processes. Enzymes that are important for normal metabolism are also considered regulatory molecules. The blood carries the hormones and many of the enzymes that regulate body processes from one part of the body to another.
4. *Regulation of pH and osmosis*. Buffers (see chapter 2), which help keep the blood's pH within its normal range of 7.35–7.45, are in the blood. The osmotic composition of blood is also critical for maintaining normal fluid and ion balance throughout the body (see chapter 27).
5. *Maintenance of body temperature*. Body temperature regulation involves several mechanisms, including the movement of warm blood from the interior of the body to its surface, where heat is released.
6. *Protection against foreign substances*. Certain cells and chemicals in the blood make up an important part of the immune system, protecting against foreign substances, such as microorganisms and toxins.
7. *Clot formation*. Blood clotting protects against excessive blood loss when blood vessels are damaged. The blood clot that forms in damaged tissue is also the first step in tissue repair and the restoration of normal function (see chapter 4).

ASSESS YOUR PROGRESS

Answers to these questions are found in the section you have just completed. Re-read the section if you need help in answering these questions.

1. *List the ways that blood helps maintain homeostasis in the body.*
2. *What substances are transported by the blood?*
3. *What is the normal pH range of the blood?*
4. *How does the blood provide protection?*

19.2 Composition of Blood

LEARNING OUTCOMES

After reading this section, you should be able to

A. **List the components of blood.**

B. **Relate the average total blood volume for females and for males.**

Blood is a type of connective tissue consisting of a liquid matrix containing cells and cell fragments. **Plasma** is the liquid matrix, and the **formed elements** are the cells and cell fragments. The plasma makes up 55% of the total blood volume, and the formed elements make up 45% (figure 19.1). The total blood volume in the average adult female is about 4–5 L. The total blood volume in the average adult male is 5–6 L. Blood makes up about 8% of the total weight of the body.

ASSESS YOUR PROGRESS

5. *What are the two major components of blood? What portion of the total blood volume does each compose?*
6. *What is the average total blood volume for females and for males?*

19.3 Plasma

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Name the components of blood plasma.**

B. **List the three major plasma proteins and describe their functions.**

Plasma (plaz′mă) is the liquid matrix of blood. It is a pale yellow fluid that consists of about 91% water and 9% other substances, such as proteins, ions, nutrients, gases, waste products, and regulatory substances (table 19.1). Plasma is a **colloid** (kol′oyd), which is a liquid containing suspended substances that do not settle out of solution. Most of the suspended substances are plasma proteins, which make up about 7% of the volume of plasma (figure 19.1). Based on molecular size and charge, the plasma proteins can be classified into three groups: albumin, globulins, and fibrinogen.

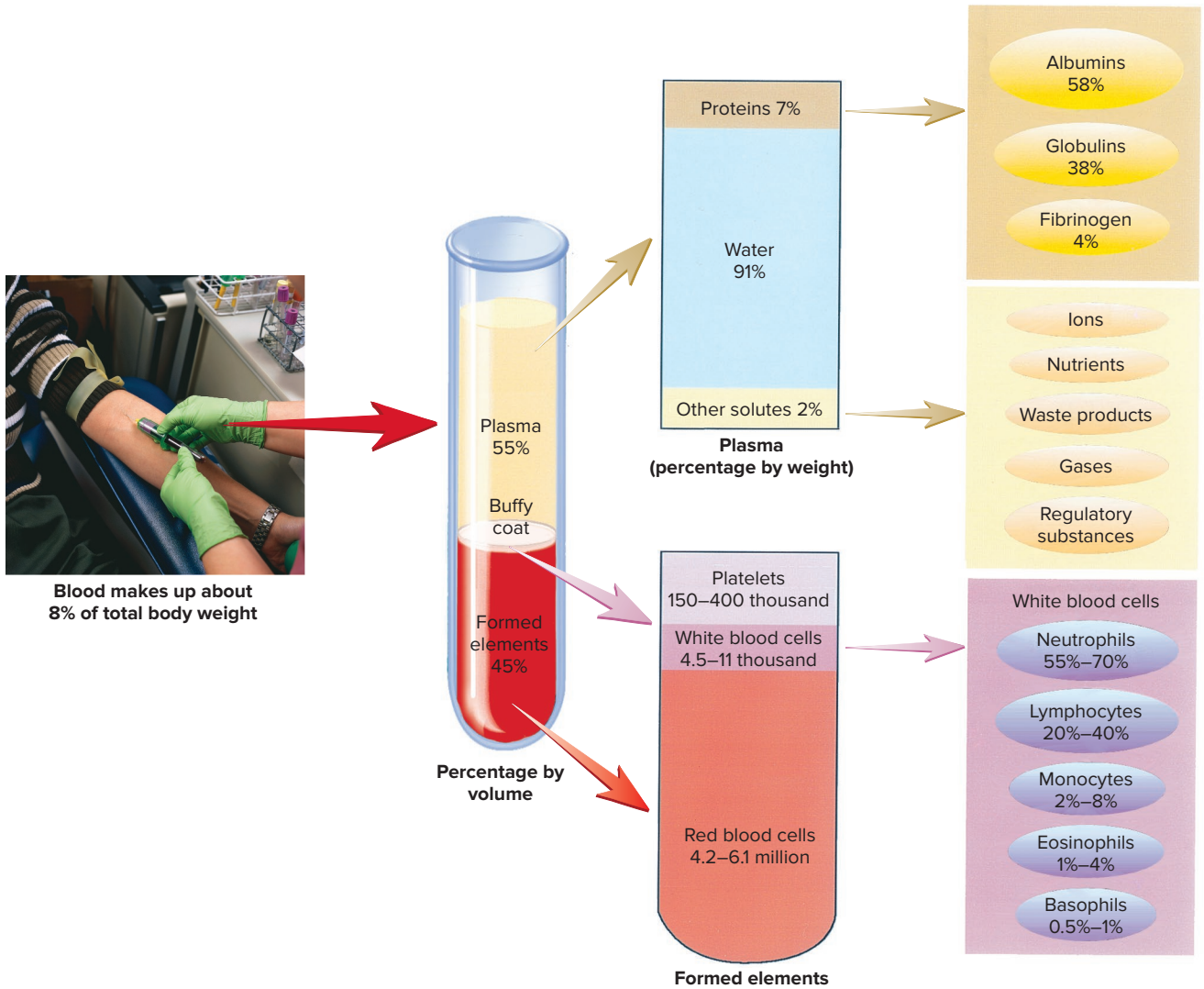


FIGURE 19.1 Composition of Blood
Approximate values for the components of blood in a normal adult. ©liquidlibrary/Getty Images AP|R

Almost all of the plasma proteins are produced by the liver or blood cells, a notable exception being protein hormones.

1. **Albumin** (al-bū′min) makes up 58% of the plasma proteins and is important in regulating the movement of water between the tissues and the blood. Albumin does not pass easily from the blood into tissues. As such, it plays an important role in maintaining blood colloid osmotic pressure (see chapters 21 and 26). Recall from chapter 3 that osmosis, the diffusion of water, occurs when solutes cannot easily move across a selectively permeable barrier and that osmotic pressure is the tendency for water to move across that barrier. Albumins also bind and transport other molecules in the blood, such as fatty acids, bilirubin, and thyroid hormones.
2. **Globulins** (glob′ū-linz) account for 38% of the plasma proteins. The globulins are subdivided into α, β, and γ globulins. Globulins function in transporting many substances in the blood. **Antibodies** are globulins that protect against microorganisms (table 19.1; see chapter 22).
3. **Fibrinogen** (fī-brin′ō-jen) constitutes 4% of the plasma proteins and is responsible for the formation of blood clots (see section 19.5). **Serum** (ser′um; whey) is plasma without the clotting factors.

Plasma composition remains relatively constant, even though material is constantly moving between the blood and the cells. Various homeostatic control mechanisms function to maintain plasma composition. The levels of water, proteins, and other substances in the blood, such as ions, nutrients, waste products, gases, and regulatory substances, are maintained within narrow limits. Normally, the amount of water taken in through the digestive tract closely matches the amount of water lost through the kidneys, lungs, digestive tract, and skin. Therefore, plasma volume also remains relatively constant. Suspended or dissolved substances in the blood come from the liver, kidneys, intestines, endocrine glands, and immune tissues, such as the lymph nodes and spleen. Oxygen enters the blood in the lungs and leaves the blood as it

TABLE 19.1 Composition of Plasma

Components	Function
Water	Acts as a solvent and suspending medium for blood components
Plasma Proteins	
Albumin	Partly responsible for blood viscosity and osmotic pressure; acts as a buffer; transports fatty acids, free bilirubin, and thyroid hormones
Globulins	
α	Protect tissues from damage by inflammation (alpha-1 antitrypsin); transport thyroid hormones (thyroid-binding globulin), cortisol (transcortin), and testosterone and estrogen (sex hormone–binding globulin); transport lipids (e.g., cholesterol in high-density lipoproteins); convert ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}), which promotes iron transport by transferrin (ceruloplasmin); transport hemoglobin released from damaged red blood cells (haptoglobin)
β	Transport iron (transferrin); transport lipids (beta-lipoproteins), especially cholesterol in low-density lipoproteins; involved with immunity (complement); prevent blood loss (coagulation proteins)
γ	Involved in immunity (most antibodies are γ globulins, but some are β or α globulins)
Fibrinogen	Functions in blood clotting
Ions	
Sodium, potassium, calcium, magnesium, chloride, iron, phosphate, hydrogen, hydroxide, bicarbonate	Involved in osmosis, membrane potentials, and acid-base balance
Nutrients	
Glucose, amino acids, triglycerides, cholesterol	Source of energy and basic "building blocks" of more complex molecules
Vitamins	Promote enzyme activity
Waste Products	
Urea, uric acid, creatinine, ammonia salts	Breakdown products of protein metabolism; excreted by the kidneys
Bilirubin	Breakdown product of red blood cells; excreted as part of the bile from the liver into the small intestine
Lactate	End product of anaerobic respiration; converted to glucose by the liver
Gases	
Oxygen	Necessary for aerobic respiration; terminal electron acceptor in electron-transport chain
Carbon dioxide	Waste product of aerobic respiration; as bicarbonate, helps buffer blood
Nitrogen	Inert
Regulatory Substances	Enzymes catalyze chemical reactions; hormones stimulate or inhibit many body functions

flows through tissues. Carbon dioxide enters the blood from the tissues and leaves the blood as it flows through the lungs.

ASSESS YOUR PROGRESS

7. *What is plasma, and what does it consist of? Why is plasma a colloid?*
8. *What are the three major plasma proteins, and what roles do they play in the blood?*
9. *Explain how plasma volume remains relatively constant.*

19.4 Formed Elements

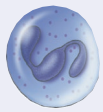
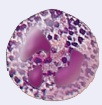
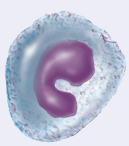
LEARNING OUTCOMES

After reading this section, you should be able to

A. **List the three kinds of formed elements using both their common and technical names.**
B. **Describe the origin and production of the formed elements.**
C. **Describe the structure and function of hemoglobin and relate which gases associate with hemoglobin and how.**
D. **Compare fetal and adult hemoglobin as to structure and affinity for oxygen.**
E. **Discuss the life history of red blood cells.**
F. **Compare the structures and functions of the five types of white blood cells.**
G. **Describe the origin and structure of platelets.**
H. **Relate the functions of platelets in preventing blood loss.**

The **formed elements** of blood consist of cells and cell fragments. The cells include red blood cells and white blood cells. Cell fragments are more commonly called **platelets.** Recall that the formed elements make up 45% of the total blood volume.

TABLE 19.2 Formed Elements of the Blood

Cell Type	Illustration	Description	Function	Abundance (cells/μL)*
Red Blood Cell		Biconcave disc; no nucleus; contains hemoglobin, which colors the cell red; 7.5 μm in diameter	Transports O_2 and CO_2	4.2–5.4 million (females) 4.7–6.1 million (males)
White Blood Cells		Spherical cells with a nucleus	Five types of white blood cells, each with specific functions	4500–11,000
Granulocytes				
Neutrophil		Nucleus with two to five lobes connected by thin filaments; cytoplasmic granules stain a light pink or reddish-purple; 10–12 μm in diameter	Phagocytizes microorganisms and other substances	55–70% of WBC
Eosinophil		Nucleus often bilobed; cytoplasmic granules stain orange-red or bright red; 11–14 μm in diameter	Attacks certain worm parasites; releases chemicals that modulate inflammation; negatively impacts airways during asthma attacks	1–4% of WBC
Basophil		Nucleus with two indistinct lobes; cytoplasmic granules stain blue-purple; 10–12 μm in diameter	Releases histamine, which promotes inflammation, and heparin, which prevents clot formation	0.5–1% of WBC
Agranulocytes				
Lymphocyte		Round nucleus; cytoplasm forms a thin ring around the nucleus; 6–14 μm in diameter	Produces antibodies and other chemicals responsible for destroying microorganisms; contributes to allergic reactions, graft rejection, tumor control, and regulation of the immune system	20–40% of WBC
Monocyte		Nucleus round, kidney-shaped, or horseshoe-shaped; contains more cytoplasm than lymphocyte does; 12–20 μm in diameter	Phagocytic cell in the blood; leaves the blood and becomes a macrophage, which phagocytizes bacteria, dead cells, cell fragments, and other debris within tissues	2–8% of WBC
Platelet		Cell fragment surrounded by plasma membrane and containing granules; 2–4 μm in diameter	Forms platelet plugs; releases chemicals necessary for blood clotting	150,000–400,000

*White blood cell counts are listed as percentage of total white blood cells.

Red blood cells, or *erythrocytes* (ĕ-rith′rō-sītz), are the most abundant blood cell type, making up about 95% of the volume of the formed elements. The remaining 5% consists of white blood cells, or *leukocytes* (loo′kō-sītz), and platelets, or *thrombocytes* (throm′bō-sītz). Table 19.2 illustrates the formed elements of the blood. In healthy adults, white blood cells are the only formed elements possessing nuclei; red blood cells and platelets lack nuclei.

Predict 1

Using table 19.1, develop a diagram that illustrates the order of the formed elements by size, from smallest to largest. *Note:* Ranges are provided for several of the formed elements.

Production of Formed Elements

The process of blood cell production is called **hematopoiesis** (hē′mă-tō-poy-ē′sis, hem′ă-to-poy-ē′sis), or *hemopoiesis* (hē′mō-poy-ē′sis). In the embryo and fetus, hematopoiesis occurs in many different tissues such as the yolk sac of the embryo, liver, thymus, spleen, lymph nodes, and red bone marrow. After birth, hematopoiesis is confined primarily to red bone marrow, though some white blood cells, specifically lymphocytes, complete their development in lymphatic tissue (see chapter 22). In young children, nearly all the bone marrow is red bone marrow. In adults, however, red bone marrow is confined to the ribs, sternum, vertebrae, pelvis, proximal femur, and proximal humerus. Yellow bone marrow replaces red bone marrow in other body locations (see chapter 6).

All the formed elements of the blood are derived from a single population of stem cells called **hemocytoblasts,** located in the red bone marrow. Hemocytoblasts are precursor cells capable of dividing to produce daughter cells that can differentiate into various types of blood cells (figure 19.2). When a hemocytoblast divides, one daughter cell remains a hemocytoblast while the other daughter cell differentiates to form one of two types of intermediate stem cells: a **myeloid stem cell** or a **lymphoid stem cell.** Red blood cells, platelets, and most of the white blood cells develop from myeloid stem cells. Myeloid stem cells give rise to several

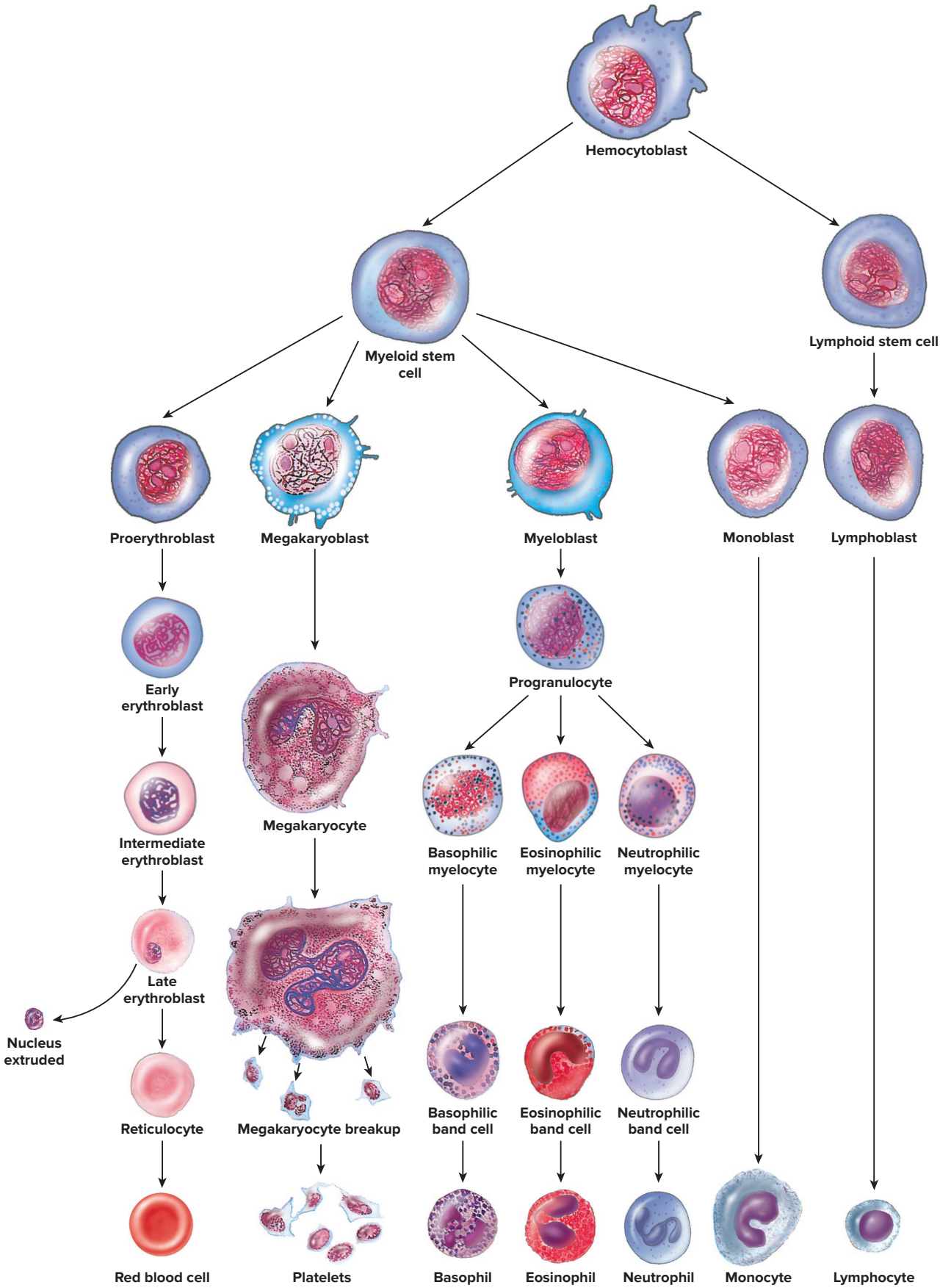


FIGURE 19.2 Hematopoiesis

Stem cells give rise to the cell lines that produce the formed elements. The production of red blood cells (far left column) is called erythropoiesis. AP|R

intermediate cell types. These intermediates include **proerythroblasts** (prō-ĕ-rith′rō-blastz), which produce red blood cells; **myeloblasts** (mī′ĕ-lō-blastz), which produce basophils, eosinophils, and neutrophils; **monoblasts** (mon′ō-blastz), which produce monocytes; and **megakaryoblasts** (meg-ă-kar′ē-ō-blastz), which produce platelets. Lymphoid stem cells give rise to lymphocytes.

Chemical signals regulate the development of the different types of formed elements. These chemical signals include **colony-stimulating factors (CSFs)** and hormones transported to the bone marrow through the blood or substances released by bone marrow cells. **Erythropoietin (EPO)** is an example of a hormone, secreted by endocrine cells of the kidneys, that stimulates myeloid stem cells to develop into red blood cells.

ASSESS YOUR PROGRESS

10. *Name the three general types of formed elements in the blood, using both their common and technical names.*
11. *What is hematopoiesis? Where does the process occur before birth? After birth? What type of stem cell are all formed elements derived from? Distinguish between myeloid stem cells and lymphoid stem cells.*
12. *What types of formed elements develop from each of the following cells: proerythroblasts, myeloblasts, lymphoblasts, monoblasts, and megakaryocytes?*

Red Blood Cells

Red blood cells (RBCs), or *erythrocytes,* are about 700 times more numerous than white blood cells and 17 times more numerous than platelets in the blood (figure 19.3*a*). Males have 4.7–6.1 million red blood cells per microliter (μL; 1 mm^3, or 10^{-6} L), whereas females have about 4.2–5.4 million/μL.

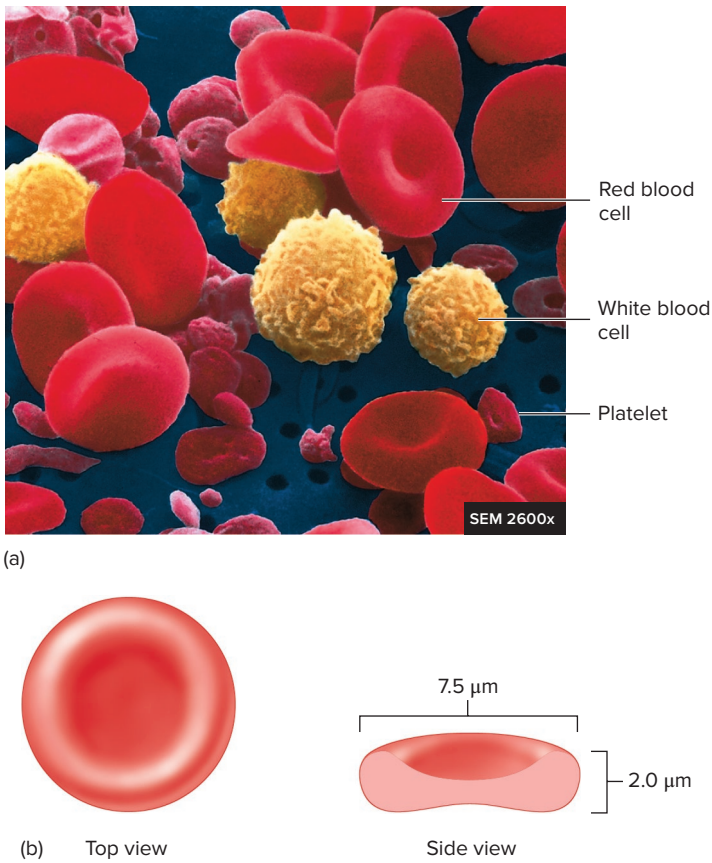
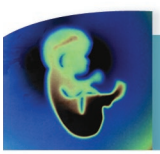


FIGURE 19.3 Formed Elements
(*a*) Color-enhanced scanning electron micrograph of formed elements: red blood cells (*red doughnut shapes*), white blood cells (*yellow*), and platelets (*red, irregular shapes*). (*b*) Shape and dimensions of a red blood cell.
(a) ©National Cancer Institute/Science Photo Library/Science Source APR

Structure

Normal red blood cells are discs about 7.5 μm in diameter, and they are biconcave, meaning that their edges are thicker than their center (figure 19.3*b*). Red blood cell structure enhances its function. Researchers have long proposed that the biconcave shape of a red blood cell increases the cell's surface area, thereby allowing gases to move into and out of the red blood cell more rapidly as compared to a flat disc of the same size. However, recent evidence suggests that this may not be as important to red blood cell function. Gases enter and exit the red blood cells most often when the cells are in small blood vessels called capillaries. As the red blood cells move through these small vessels, they change shape, so the surface area to volume association is not as obvious. But the fact that the cells change shape is of interest. Because of its biconcave shape, the red blood cell can bend or fold around its thin center, thereby decreasing its size and enabling it to pass more easily through smaller blood vessels. Research has also shown that the biconcave disc shape of red blood cells may also improve blood flow in larger vessels as well. However, red blood cells cannot move on their own; they are passively moved by forces that cause the blood to circulate.

Red blood cells are derived from specialized cells that lose their nuclei and nearly all their cellular organelles during maturation. The main component of the red blood cell is the pigmented



Clinical IMPACT 19.1

Stem Cells and Cancer Therapy

Many cancer therapies affect the type of rapidly dividing cells found in tumors. However, an undesirable side effect of such therapies can be the destruction of nontumor cells that are dividing, such as the stem cells and their derivatives in red bone marrow. After being treated for cancer, some patients are prescribed growth factors to stimulate the rapid regeneration of the red bone marrow. Although not a cure for cancer, the growth factors can speed recovery from the side effects of cancer therapy.

Some types of leukemia and genetic immune deficiency diseases can be treated with a bone marrow transplant that provides stem cells to the patient. To avoid tissue rejection, families with a history of these disorders can freeze the umbilical cord blood of their newborn children. The cord blood, which contains many stem cells, can be used instead of bone marrow.

protein **hemoglobin** (hē-mō-glō′bin). Hemoglobin occupies about one-third of the total volume of a red blood cell and accounts for its red color. Other red blood cell contents include lipids, adenosine triphosphate (ATP), and the enzyme carbonic anhydrase, which is important in the regulation of blood pH (see chapters 23 and 26).

Functions

The primary functions of red blood cells are to transport O_2 from the lungs to the various body tissues and to transport CO_2 from the tissues to the lungs. Approximately 98.5% of the O_2 in the blood is transported in combination with the hemoglobin in the red blood cells. The remaining 1.5% is dissolved in the plasma.

Carbon dioxide is transported in the blood in three major ways: (1) Approximately 7% is dissolved in the plasma; (2) approximately 23% is combined with hemoglobin; and (3) 70% is converted to bicarbonate ions. The bicarbonate ions (HCO_3^-) are produced when carbon dioxide (CO_2) and water (H_2O) combine to form carbonic acid (H_2CO_3). Carbonic acid quickly dissociates to form hydrogen (H^+) and bicarbonate ions. The combination of carbon dioxide and water is catalyzed by an enzyme, **carbonic anhydrase,** which is located primarily within red blood cells.

$$\underset{\text{Carbon dioxide}}{CO_2} + \underset{\text{Water}}{H_2O} \overset{\text{Carbonic anhydrase}}{\rightleftarrows} \underset{\text{Carbonic acid}}{H_2CO_3} \rightleftarrows \underset{\text{Hydrogen ion}}{H^+} + \underset{\text{Bicarbonate ion}}{HCO_3^-}$$

Hemoglobin

Hemoglobin is a complex protein consisting of four subunits. Each subunit is composed of one polypeptide chain called **globin** (glō′bin) that is bound to one heme (hēm) group. Each heme is a red-pigment molecule containing one iron atom (figure 19.4). There are three forms of hemoglobin: (1) embryonic, (2) fetal, and (3) adult. Embryonic hemoglobin is the first type of hemoglobin produced during development. By the third month of development, embryonic hemoglobin has been replaced with fetal hemoglobin. At birth, 60–90% of the hemoglobin is adult hemoglobin. At 2 to 4 years of age, fetal hemoglobin makes up less than 2% of the hemoglobin, and in adulthood only traces of fetal hemoglobin can be found.

The different forms of hemoglobin have different affinities for, or abilities to bind to, O_2. Embryonic and fetal hemoglobin have a higher affinity for O_2 than adult hemoglobin does. In the embryo and fetus, hemoglobin picks up O_2 from the mother's blood at the placenta. Even though placental blood contains less O_2 than does air in the mother's lungs, adequate amounts of O_2 are picked up because of the higher affinity of embryonic and fetal hemoglobin for O_2. After birth, hemoglobin picks up O_2 from the air in the baby's lungs.

Predict 2

What would happen to a fetus if hemoglobin of the maternal blood had an affinity for O_2 that was equal to or greater than the hemoglobin of fetal blood?

Although embryonic, fetal, and adult hemoglobin each have four globins, the types of globins are different. There are nine types of globins, each produced from a different gene and each with a slightly different amino acid composition. For example, there are two types of alpha globins, which differ from each other by one amino acid. Because they are so similar, they are usually referred to simply as alpha globins. There are also a beta globin, two kinds of gamma globins, a delta globin, and three kinds of embryonic globins. The different genes are active during different developmental stages and therefore allow for the production of three unique forms of hemoglobin. Most adult hemoglobin has two alpha globins (one of each type) and two beta globins (figure 19.4). Fetal hemoglobin has two alpha globins (one of each type) and two gamma globins (one of each type).

Oxygen molecules bind to the heme group. Specifically, each O_2 molecule that is transported by hemoglobin is associated with an iron atom at the center of a heme group; therefore, iron is necessary for

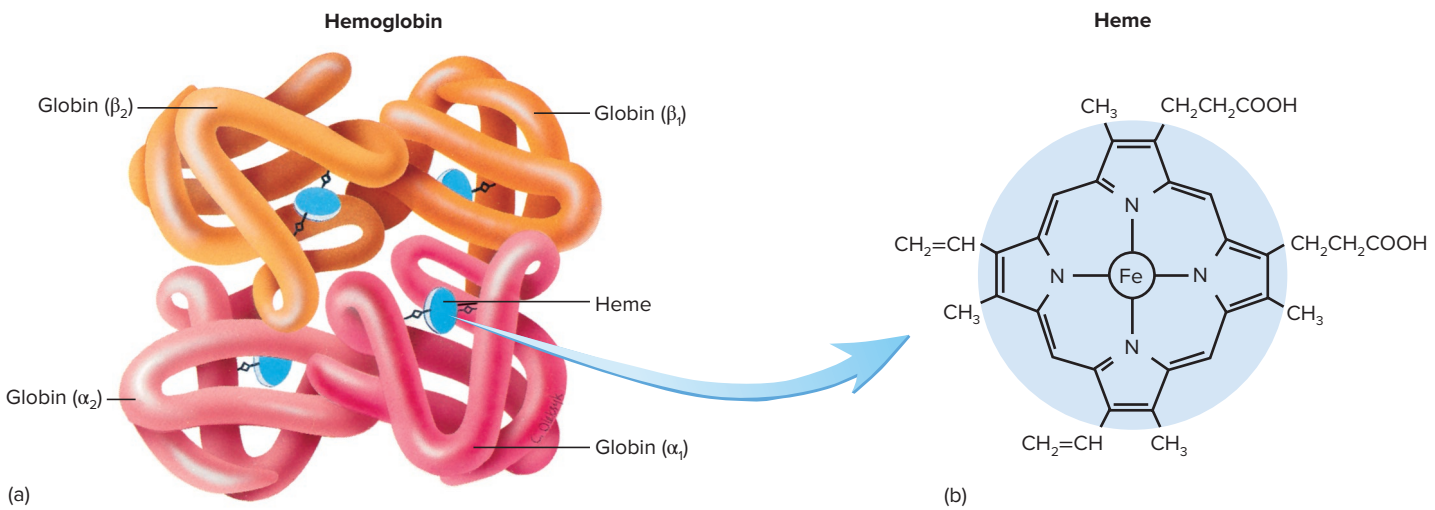


FIGURE 19.4 Hemoglobin

(*a*) Hemoglobin consists of four subunits, each with a globin and a heme. There are two alpha (α) globins and two beta (β) globins. A heme is associated with each globin. (*b*) Each heme contains one iron atom.

Clinical GENETICS 19.1 Sickle-Cell Disease

Sickle-cell disease is a disorder in which red blood cells become sickle-shaped. It results from a mutation in the gene that codes for the beta globin chain of hemoglobin. The mutation is a change in one nucleotide in the DNA that leads to a change in one amino acid in beta globin. The single amino acid change in beta globin has a dramatic effect on hemoglobin. When blood O_2 levels decrease, as when O_2 diffuses away from hemoglobin in tissue capillaries, the abnormal hemoglobin molecules join together, causing a change in red blood cell shape (figure 19.5). When blood O_2 levels increase, as in the lungs, the abnormal hemoglobin molecules separate, and red blood cells can resume their normal shape.

Sickle-shaped red blood cells are less able to squeeze through small capillaries. Consequently, they become lodged in capillaries, blocking blood flow through them. This causes a further decrease in O_2 levels, which promotes more sickling. As O_2 levels decrease further, more capillary blockage is promoted, and so on. After repeated cycles of sickling, red blood cells lose their ability to resume their normal shape. This increases the number of sickled cells.

The major consequence of sickle-cell disease is tissue damage resulting from reduced blood flow through tissues. As tissues are deprived of blood, the most common symptom is pain, which is often severe. In addition, spleen and liver enlargement, kidney and lung damage, and stroke can occur. Priapism (prī′ă-pizm), a prolonged, painful erection due to venous blockage, can develop in men. Sickle-shaped red blood cells are also likely to rupture, which can result in hemolytic anemia (see table 19.4).

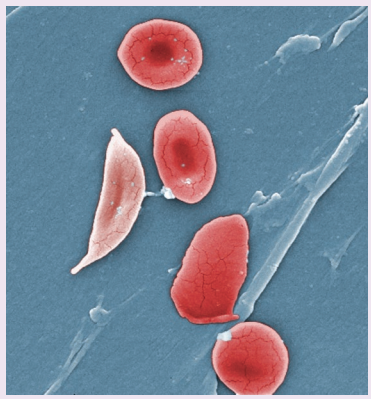


FIGURE 19.5 Sickle-Cell Disease
Red blood cells in a person with sickle-cell disease appear normal in oxygenated blood. In deoxygenated blood, hemoglobin changes shape and causes the cells to become sickle-shaped and rigid. ©CDC/Sickle Cell Foundation of Georgia: Jackie George, Beverly Sinclair/photo by Janice Haney Carr

Sickle-cell disease is an autosomal recessive disorder. Only individuals who have two mutated beta globin alleles express the disease. Individuals who are heterozygous have a normal beta globin allele and produce sufficient amounts of normal beta globin, so their red blood cells do not usually become sickle-shaped. Heterozygotes are carriers (see chapter 29) and are said to have **sickle-cell trait.**

Sickle-cell disease is an example of a genetic disorder in which the heterozygote has a better ability to survive under certain circumstances than homozygous individuals. Carriers (heterozygotes) with sickle-cell trait have increased resistance to malaria. Malaria is a disease caused by a parasitic protozoan that reproduces inside red blood cells. The parasite is usually transmitted from one person to another through the bite of a mosquito. The red blood cells of people with sickle-cell trait tend to rupture before the parasite successfully reproduces. Therefore, those people are less likely to contract malaria, and the disease is much milder if they do.

The highest percentage of people with sickle-cell trait occurs in populations exposed to malaria or whose ancestors were exposed to malaria. In certain parts of Africa where malaria is rampant, the percentage of sickle-cell carriers can be as high as 50%. In the United States, 8% of African-Americans are sickle-cell carriers, and 0.8% have sickle-cell disease. The mutant gene can also be found in other groups, but at lower frequencies.

Treatment for sickle-cell disease attempts to reduce the blockage of blood vessels, alleviate pain, and prevent infections. Hydroxyurea (hī-drok′sē-ū-rē′ă) stimulates the production of gamma (fetal) globins. When the gamma globins combine with defective beta globins, the formation of sickle-shaped cells slows. Bone marrow transplants can cure sickle-cell disease, but such transplants can be dangerous and even fatal. Gene therapy is under investigation.

normal hemoglobin function. The adult human body normally contains about 4 g of iron, two-thirds of which is associated with hemoglobin. Small amounts of iron are regularly lost from the body in waste products, such as urine and feces. Females lose additional iron as a result of menstrual bleeding and, therefore, require more dietary iron than males do. Dietary iron is absorbed into the blood from the upper part of the intestinal tract. Stomach acid and vitamin C in food increase iron absorption by converting ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}), which is more readily absorbed.

When hemoglobin is exposed to O_2, one O_2 molecule can become associated with each heme group. So one hemoglobin molecule can carry up to four oxygen molecules. This oxygenated form of hemoglobin is called **oxyhemoglobin** (ok′sē-hē-mō-glō′bin). The oxyhemoglobin in one red blood cell transports about 1 billion molecules of O_2. This estimate becomes clear when we consider that a single red blood cell contains about 280 million hemoglobin molecules, each of which carries up to four oxygen molecules. Hemoglobin not bound to O_2 is called **deoxyhemoglobin.** Interestingly, hemoglobin color changes depending on whether or not it is oxygenated. Oxyhemoglobin is bright red, whereas deoxyhemoglobin is a darker red color.

Hemoglobin also transports CO_2; however, CO_2 does not combine with the iron atoms as oxygen molecules do. Instead, CO_2 attaches to the globin molecule. This hemoglobin form is **carbaminohemoglobin** (kar-bam′i-nō-hē-mō-glō′bin). The transport of O_2 and CO_2 by the blood is discussed more fully in chapter 23.

Additionally, hemoglobin transports nitric oxide (NO), which is produced by the endothelial cells lining the blood vessels. At the same time that hemoglobin picks up O_2 in the lungs, a sulfur-containing amino acid, cysteine, in each β-globin binds with a NO molecule to form *S*-nitrosothiol (nī-trōs′ō-thī-ol; SNO). When O_2 is released in tissues, so is the NO, where it functions as a chemical messenger that induces the relaxation of the smooth muscle of blood vessels. By affecting the amount of NO in tissues, hemoglobin

may play a role in regulating blood pressure because the relaxation of blood vessels results in decreased blood pressure (see chapter 21).

Various types of poisons affect the hemoglobin molecule. Carbon monoxide (CO), which is produced by the incomplete combustion of gasoline, binds very strongly to the iron of hemoglobin to form the relatively stable compound **carboxyhemoglobin** (kar-bok′sē-hē-mō-glō′bin). As a result of the stable binding of CO, hemoglobin cannot transport O_2. Nausea, headache, unconsciousness, and death are possible consequences of prolonged exposure to CO. Interestingly, CO is found in cigarette smoke, and the blood of smokers can contain 5–15% carboxyhemoglobin.

Life History of Red Blood Cells

Under normal conditions, about 2.5 million red blood cells are destroyed every second. This loss seems staggering, but it represents only 0.00001% of the total 25 trillion red blood cells contained in the normal adult circulation. Homeostasis is maintained by replacing the 2.5 million cells lost every second with an equal number of new red blood cells. Thus, approximately 1% of the total number of red blood cells is replaced each day.

The process by which new red blood cells are produced is called **erythropoiesis** (ĕ-rith′rō-poy-ē′sis; see figure 19.2). The time required to produce a single red blood cell is about 4 days. Myeloid stem cells, derived from hemocytoblasts, give rise to **proerythroblasts.** After several mitotic divisions, proerythroblasts become **early erythroblasts.** These cells are also called *basophilic erythroblasts* because they stain with a basic dye. The dye binds to the large number of ribosomes necessary for the production of hemoglobin, giving the cytoplasm a purplish color. Early erythroblasts give rise to **intermediate erythroblasts.** These cells are also called *polychromatic erythroblasts* because they stain different colors with basic and acidic dyes. For example, when an acidic dye is used, intermediate erythroblasts stain a reddish color when it interacts with the hemoglobin accumulating in the cytoplasm. Intermediate erythroblasts continue to produce hemoglobin, and then most of their ribosomes and other organelles degenerate. The resulting **late erythroblasts** have a reddish color because about one-third of the cytoplasm is hemoglobin.

The late erythroblasts lose their nuclei to become immature red blood cells, called **reticulocytes** (re-tik′ū-lō-sīts). *Reticulocyte* refers to a reticulum, or network, that can be observed in the cytoplasm when a special staining technique is used. The reticulum is artificially produced by the reaction of the dye with the few remaining ribosomes in the reticulocyte. Reticulocytes are released from the bone marrow into the circulating blood. A normal reticulocyte level is 0.5–2% of circulating red blood cells. Reticulocyte counts are clinically useful to monitor red blood cell production, particularly when monitoring treatments for anemia. Also, reticulocyte counts can provide information about the health of the hemocytoblasts in the red bone marrow. Within 2 days, the ribosomes in the reticulocytes degenerate, and the reticulocytes become mature red blood cells.

Predict 3

During a local Red Cross blood drive, Juan donated one unit of blood (about 500 mL). Predict how his reticulocyte count changed during the week after he donated blood, and explain why the change occurred.

Cell division requires the B vitamins folate and B_{12}, which are necessary for the synthesis of DNA (see chapter 3). Hemoglobin production requires iron. Consequently, adequate amounts of folate, vitamin B_{12}, and iron are necessary for normal red blood cell production.

Red blood cell production is stimulated by low blood O_2 levels, which result from several conditions: decreased numbers of red blood cells, decreased or defective hemoglobin, diseases of the lungs, high altitude, inability of the cardiovascular system to deliver blood to tissues, and increased tissue demands for O_2—for example, during endurance exercises.

Red blood cell production is regulated by the glycoprotein **erythropoietin** (ĕ-rith-rō-poy′ĕ-tin), a hormone produced mostly by the kidneys (figure 19.6). Erythropoietin secretion increases when blood O_2 levels are low, a condition known as **hypoxia.** This stimulates red bone marrow to produce more red blood cells by increasing the number of proerythroblasts formed and by decreasing the time required for red blood cells to mature. Thus, when blood O_2 levels decrease, erythropoietin production increases, which increases red blood cell production. The greater number of red blood cells increases the blood's ability to transport O_2. This negative-feedback mechanism returns blood O_2 levels to normal and maintains homeostasis by increasing the delivery of O_2 to tissues. Conversely, if blood O_2 levels rise, less erythropoietin is released, and red blood cell production decreases.

Predict 4

Cigarette smoke produces carbon monoxide. If a nonsmoker smoked a pack of cigarettes a day for a few weeks, what would happen to the number of red blood cells in the person's blood? Explain.

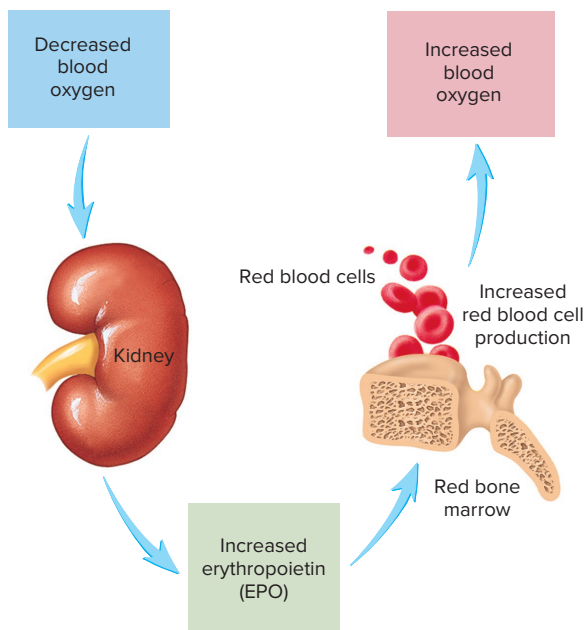
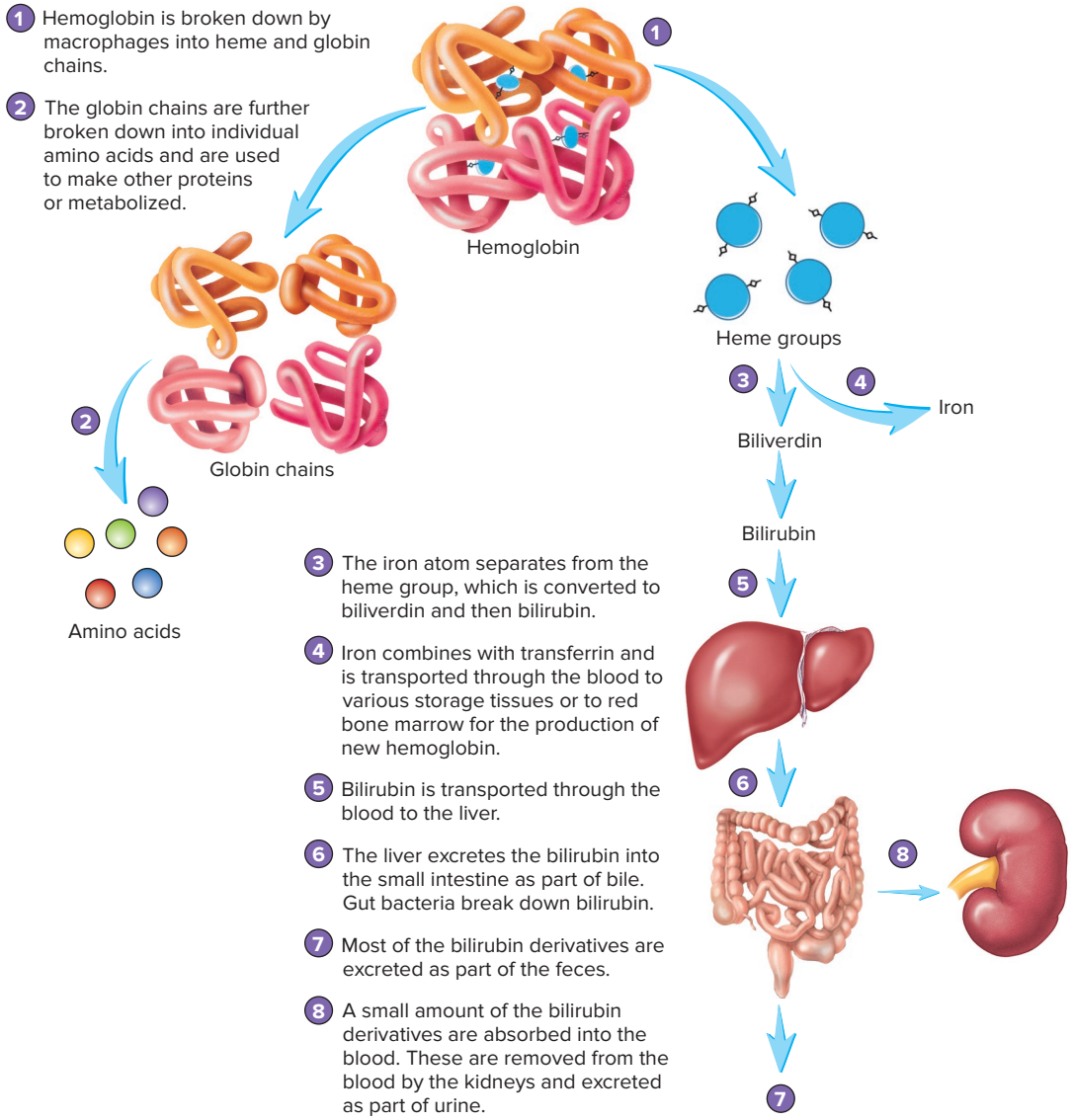


FIGURE 19.6 Red Blood Cell Production
In response to decreased blood oxygen, the kidneys release erythropoietin into the bloodstream. The increased erythropoietin stimulates red blood cell production in the red bone marrow. This process increases blood oxygen levels, restoring homeostasis.



PROCESS FIGURE 19.7 Hemoglobin Breakdown

Macrophages break down hemoglobin, and the breakdown products are used or excreted. AP|R

? *Some forms of anemia result from fewer, smaller red blood cells. These individuals produce feces that are light or white in color. Explain why this is expected.*

The normal lifespan of a red blood cell is about 120 days in males and 110 days in females. These cells have no nuclei and therefore cannot produce new proteins or divide. As their existing proteins, enzymes, plasma membrane components, and other structures degenerate, the red blood cells are less able to transport O_2, and their plasma membranes become more fragile. Eventually, the red blood cells rupture as they squeeze through a tight spot in the circulation. **Hemolysis** (hē-mol′i-sis) occurs when red blood cells rupture and the hemoglobin is released into the plasma. Hemoglobin released into the plasma will denature as the molecules change shape in a new environment (see chapter 2). Hemolysis occurs as old red blood cells rupture or as a result of hemolytic anemia (see table 19.4), transfusion reactions, hemolytic disease of the newborn, and malaria.

Macrophages located in the spleen, liver, and other lymphatic tissue take up the hemoglobin released from ruptured red blood cells (figure 19.7). Within a macrophage, lysosomal enzymes digest the hemoglobin to yield amino acids, iron, and bilirubin.

- The globin part of hemoglobin is broken down into its component amino acids. Most of the amino acids are reused to produce other proteins.
- The heme groups are broken down, releasing the iron atoms. Iron atoms released from heme are carried by the blood to red bone marrow, where they are incorporated into new hemoglobin molecules.

- After the removal of the iron atoms, the non-iron part of the heme groups is first converted to **biliverdin** (bil-i-ver′din) and then to **bilirubin** (bil-i-roo′bin). The bilirubin is then released into the plasma, where it binds to albumin and is transported to liver cells. This bilirubin, called **free bilirubin,** is taken up by the liver cells and conjugated, or joined, to glucuronic acid to form **conjugated bilirubin,** which is more water-soluble than free bilirubin. The conjugated bilirubin becomes part of the **bile,** which is the fluid secreted from the liver into the small intestine. In the intestine, bacteria convert bilirubin into the pigments that give feces its characteristic brownish color. Some of these pigments are absorbed from the intestine, modified in the kidneys, and excreted in the urine, thus contributing to the characteristic yellowish color of urine.

Jaundice (jawn′dis) is a yellowish staining of the skin and the sclerae of the eyes caused by a buildup of bile pigments in the blood and some tissues. Any process that causes increased destruction of red blood cells can cause jaundice, such as damage by toxins, genetic defects in red blood cell plasma membranes, infections, and immune reactions. Other causes of jaundice are dysfunction or destruction of liver tissue and blockage of the duct system that drains bile from the liver (see chapter 24).

ASSESS YOUR PROGRESS

13. *What is the normal amount of red blood cells in a male? In a female?*
14. *How does the shape of red blood cells enable them to exchange gases and move through blood vessels more easily?*
15. *What is the main component of a red blood cell? What is the primary function of red blood cells?*
16. *Give the percentage for each of the ways that oxygen and carbon dioxide are transported in the blood. What is the function of carbonic anhydrase?*
17. *Describe the two basic parts of a hemoglobin molecule. Which part is associated with iron? What gases are transported by each part?*
18. *What is the significance of fetal hemoglobin's difference from adult hemoglobin?*
19. *Describe the process of erythropoiesis, beginning with hemocytoblasts in the red bone marrow.*
20. *What is erythropoietin, where is it produced, what causes it to be produced, and what effect does it have on red blood cell production?*
21. *How long do red blood cells normally stay in circulation? Where are red blood cells removed from the blood? List the three breakdown products of hemoglobin, and explain what happens to them.*

White Blood Cells

When the components of blood are separated from each other (see figure 19.1), **white blood cells (WBCs),** or *leukocytes,* form a thin, white layer of cells between the plasma and the red blood cells. This layer is often referred to as the *buffy coat*. White blood cells have a nucleus. In stained preparations, white blood cells attract stain, whereas red blood cells remain relatively unstained (figure 19.8; table 19.2).

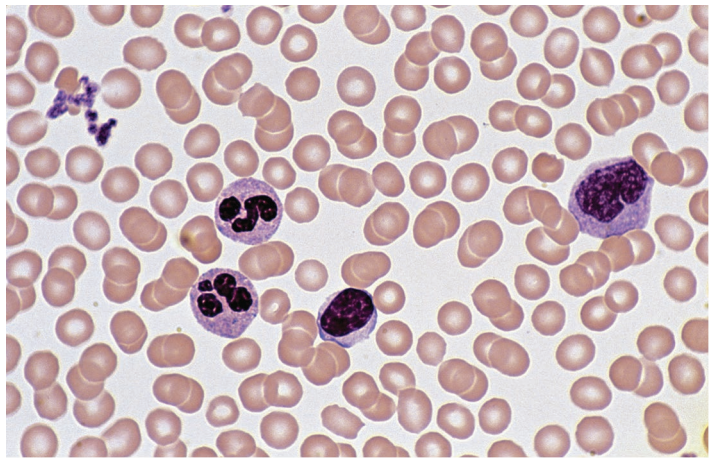


FIGURE 19.8 Standard Blood Smear
A thin film of blood is spread on a microscope slide and stained. The white blood cells have pink-colored cytoplasm and purple-colored nuclei. The red blood cells do not have nuclei. The center of a red blood cell appears whitish because light more readily shines through the thin center of the disc than through the thicker edges. The platelets are purple cell fragments. ©Ed Reschke/Getty Images

White blood cells are grouped into two categories based on their appearance in stained preparations: (1) granulocytes and (2) agranulocytes. **Granulocytes** (gran′yū-lō-sītz) are white blood cells with large cytoplasmic granules and lobed nuclei (table 19.2). Their granules stain with dyes that make the cells more visible when viewed through a light microscope. The three types of granulocytes are named according to the staining characteristics of their granules: (1) **Neutrophils** (nu′trō-filz) stain with acidic and basic dyes, (2) **eosinophils** (ē-ō-sin′ō-filz) stain red with acidic dyes, and (3) **basophils** (bā′sō-filz) stain dark purple with basic dyes. **Agranulocytes** (ă-gran′yū-lō-sītz) are white blood cells that appear to have no granules when viewed with a light microscope. Actually, agranulocytes have granules, but they are so small that they cannot be seen easily with the light microscope. The two types of agranulocytes are (1) **lymphocytes** (lim′fō-sītz) and (2) **monocytes** (mon′ō-sītz). They have nuclei that are not lobed.

White blood cells protect the body against invading microorganisms and remove dead cells and debris from the body. Three characteristics—ameboid movement, diapedesis, and chemotaxis—allow white blood cells to carry out their function of protection.

1. Most white blood cells are motile, exhibiting **ameboid movement.** This is the ability to move as an ameba does, by putting out irregular cytoplasmic projections. Ameboid movement allows white blood cells to have more directed movement, instead of moving only with the flow of blood, like red blood cells.
2. White blood cells also have the ability to leave the blood and enter other tissues. They accomplish this by the process of **diapedesis** (dī′ă-pĕ-dē′sis), in which they become thin and elongated and slip between or through the cells of blood vessel walls.
3. The white blood cells can then be attracted to foreign materials or dead cells within the tissue by **chemotaxis** (kē-mō-tak′sis; see chapter 22). At the site of an infection, white blood cells

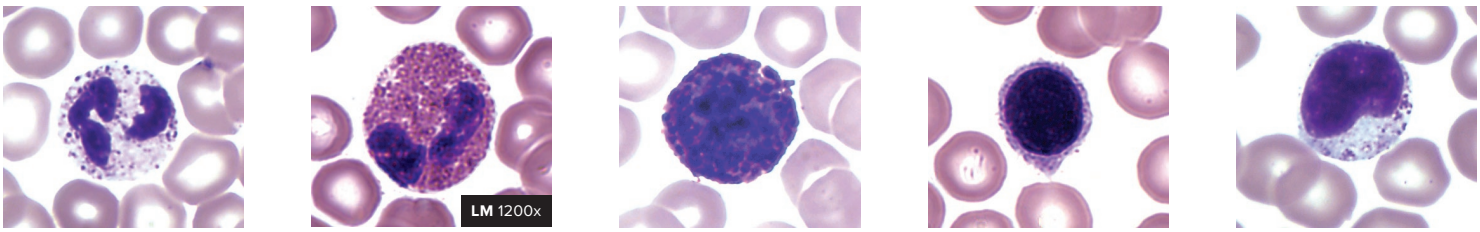


FIGURE 19.9 Types of White Blood Cells
(*a*) Neutrophil, (*b*) eosinophil, (*c*) basophil, (*d*) lymphocyte, (*e*) monocyte/macrophage. ©McGraw-Hill Education/Al Telser, photographer AP|R

accumulate and phagocytize bacteria, dirt, and dead cells; then they die. **Pus** is the accumulation of dead white blood cells and bacteria, along with fluid and cell debris.

Following are detailed descriptions of the five types of white blood cells: (1) neutrophils, (2) eosinophils, (3) basophils, (4) lymphocytes, and (5) monocytes.

Neutrophils

Neutrophils compose 55–70% of white blood cells (figure 19.9*a*; table 19.2). They have small cytoplasmic granules that stain with both acidic and basic dyes. Commonly, their nuclei are lobed, with the number of lobes varying from two to five. Neutrophils are often called *polymorphonuclear* (pol′ē-mōr-fō-noo′klē-ăr) *neutrophils,* or *PMNs,* to indicate that their nuclei can occur in more than one (*poly*) form (*morph*). Neutrophils are usually the first of the white blood cells to respond to infection. They normally remain in the blood for about 10–12 hours and then move into other tissues. Once neutrophils leave the blood, they seek out and phagocytize bacteria, antigen-antibody complexes (antigens and antibodies bound together), and other foreign matter. Neutrophils also secrete a class of enzymes called **lysozymes** (lī′sō-zīmz), which are capable of destroying certain bacteria. Neutrophils usually survive 1–2 days after leaving the blood.

Eosinophils

Eosinophils compose 1–4% of white blood cells (figure 19.9*b*; table 19.2). They contain cytoplasmic granules that stain bright red with eosin, an acidic stain. They often have a two-lobed nucleus. Eosinophils are important in the defense against certain worm parasites. Although the eosinophils are not able to phagocytize the large parasites, they attach to the worms and release substances that kill the parasites. Eosinophils also increase in number in tissues experiencing inflammation, such as during allergic reactions. Eosinophils apparently modulate the inflammatory response by producing enzymes that destroy inflammatory chemicals, such as histamine. However, research has shown that eosinophils have harmful effects on respiratory airways in certain forms of asthma.

Basophils

Basophils compose 0.5–1% of white blood cells (figure 19.9*c*; table 19.2). They contain large cytoplasmic granules that stain blue or purple with basic dyes. Basophils, like eosinophils and neutrophils, leave the blood and migrate through other tissues. They increase in number in both allergic and inflammatory reactions. Basophils contain large amounts of **histamine** (see chapter 22), which they release within tissues to increase inflammation. They also release **heparin,** which inhibits blood clotting.

Lymphocytes

Lymphocytes compose 20–40% of white blood cells (figure 19.9*d*; table 19.2). They are the smallest white blood cells, usually slightly larger in diameter than red blood cells. A lymphocyte's cytoplasm consists of only a thin, sometimes imperceptible, ring around the nucleus. Although lymphocytes originate in red bone marrow, they migrate through the blood to lymphatic tissues, where they can proliferate and produce more lymphocytes. The majority of the body's total lymphocyte population is in the lymphatic tissues: the lymph nodes, spleen, tonsils, lymphatic nodules, and thymus.

Some specific types of lymphocytes play important roles in immunity (see chapter 22). For example, **B cells** are a type of lymphocyte that can be stimulated by bacteria or toxins to divide and form cells that produce **antibodies,** a class of plasma proteins also called immunoglobulins. Antibodies can attach to bacteria and activate mechanisms that destroy the bacteria. **T cells** are another type of lymphocyte that protect against viruses and other intracellular microorganisms by attacking and destroying the cells in which they are found. In addition, T cells are involved in the destruction of tumor cells and in tissue graft rejections.

Monocytes

Monocytes compose 2–8% of white blood cells (figure 19.9*e*; table 19.2). They are typically the largest of the white blood cells. Monocytes normally remain in the blood for about 3 days. Then they leave the blood and are transformed into macrophages. Macrophages migrate through various tissues, where they phagocytize bacteria, dead cells, cell fragments, and other debris. An increase in the number of monocytes in the blood is often associated with chronic infection. Macrophages also stimulate responses from other cells in two ways: (1) by releasing chemical messengers and (2) by phagocytizing and processing foreign substances, which are then presented to lymphocytes. The responses of these other cells help protect against microorganisms and other foreign substances (see chapter 22).

ASSESS YOUR PROGRESS

22. *What are the two major functions of white blood cells? Define* ameboid movement, diapedesis, *and* chemotaxis.

23. *Describe the morphology of the five types of white blood cells.*

24. *Name the two white blood cells that function primarily as phagocytic cells. What are lysozymes?*
25. *Which white blood cell defends against parasitic worms?*
26. *Which white blood cell releases histamine and promotes inflammation?*
27. *B cells and T cells are examples of which type of white blood cell? How do these cells protect against bacteria and viruses?*

Platelets

Platelets, or *thrombocytes* (table 19.2; see figure 19.8), are minute fragments of cells. They consist of a small amount of cytoplasm surrounded by a plasma membrane. Platelets are roughly disc-shaped and average about 3 µm in diameter. Glycoproteins and proteins on their surface allow platelets to attach to other molecules, such as collagen in connective tissue. Some of these surface molecules, as well as molecules released from granules in the platelet cytoplasm, play important roles in controlling blood loss. The platelet cytoplasm also contains actin and myosin, which can cause contraction of the platelet (see section 19.5).

The life expectancy of platelets is about 5–9 days. Platelets are derived from **megakaryocytes** (meg-ă-kar′ē-ō-sitz), which are extremely large cells found in the red bone marrow. Small fragments of these cells break off and enter the blood as platelets.

Platelets play an important role in preventing blood loss by (1) forming platelet plugs that seal holes in small vessels and (2) promoting the formation and contraction of clots that help seal off larger wounds in the vessels.

ASSESS YOUR PROGRESS

28. *What is a platelet? How do platelets form?*
29. *What are the two major roles of platelets in preventing blood loss?*

19.5 Hemostasis

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Explain the three processes that can lead to hemostasis: vascular spasm, platelet plug formation, and coagulation.**
B. **Describe how aspirin affects the action of platelets.**
C. **Describe the regulation of clot formation and how clots are removed.**

Hemostasis (hē′mō-stā-sis, hē-mos′tă-sis), the cessation of bleeding, is very important to the maintenance of homeostasis. If not stopped, excessive bleeding from a cut or torn blood vessel can result in a positive-feedback cycle, consisting of ever-decreasing blood volume and blood pressure that disrupts homeostasis and results in death. Fortunately, when a blood vessel is damaged, a series of events helps prevent excessive blood loss. Hemostasis involves three processes: (1) vascular spasm, (2) platelet plug formation, and (3) coagulation.

Vascular Spasm

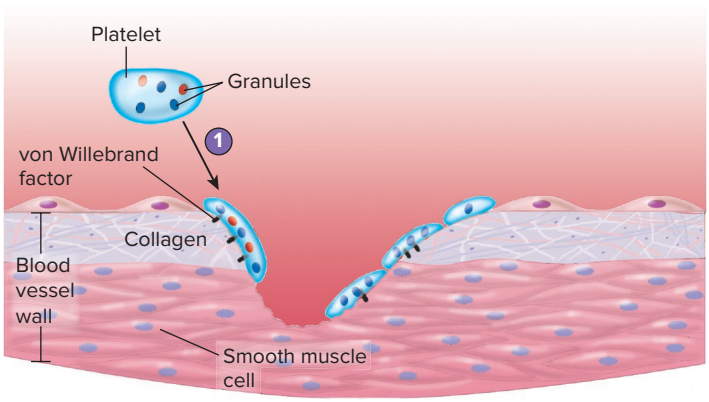
Vascular spasm is the immediate but temporary constriction of a blood vessel. Vascular spasm occurs when smooth muscle within the wall of the vessel contracts. This constriction can close small vessels completely and stop the flow of blood through them. Damage to blood vessels can activate nervous system reflexes that cause vascular spasms. Chemicals released by cells of the damaged vessel as well as platelets also stimulate vascular spasms. For example, endothelial cells release the peptide **endothelin** (en-do′the-lin), which leads to constriction of blood vessels. Also, during the formation of a platelet plug, platelets release **thromboxanes** (throm′bok-zānz), which are derived from certain prostaglandins. Thromboxanes also lead to constriction of blood vessels.

Platelet Plug Formation

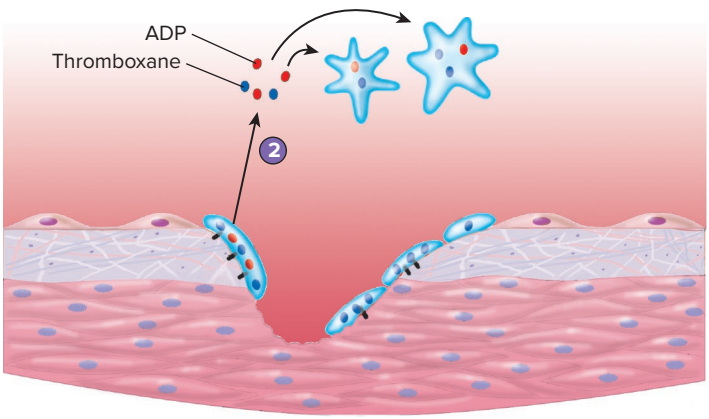
A **platelet plug** is an accumulation of platelets that can seal small breaks in blood vessels. A platelet plug is not the same thing as a blood clot, but the formation of the platelet plug is an important step in blood clot formation. Platelet plug formation is very important in maintaining the integrity of the circulatory system. Small tears occur in the smaller vessels and capillaries many times each day, and platelet plug formation quickly closes them. People who lack the normal number of platelets tend to develop numerous small hemorrhages in their skin and internal organs.

The formation of a platelet plug can be described as a series of steps, but in actuality many of the steps take place simultaneously (figure 19.10):

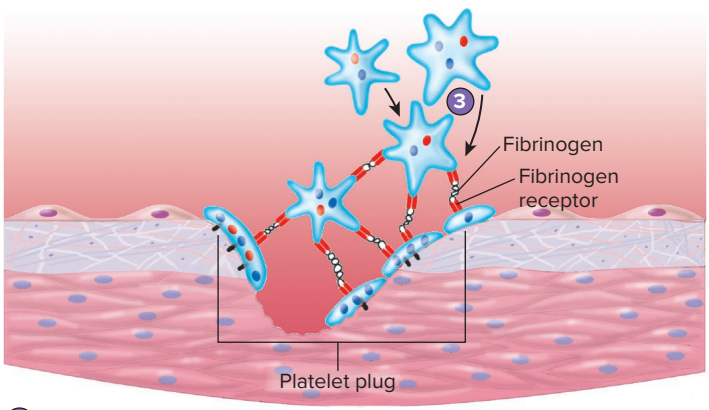
1. **Platelet adhesion** occurs when platelets bind to collagen that is exposed when a blood vessel is damaged. Most platelet adhesion is mediated through **von Willebrand factor (vWF),** a protein produced and secreted by blood vessel endothelial cells. Platelets have surface receptors on their membrane. These surface receptors bind to von Willebrand factor released from damaged blood vessels. Von Willebrand factor also binds to the exposed collagen of the damaged vessel, thereby forming a bridge between exposed collagen and platelets. In addition, other platelet surface receptors can bind directly to collagen.
2. After platelets adhere to collagen, they become activated. These activated platelets then initiate the **platelet release reaction,** in which adenosine diphosphate (ADP), thromboxanes, and other chemicals are released from the activated platelets by exocytosis. The ADP and thromboxane bind to their respective receptors on the surfaces of other platelets, activating them. These activated platelets release additional chemicals, thereby producing a cascade of chemical release by the platelets. Thus, more and more platelets become activated. This is an example of positive feedback.
3. As platelets become activated, they change shape and express fibrinogen receptors that can bind to fibrinogen, a plasma protein. In **platelet aggregation,** fibrinogen forms a bridge between the fibrinogen receptors of different platelets, resulting in a platelet plug.



1 Platelet adhesion occurs when von Willebrand factor connects exposed collagen to platelets.



2 During the platelet release reaction, ADP, thromboxanes, and other chemicals are released and activate other platelets.



3 Platelet aggregation occurs when fibrinogen receptors on activated platelets bind to fibrinogen, connecting the platelets to one another. The accumulating mass of platelets forms a platelet plug.

PROCESS FIGURE 19.10 Platelet Plug Formation

During platelet plug formation, platelets adhere to the surface of the damaged vessel and to other platelets, reducing blood loss at the injury site.

? *Among other effects, aspirin inhibits thromboxane activity. How will this affect platelet plug formation?*

In addition to forming a platelet plug, activated platelets also release phospholipids (platelet factor III) and coagulation factor V, which are important in clot formation.

Coagulation

Vascular spasms and platelet plugs alone are not sufficient to close large tears or cuts. When a blood vessel is severely damaged, **coagulation** (kō-ag-ū-lā′shŭn), or blood clotting, results in the formation of a clot. A **blood clot** is a network of threadlike protein fibers, called **fibrin,** that traps blood cells, platelets, and fluid (figure 19.11).

Blood clot formation depends on a number of **clotting factors,** or *coagulation factors,* which are proteins found within plasma (table 19.3). Normally, the clotting factors are in an inactive state and do not cause clotting. After injury, the clotting factors are activated. The activation of clotting factors is a complex process involving many chemical reactions, some of which require calcium ions (Ca^{2+}) and molecules on the surface of activated platelets, such as phospholipids and factor V.

Predict 5

Why is it advantageous for clot formation to involve molecules on the surface of activated platelets?

Clotting factors are activated in two ways: (1) the extrinsic pathway and (2) the intrinsic pathway (figure 19.12). These two pathways converge to form the common pathway, which results in the formation of a fibrin clot.

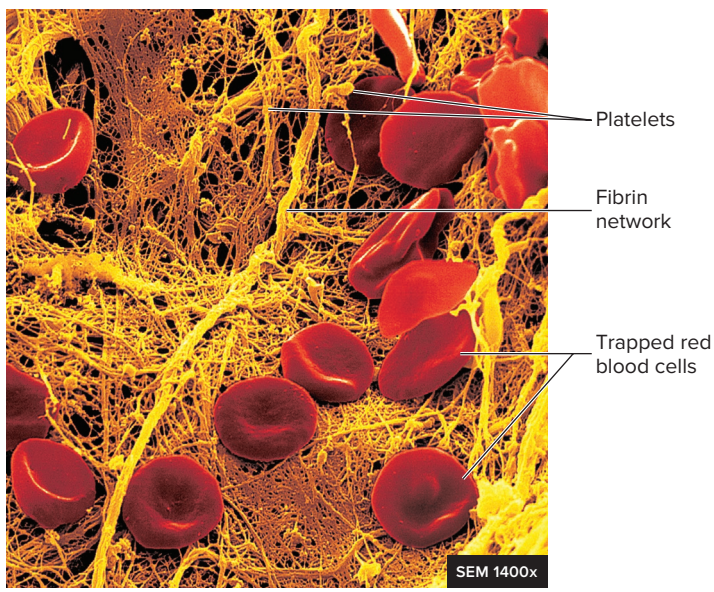
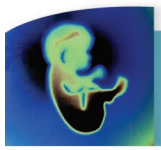


FIGURE 19.11 Blood Clot

A blood clot consists of fibrin, which traps red blood cells, platelets, and fluid.



Clinical IMPACT 19.2 Clinical Importance of Taking Aspirin

Platelet activation results in platelet plug formation and the production of chemicals, such as phospholipids, that are important for blood clotting. Alternatively, the inhibition of platelet activation reduces the formation of blood clots. Understanding how this occurs requires knowledge of the chemical behavior of the **eicosanoids,** a group that includes prostaglandins, thromboxanes, and leukotrienes, the compounds involved in platelet activation. In humans, arachidonic acid is the most common precursor molecule for the eicosanoids. The enzyme cyclooxygenase (COX) converts arachidonic acid into a prostaglandin that can be converted into thromboxane. However, the actions of COX are inhibited by aspirin, which inhibits prostaglandin and thromboxane synthesis. As a result, aspirin reduces platelet activation.

Taking aspirin can have harmful or beneficial effects, depending on the circumstances. If an expectant mother ingests aspirin near the end of pregnancy, thromboxane synthesis is inhibited and several effects are possible. The mother can experience excessive bleeding after delivery because of decreased platelet function, and the baby can exhibit numerous localized hemorrhages called **petechiae** (pe-tē′kē-ē) over the surface of its body as a result of decreased platelet function. If the quantity of ingested aspirin is large, the infant, the mother, or both may die as a result of hemorrhage.

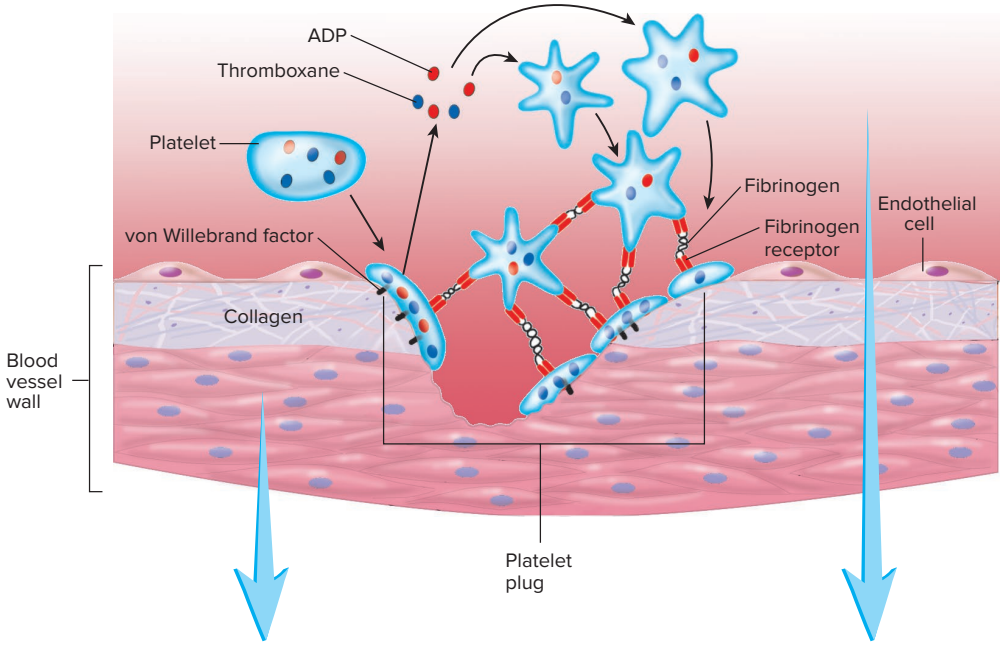
On the other hand, platelet plugs and blood clots can block blood vessels, producing heart attacks and strokes. Therefore, suspected heart attack victims are routinely given aspirin en route to the emergency room to reduce further clotting. The United States Preventive Services Task Force (USPSTF) and the American Heart Association (AHA) recommend low-dose aspirin therapy (75–160 mg/day) for all men and women at high risk for cardiovascular disease. Determining risk involves analyzing many factors and should be done in consultation with a physician. The decreased risk for cardiovascular disease from aspirin therapy must be weighed against the increased risk for hemorrhagic stroke and gastrointestinal bleeding.

The drug Plavix (clopidogrel bisulfate) reduces the activation of platelets by blocking the ADP receptors on the surface of platelets. It is used to prevent clotting and, with other anticlotting drugs, to treat heart attacks.

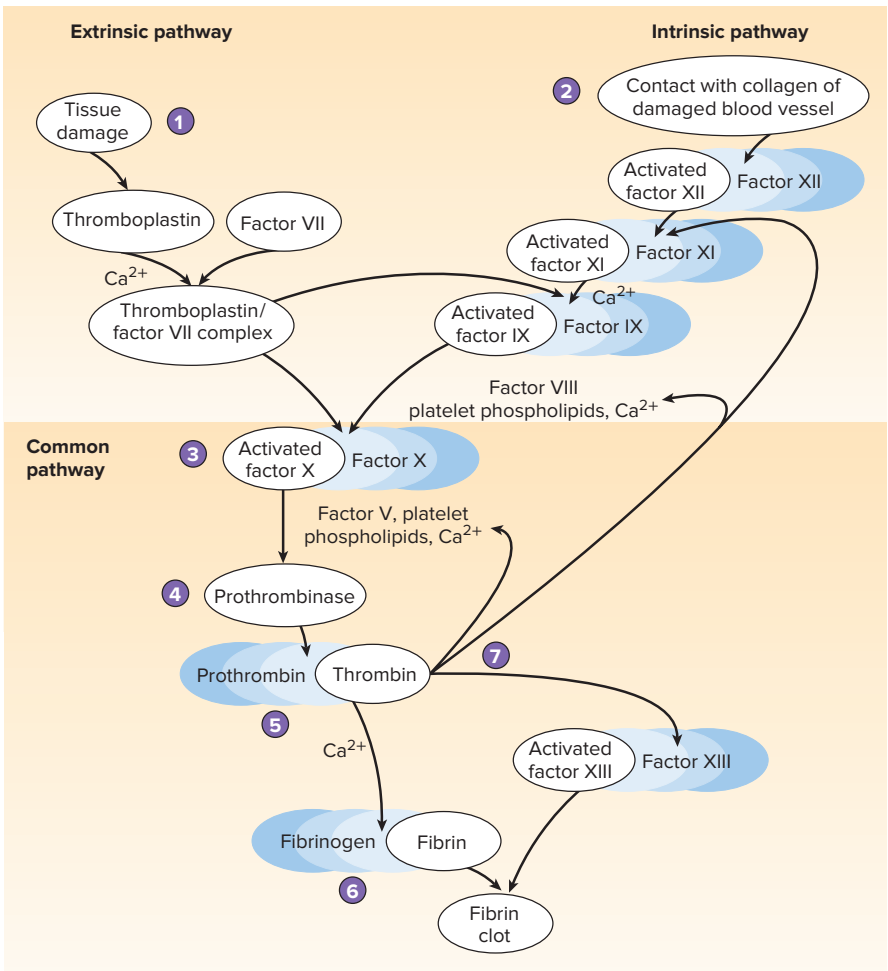
TABLE 19.3 Clotting Factors

Factor Number	Name (Synonym)	Description and Function
I	Fibrinogen	Plasma protein synthesized in the liver; converted to fibrin in the common pathway
II	Prothrombin	Plasma protein synthesized in the liver (requires vitamin K); converted to thrombin in the common pathway
III	Thromboplastin (tissue factor)	Mixture of lipoproteins released from damaged tissue; required in the extrinsic pathway
IV	Calcium ion	Required throughout the clotting sequence
V	Proaccelerin (labile factor)	Plasma protein synthesized in the liver; activated form functions in the intrinsic and extrinsic pathways
VII	Serum prothrombin conversion accelerator (stable factor, proconvertin)	Plasma protein synthesized in the liver (requires vitamin K); functions in the extrinsic pathway
VIII	Antihemophilic factor (antihemophilic globulin)	Plasma protein synthesized in megakaryocytes and endothelial cells; required in the intrinsic pathway
IX	Plasma thromboplastin component (Christmas factor)	Plasma protein synthesized in the liver (requires vitamin K); required in the intrinsic pathway
X	Stuart factor (Stuart-Prower factor)	Plasma protein synthesized in the liver (requires vitamin K); required in the common pathway
XI	Plasma thromboplastin antecedent	Plasma protein synthesized in the liver; required in the intrinsic pathway
XII	Hageman factor	Plasma protein required in the intrinsic pathway
XIII	Fibrin-stabilizing factor	Protein found in plasma and platelets; required in the common pathway
Platelet Factors		
I	Platelet accelerator	Same as plasma factor V
II	Thrombin accelerator	Accelerates thrombin and fibrin production
III		Phospholipids necessary for the intrinsic and extrinsic pathways
IV		Binds heparin, which prevents clot formation

Note: Factor VI was once thought to be involved but is no longer accepted as playing a role in clotting; apparently the same as activated factor V.



1. The extrinsic pathway of clotting is stimulated by thromboplastin, released by damaged tissue.
2. The intrinsic pathway of clotting starts when inactive factor XII, which is in the blood, is activated by coming into contact with a damaged blood vessel.
3. Activation of the extrinsic or intrinsic pathway results in the production of activated factor X.
4. Activated factor X, factor V, phospholipids, and Ca^{2+} form prothrombinase.
5. Prothrombinase converts prothrombin to thrombin.
6. Thrombin converts fibrinogen to fibrin (the clot).
7. Thrombin activates clotting factors, promoting clot formation and stabilizing the fibrin clot.



PROCESS FIGURE 19.12 Clot Formation

In a sequence of chemical reactions, activated clotting factors (*white ovals*) activate inactive clotting factors (*blue ovals*). Clot formation begins through either the extrinsic or the intrinsic pathway. The common pathway starts with factor X and results in a fibrin clot.

? *Heparin is an anticoagulant that activates an enzyme called antithrombin. Based on its name, how would antithrombin disrupt blood clotting?*

Extrinsic Pathway

The extrinsic pathway is so named because it begins with chemicals that are outside of, or extrinsic to, the blood (figure 19.12). Damaged tissues release a mixture of lipoproteins and phospholipids called **thromboplastin** (throm-bō-plas′tin), also known as *tissue factor* (*TF*) or factor III. Thromboplastin, in the presence of Ca^{2+}, forms a complex with factor VII that activates factor X, which is the clotting factor that initiates the common pathway.

Intrinsic Pathway

The intrinsic pathway is so named because it begins with chemicals that are inside, or intrinsic to, the blood (figure 19.12). Damage to blood vessels can expose collagen in the connective tissue beneath the endothelium of the blood vessel. When plasma factor XII comes into contact with collagen, factor XII is activated. Subsequently, activated factor XII stimulates factor XI, which in turn activates factor IX. Activated factor IX joins with factor VIII, platelet phospholipids, and Ca^{2+} to activate factor X, which, as stated in the extrinsic pathway description, initiates the common pathway.

Although the extrinsic and intrinsic pathways were once considered distinct, we now know that the extrinsic pathway can activate the clotting factors in the intrinsic pathway. The thromboplastin/factor VII complex from the extrinsic pathway can stimulate the formation of activated factor IX in the intrinsic pathway.

Common Pathway

On the surface of platelets, activated factor X, factor V, platelet phospholipids, and Ca^{2+} combine to form **prothrombinase,** or *prothrombin activator*. Prothrombinase converts the soluble plasma protein **prothrombin** to the enzyme **thrombin.** A major function of thrombin is to convert the soluble plasma protein fibrinogen to the insoluble protein fibrin. Fibrin is the protein that forms the fibrous network of the blood clot (see figure 19.11). In addition, thrombin also stimulates factor XIII activation, which is necessary to stabilize the clot.

Thrombin can also activate many of the clotting proteins, such as factor XI and prothrombinase. Thus, a positive-feedback system operates whereby thrombin production stimulates the production of additional thrombin. Thrombin also has a positive-feedback effect on platelet aggregation by stimulating platelet activation.

Vitamin K is required for the formation of many of the factors involved in blood clot formation (table 19.3). Humans rely on two sources for vitamin K. About half comes from the diet, and half comes from bacteria within the large intestine. Antibiotics taken to fight bacterial infections sometimes kill these intestinal bacteria, thereby reducing vitamin K levels and causing bleeding. Vitamin K supplements may be necessary for patients on prolonged antibiotic therapy. Newborns lack these intestinal bacteria; thus, they routinely receive a vitamin K injection at birth. Infants can also obtain vitamin K from food, such as milk.

The absorption of vitamin K from the large intestine requires the presence of bile because vitamin K is fat-soluble. Therefore, disorders involving an obstruction of bile flow to the intestine can interfere with vitamin K absorption and lead to insufficient blood clotting. Liver diseases that result in the decreased synthesis of clotting factors can also cause insufficient blood clotting.

Control of Clot Formation

Without control, clot formation would spread from the point of initiation through the entire circulatory system. Furthermore, blood vessels in a healthy person contain rough areas that can stimulate clot formation, and small amounts of prothrombin are constantly being converted into thrombin. To prevent unwanted clotting, the blood contains several **anticoagulants** (an′tē-kō-ag′ū-lantz). These anticoagulants prevent clotting factors from initiating clot formation under normal concentrations in the blood. Only when clotting factor concentrations exceed a given threshold in a local area does clot formation occur. At the site of injury, so many clotting factors are activated that the anticoagulants are unable to prevent clot formation. However, away from the injury site, the activated clotting factors are diluted in the blood, anticoagulants neutralize them, and clotting is prevented.

Examples of anticoagulants in the blood are antithrombin, heparin, and prostacyclin. **Antithrombin,** a plasma protein produced by the liver, slowly inactivates thrombin. Heparin, produced by basophils and endothelial cells, works with antithrombin to rapidly inactivate thrombin. **Prostacyclin** (pros-tă-sī′klin) is a prostaglandin derivative produced by endothelial cells. It counteracts the effects of thrombin by causing vasodilation and inhibiting the release of clotting factors from platelets.

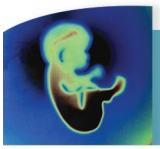
Anticoagulants are also important when blood is outside the body. They prevent the clotting of blood used in transfusions and laboratory blood tests. Besides heparin, examples include **ethylenediaminetetraacetic** (eth′il-ēn-dī′ă-mēn-tet-ră-ă-sē′tik) **acid (EDTA)** and sodium citrate. EDTA and sodium citrate prevent clot formation by binding to Ca^{2+}, thus making the ions inaccessible for clotting reactions.

Clot Retraction and Dissolution

The fibrin meshwork constituting a clot adheres to the walls of the blood vessel. Once a clot has formed, **clot retraction** occurs, a process whereby the blood clot condenses into a denser, compact structure. Platelets contain the contractile proteins actin and myosin, which operate in a similar fashion to actin and myosin in smooth muscle (see chapter 9). Platelets form extensions, which attach to fibrinogen through fibrinogen receptors (see figure 19.10). Contraction of the extensions pulls on the fibrinogen and leads to clot retraction. As the clot retracts, a fluid called **serum** (sēr′ŭm) is squeezed out of the clot. Serum is plasma from which fibrinogen and some of the clotting factors have been removed.

Clot retraction pulls the edges of the damaged blood vessel together, helping stop blood flow, reducing infection, and enhancing healing. The damaged vessel is repaired as fibroblasts move into the damaged area and new connective tissue forms. In addition, epithelial cells around the wound proliferate and fill in the torn area.

The blood clot is usually dissolved within a few days after clot formation. The process that dissolves the blood clot is called **fibrinolysis** (fī-bri-nol′i-sis). During this process, an enzyme called **plasmin** (plaz′min) hydrolyzes, or breaks, fibrin, thereby dissolving the clot. Plasmin forms from inactive plasminogen, a normal blood protein produced by the liver. Plasmin becomes part of the clot as it forms. Plasmin is activated by many substances, including thrombin, factor XII, tissue plasminogen activator (t-PA),



Clinical IMPACT 19.3

The Danger of Unwanted Clots

When platelets encounter damaged or diseased areas on the walls of blood vessels or the heart, an attached clot called a **thrombus** (throm′bŭs) may form. A thrombus that breaks loose and begins to float through the blood is called an **embolus** (em′bō-lŭs). Both thrombi and emboli can cause death if they block vessels that supply blood to essential organs, such as the heart, brain, or lungs. Abnormal clotting can be prevented or hindered by administering an anticoagulant, such as heparin, which acts rapidly. Warfarin (war′fă-rin), commonly referred to by the brand name Coumadin® (koo′mă-din), acts more slowly than heparin. Coumadin prevents clot formation by suppressing the liver's production of vitamin K–dependent clotting factors (II, VII, IX, and X). Warfarin was first used as a rat poison by causing rats to bleed to death. In small doses, Coumadin is a proven, effective anticoagulant in humans. However, caution is necessary with anticoagulant treatment because the patient can hemorrhage internally or bleed excessively when cut.

urokinase, and lysosomal enzymes released from damaged tissues. Understanding how plasmin is activated has been useful for treating some clotting disorders. In disorders resulting from a blood clot blocking normal blood flow through a vessel, such as a heart attack, dissolving the clot can restore blood flow and reduce damage to tissues. For example, t-PA, urokinase, or streptokinase (a bacterial enzyme) can be injected into the blood or introduced at the clot site by means of a catheter. These substances activate plasmin, which breaks down the clot.

Predict 6

Cedric's doctor recommended taking a small amount of aspirin each morning because Cedric has substantial atherosclerotic plaques in his coronary arteries. One morning, Cedric took his aspirin as usual, but that afternoon he was transported to the emergency room because of a coronary thrombosis. The ER team administered t-PA, and Cedric recovered quickly. What contributed to the rapid improvement in his condition?

ASSESS YOUR PROGRESS

30. *What is a vascular spasm? Name two factors that produce it. What is the source of thromboxanes and endothelin?*

31. *What is the function of a platelet plug? Describe the process of platelet plug formation. How are platelets important to clot formation?*

32. *What is a clot, and what is its function?*

33. *What are clotting factors? What vitamin is required to produce many clotting factors?*

34. *What is the difference between extrinsic and intrinsic activation of clotting? What factor is activated by both pathways?*

35. *What are the three reactions that occur in the common pathway of clotting? What ion is a necessary part of the clotting process?*

36. *What is the function of anticoagulants in blood? Name three anticoagulants in blood, and explain how they prevent clot formation.*

37. *Describe the process of clot retraction. What is serum?*

38. *What is fibrinolysis? How does it occur?*

19.6 Blood Grouping

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Explain the basis of the ABO blood group system and how incompatibilities occur.**

B. **Describe the Rh blood group and its connection to hemolytic disease of the newborn (HDN).**

If large quantities of blood are lost during surgery or due to injury, the patient can go into shock and die unless red blood cells are replaced to restore the blood's oxygen-carrying capacity. In this event, a transfusion or an infusion is required. A **transfusion** is the transfer of blood or blood components from one individual to another. An **infusion,** on the other hand, is the introduction of a fluid other than blood, such as a saline or glucose solution, into the blood. It may be surprising that an infusion would be used to treat someone who has lost a large volume of blood, but in many cases the return of blood volume to normal levels is all that is necessary to prevent shock. Eventually, the body produces enough red blood cells to replace those that were lost.

Early attempts to transfuse blood from one person to another were often unsuccessful because they resulted in transfusion reactions, characterized by clotting within blood vessels, kidney damage, and death. We now know that transfusion reactions are caused by interactions between antigens and antibodies (see chapter 22). Recall from chapter 3 that cells have marker molecules on their membranes to identify them as normal cells of the body. The surfaces of red blood cells have marker molecules called **antigens** (an′ti-jenz), which identify the cells. The plasma contains proteins called **antibodies,** which bind to antigens. Antibodies are very specific, meaning that each antibody can bind only to a certain antigen. When the antibodies in the plasma bind to the antigens on the surfaces of the red blood cells, they form molecular bridges that connect the red blood cells. As a result, **agglutination** (ă-gloo-ti-nā′shŭn), or clumping, of the cells occurs. The combination of the antibodies with the antigens can also initiate reactions that cause hemolysis. Because the antigen-antibody combinations can cause agglutination, the antigens are often called **agglutinogens** (ă-gloo-tin′ō-jenz), and the antibodies are called **agglutinins** (ă-gloo′ti-ninz).

The antigens on the surface of red blood cells have been categorized into **blood groups,** and more than 35 blood groups, most of them rare, have been identified. For transfusions, the ABO and Rh blood groups are among the most important and are described in this text. Other well-known groups, not discussed in this text, are the Lewis, Duffy, MNSs, Kidd, Kell, and Lutheran groups.

ABO Blood Group

The **ABO blood group** system is used to categorize human blood based on the presence or absence of A and B antigens on the surface of red blood cells. Note that there are only two possible antigens associated with the ABO blood group: antigen A and antigen B. Type A blood has type A antigens, type B blood has type B antigens, type AB blood has both A and B antigens, and type O blood has neither A nor B antigens on the surface of red blood cells (figure 19.13). The ABO blood group is an example of codominance in that the A and B antigens can be expressed at the same time (see chapter 29).

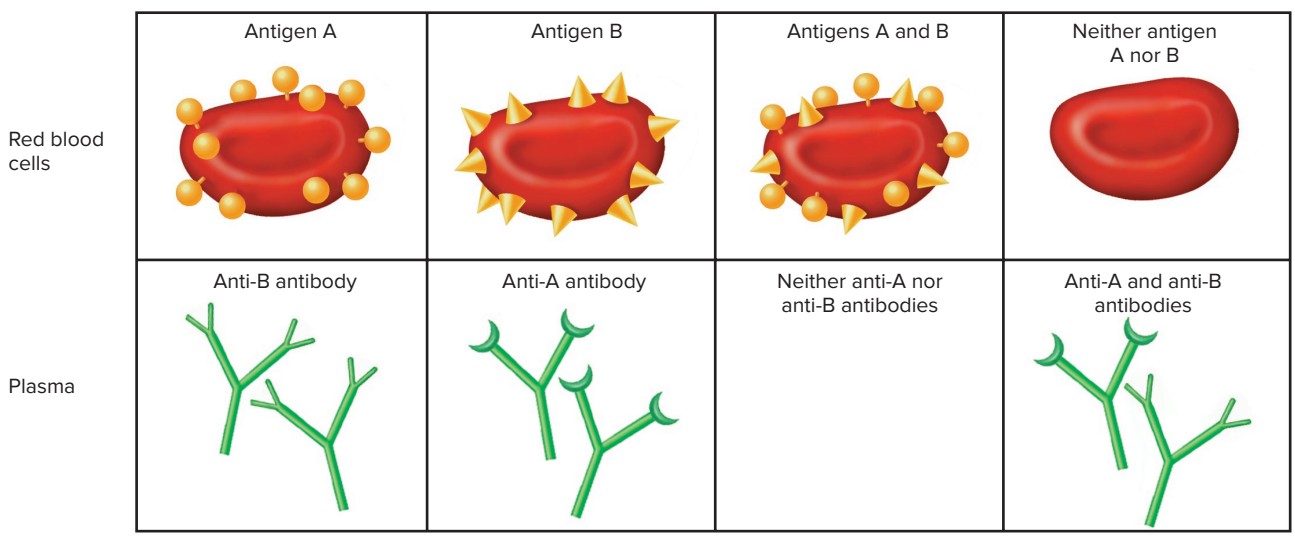
In addition to the type A and type B antigens of the ABO group, there are two types of antibodies associated with this blood group: anti-A antibody and anti-B antibody. Anti-A antibodies act against type A antigens and anti-B antibodies act against type B antigens. Because the interaction between antigens and antibodies leads to the destruction of the red blood cells, we would not expect to find matching antigens and antibodies occurring naturally in the blood. Instead, we would expect to find antibodies for the antigens that are not present. Thus, plasma from type A blood contains anti-B antibodies, and plasma from type B blood contains anti-A antibodies. Type AB blood has neither type of antibody, and type O blood has both anti-A and anti-B antibodies (see figure 19.13).

The ABO blood types do not exist in equal numbers in a population. In Caucasians in the United States, the distribution is 47% type O, 41% type A, 9% type B, and 3% type AB. Among African-Americans, the distribution is 46% type O, 27% type A, 20% type B, and 7% type AB.

Normally, antibodies do not develop against an antigen unless the body is exposed to that antigen. In the case of the antibodies associated with the ABO blood group, scientists are unsure exactly how this exposure occurs. One possible explanation for the production of anti-A and/or anti-B antibodies is that type A or B antigens on bacteria or food in the digestive tract stimulate the formation of antibodies against antigens that are different from the body's own antigens. In support of this explanation, anti-A and anti-B antibodies are not found in the blood until about 2 months after birth. It is possible that an infant with type A blood produces anti-B antibodies against the B antigens on bacteria or food. Meanwhile, an infant with A antigens does not produce antibodies against the A antigens on bacteria or food because mechanisms exist in the body to prevent the production of antibodies that react with the body's own antigens (see chapter 22).

In the event of a blood transfusion, it is very important to match the blood types of both the donor and the recipient to avoid transfusion reactions. When a blood transfusion is performed, the **donor** is the person who gives blood, and the **recipient** is the person who receives it. Usually, a recipient can successfully receive blood from a donor as long as they both have the same blood type. For example, a person with type A blood can receive blood from a person with type A blood. No ABO transfusion reaction occurs because the recipient has no anti-A antibodies against the type A antigen. On the other hand, if type A blood were donated to a person with type B blood, a transfusion reaction would occur because the person with type B blood has anti-A antibodies. These anti-A antibodies would act against the type A antigens on the red blood cells in the donated blood, causing agglutination (figure 19.14).

Type O blood is characterized by the absences of either type A or type B antigens. Because the red blood cells lack the antigens, neither anti-A nor anti-B antigens can react with these cells. People with type O blood are often called universal donors because they can usually give blood to the other ABO blood types without



Type A
Red blood cells with type A surface antigens and plasma with anti-B antibodies

Type B
Red blood cells with type B surface antigens and plasma with anti-A antibodies

Type AB
Red blood cells with both type A and type B surface antigens and neither anti-A nor anti-B plasma antibodies

Type O
Red blood cells with neither type A nor type B surface antigens but both anti-A and anti-B plasma antibodies

FIGURE 19.13 ABO Blood Groups
For simplicity, only parts of the anti-A and anti-B antibodies are illustrated. Each antibody has five identical, Y-shaped arms (see chapter 22).

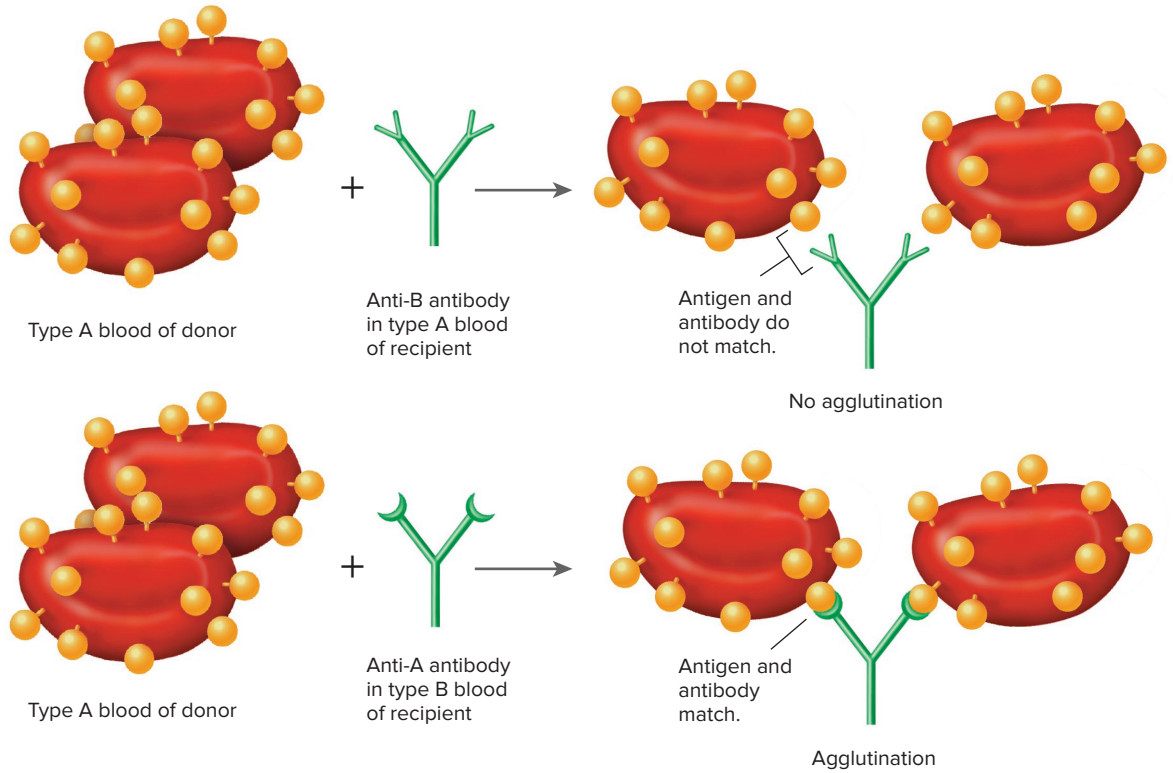


FIGURE 19.14 Agglutination Reaction

(*a*) Because the donor blood and recipient blood have the same antigens (type A) on the red blood cells, no agglutination reaction occurs. (*b*) An agglutination reaction occurs when the anti-A antibodies of the recipient attach to the type A antigens on the red blood cells in the donor blood. For simplicity, only parts of the anti-A and anti-B antibodies are illustrated. Each antibody has five identical, Y-shaped arms (see chapter 22).

causing an ABO transfusion reaction. For example, if a person with type A blood receives type O blood, the type O red blood cells do not react with the anti-B antibodies in the recipient's blood.

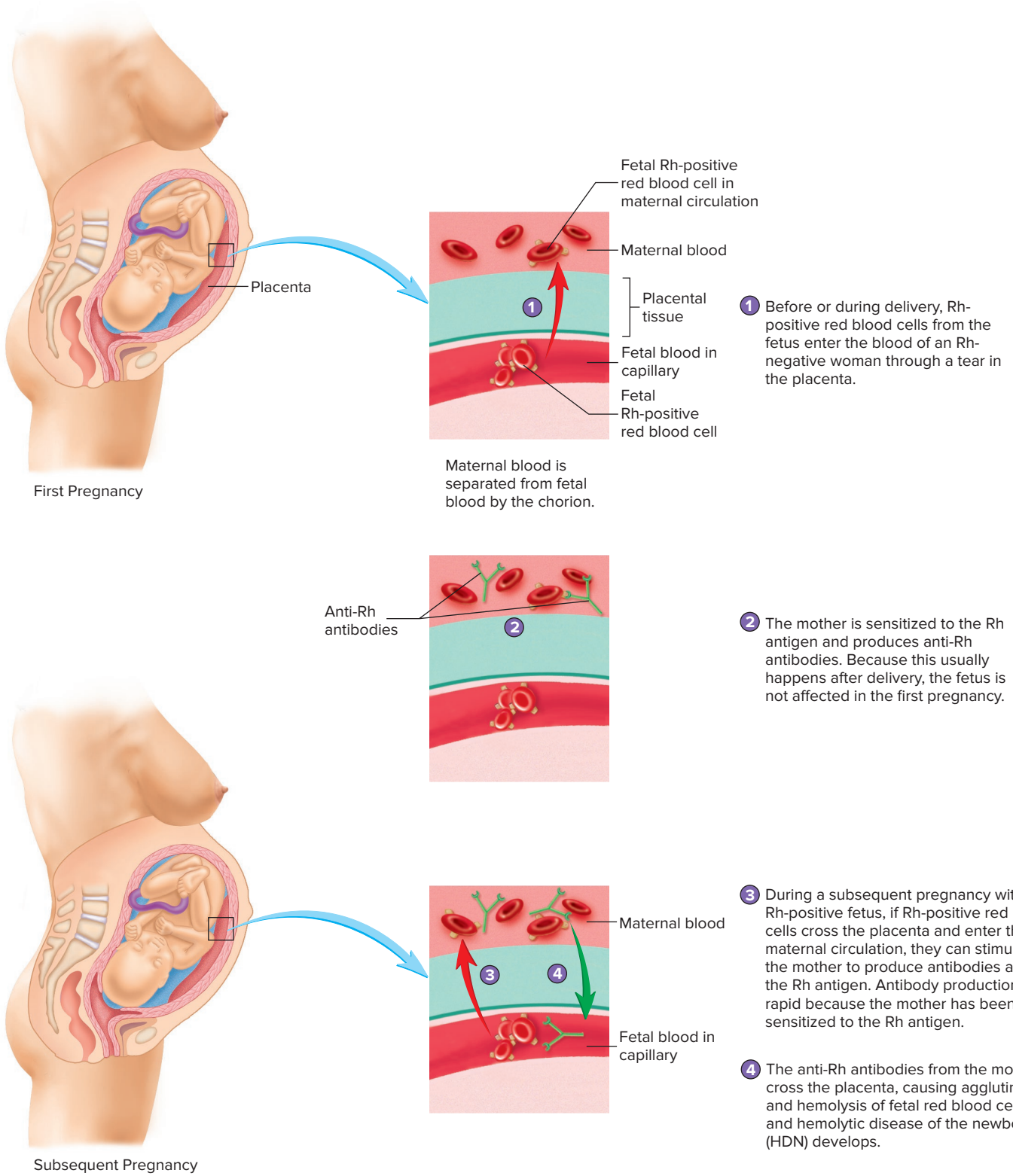
The term *universal donor* is misleading, however. Transfusion of type O blood can still produce a transfusion reaction in one of two ways: First, other blood groups can cause a transfusion reaction. Second, antibodies in the donor's blood can react with antigens in the recipient's blood. For example, type O blood has anti-A and anti-B antibodies. If type O blood is transfused into a person with type A blood, the anti-A antibodies (in the type O blood) react against the A antigens (in the type A blood). Usually, such reactions are not serious because the antibodies in the donor's blood are diluted in the larger volume of the recipient's blood, and few reactions take place. Blood banks separate donated blood into several products, such as packed red blood cells, plasma, platelets, and cryoprecipitate, which contains von Willebrand factor, clotting factors, and fibrinogen. This process allows the donated blood to be used by multiple recipients, each of whom may need only one of the blood components. Type O packed red blood cells are unlikely to cause an ABO transfusion reaction when given to a person with a different blood type because the transfusion fluid contains concentrated red blood cells with very little plasma containing anti-A and anti-B antibodies.

Rh Blood Group

A second clinically important blood group is the Rh blood group. The **Rh blood group** is so named because it was first studied in rhesus monkeys. The antigen involved in this blood group is the D antigen. People are Rh-positive if they have the D antigen on the surface of their red blood cells, and people are Rh-negative if they do not have the D antigen. About 85% of Caucasians in the United States and 88% of African-Americans are Rh-positive. The ABO blood type and the Rh blood type are usually expressed together. For example, a person designated type A in the ABO blood group and Rh-positive is said to be A-positive. The rarest combination in the United States is AB-negative, which occurs in less than 1% of the population.

Unlike the natural occurrence of anti-A and anti-B antibodies in the blood, antibodies against the Rh antigen do not develop unless an Rh-negative person is exposed to Rh-positive blood. This can occur either through a transfusion or when blood crosses the placenta to a mother from her fetus.

Rh incompatibility can pose a major problem in a pregnancy when the mother is Rh-negative and the fetus is Rh-positive. If fetal blood leaks through the placenta and mixes with the mother's blood, the mother becomes sensitized to the Rh antigen and produces anti-Rh antibodies. These antibodies can cross the placenta and enter the fetal blood. In the fetal blood, the Rh antibodies will act against the D antigens on the red blood cells and cause agglutination and hemolysis of fetal red blood cells. This disorder is called **hemolytic** (hē-mō-lit′ik) **disease of the newborn (HDN),** or *erythroblastosis fetalis* (ĕ-rith′rō-blas-tō′sis fē-ta′lis; figure 19.15). In the mother's first pregnancy, there is often no problem. The leakage of fetal blood is usually the result of a tear in the placenta that takes place



PROCESS FIGURE 19.15 Hemolytic Disease of the Newborn (HDN)

Rh incompatibility may occur in a pregnancy when the mother is Rh-negative and the fetus is Rh-positive. The concern is usually for later pregnancies, after the mother has become sensitized to the Rh antigen and is capable of producing anti-Rh antibodies at a faster and greater rate.

? *Explain why there is no concern for Rh incompatibilities in a pregnancy where the mother is Rh-positive and the fetus is Rh-negative.*

Case STUDY 19.1 Treatment of Hemolytic Disease of the Newborn

Billy was born with hemolytic disease of the newborn (HDN). He was treated with exchange transfusion, erythropoietin, and phototherapy. An exchange transfusion replaced Billy's blood with donor blood. In this procedure, as the donor's blood was transfused into Billy, his blood was withdrawn. During fetal development, the increased rate of red blood cell destruction caused by the mother's anti-Rh antibodies results in lower-than-normal numbers of red blood cells, a condition called **anemia** (ă-nē′mē-ă). It also results in increased levels of bilirubin. Although high levels of bilirubin can damage the brain by killing nerve cells, this is not usually a problem in the fetus because the bilirubin is removed by the placenta. Following birth, bilirubin levels can increase because red blood cells continue to lyse, and the newborn's liver is unable to handle the large bilirubin load. However, in phototherapy, blood that passes through the skin is exposed to blue or white lights, which break down bilirubin to less toxic compounds that the newborn's liver can remove.

Predict 7

Answer the following questions about Billy's treatment for HDN.

a. What is the purpose of giving Billy an exchange transfusion?

b. Explain the reason for giving Billy erythropoietin.

c. Just before birth, would Billy's erythropoietin levels have been higher or lower than those of a fetus without HDN?

d. After birth, but before treatment, did Billy's erythropoietin levels increase or decrease?

e. When treating HDN with an exchange transfusion, should the donor's blood be Rh-positive or Rh-negative? Explain.

f. Does giving an Rh-positive newborn a transfusion of Rh-negative blood change the newborn's blood type? Explain.

either late in the pregnancy or during delivery. Thus, there is not sufficient time for the mother to produce enough anti-Rh antibodies to harm the fetus. However, if sensitization occurs, it can cause problems in a subsequent pregnancy. First, once a woman is sensitized and produces anti-Rh antibodies, she may continue to produce the antibodies throughout her life. Thus, in a subsequent pregnancy, anti-Rh antibodies may already be present. Second, and especially dangerous in a subsequent pregnancy with an Rh-positive fetus, if any fetal blood leaks into the mother's blood, she rapidly produces large amounts of anti-Rh antibodies, resulting in HDN. Because HDN can be fatal to the fetus, the levels of anti-Rh antibodies in the mother should be monitored. If they increase to unacceptable levels, the fetus should be tested to determine the severity of the HDN. In severe cases, a transfusion to replace lost red blood cells can be performed through the umbilical cord, or the baby can be delivered if mature enough.

Prevention of HDN is often possible if the Rh-negative mother is injected with a specific type of antibody preparation, called Rh_o(D) immune globulin (RhoGAM), which contains antibodies against Rh antigens. The injection can be given during the pregnancy, before delivery, or immediately after each delivery, miscarriage, or abortion. The injected antibodies bind to the Rh antigens of any fetal red blood cells that may have entered the mother's blood. This treatment inactivates the fetal Rh antigens and prevents sensitization of the mother. However, if sensitization has already occurred, the treatment is ineffective.

ASSESS YOUR PROGRESS

39. *What are blood groups, and how do they cause transfusion reactions? What is agglutination?*

40. *What kinds of antigens and antibodies are found in each of the four ABO blood types?*

41. *Why is a person with type O blood considered a universal donor?*

42. *What does it mean to be Rh-positive?*

43. *What Rh blood types must the mother and the fetus have before HDN can occur?*

44. *Why does HDN usually not develop in the first pregnancy?*

19.7 Diagnostic Blood Tests

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Describe diagnostic blood tests and the normal values for the tests.**

B. **Give examples of disorders that produce abnormal test values.**

Type and Crossmatch

To prevent transfusion reactions, blood is typed. **Blood typing** determines the ABO and Rh blood groups of the blood sample. Typically, the cells are separated from the serum and then tested with known antibodies to determine the type of antigen on the cell surface (figure 19.16). For example, if a patient's blood cells agglutinate when mixed with anti-A antibodies but do not agglutinate when mixed with anti-B antibodies, the cells have type A antigen. In a similar fashion, the serum is mixed with known cell types (antigens) to determine the type of antibodies in the serum. Normally, donor blood must match the ABO and Rh type of the recipient.

FIGURE 19.16 Blood Typing
Blood types are often determined by separating the blood cells from the plasma and then testing them with known antibodies. Agglutination, as seen in the middle and right-hand samples on the slide, indicates the presence of the antigen for the known antibody. Lack of agglutination as seen in the left-hand sample on the slide, indicates that the antigen for the known antibody is not present. ©jarun011/Getty Images

The International Society of Blood Transfusion recognizes 29 important blood groups, including the ABO and Rh groups. Because any of these blood groups can cause a transfusion reaction, a crossmatch is performed. In a **crossmatch,** the donor's blood cells are mixed with the recipient's serum, and the donor's serum is mixed with the recipient's cells. The donor's blood is considered safe for transfusion only if no agglutination occurs in either match.

Complete Blood Count

A **complete blood count (CBC)** is an analysis of blood that provides much useful information. A CBC consists of a red blood count, hemoglobin and hematocrit measurements, a white blood count, and a differential white blood count.

Red Blood Count

Blood cell counts are usually performed with an electronic instrument, but they can also be done manually with a microscope. A **red blood count (RBC)** is the number (expressed in millions) of red blood cells per microliter of blood. A normal RBC for a male is 4.7–6.1 million/μL of blood; for a female, a normal RBC is 4.2–5.4 million/μL of blood. The condition called **erythrocytosis** (ĕ-rith′rō-sī-tō′sis) is an overabundance of red blood cells (see table 19.4).

Hemoglobin Measurement

A **hemoglobin measurement** determines the amount of hemoglobin in a given volume of blood, usually expressed as grams of hemoglobin per 100 mL of blood. The normal hemoglobin count for a male is 14–17 g/100 mL of blood, and for a female it is 12–15 g/100 mL of blood. Abnormally low hemoglobin is an indication of anemia (see table 19.4).

Hematocrit Measurement

The hematocrit (hē′mă-tō-krit, hem′ă-tō-krit) is the percentage of the total blood volume that is composed of red blood cells. One way to determine hematocrit is to place blood in a tube and spin it in a centrifuge. The formed elements, which are heavier than the plasma, are forced to one end of the tube (figure 19.17). Of these, the white blood cells and platelets form a thin, whitish layer, called the buffy coat, between the plasma and the red blood cells. The red blood cells account for 40–54% of the total blood volume in males and 38–47% in females.

The number and size of red blood cells affect the hematocrit measurement. **Normocytes** (nōr′mō-sītz) are normal-sized red blood cells with a diameter of 7.5 mm. **Microcytes** (mī′krō-sītz) are smaller than normal, with a diameter of 6 μm or less, and **macrocytes** (ma′krō-sītz) are larger than normal, with a diameter of 9 μm or greater. Blood disorders can result in an abnormal hematocrit measurement because they cause red blood cell numbers to be abnormally high or low or cause the red blood cells themselves to be abnormally small or large (see table 19.4). A decreased hematocrit indicates that the volume of red blood cells is less than normal. This can result from a decreased number of normocytes or a normal number of microcytes. For example, inadequate iron in the diet can impair hemoglobin production. Consequently, during their formation, red blood cells do not fill with hemoglobin, and they remain smaller than normal.

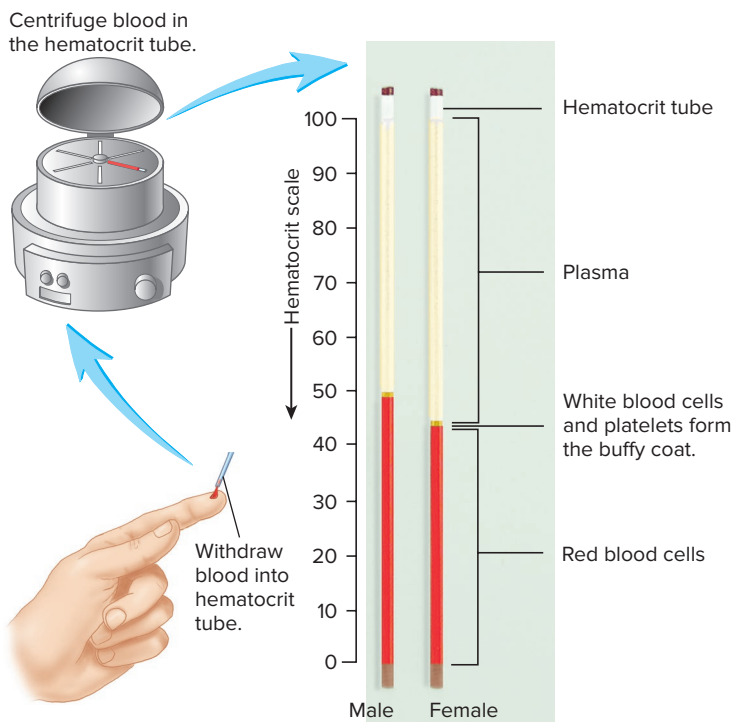


FIGURE 19.17 Hematocrit
Blood is withdrawn into a capillary tube and spun in a centrifuge. The blood is separated into plasma and red blood cells, with a narrow layer of white blood cells and platelets forming in between. The hematocrit is the percentage of the total blood volume that is composed of red blood cells. It does not include the white blood cells and platelets. Normal hematocrits for a male and a female are shown.

TABLE 19.4 Representative Diseases and Disorders of Blood

Condition	Description
Erythrocytosis	
Relative erythrocytosis	Overabundance of red blood cells due to decreased blood volume, as may result from dehydration, diuretics, or burns
Primary erythrocytosis (polycythemia vera)	Stem cell defect of unknown cause; results in overproduction of red blood cells, granulocytes, and platelets; signs include low erythropoietin levels and enlarged spleen; increased blood viscosity and blood volume can cause clogging of the capillaries and hypertension
Secondary erythrocytosis	Overabundance of red blood cells resulting from decreased O_2 supply, as occurs at high altitudes, in chronic obstructive pulmonary disease, and in congestive heart failure; decreased O_2 delivery to the kidney stimulates the secretion of erythropoietin, resulting in increased blood viscosity and blood volume that can cause clogging of the capillaries and hypertension
Anemia	Deficiency of hemoglobin in the blood
Iron-deficiency anemia	Caused by insufficient intake or absorption of iron or by excessive iron loss; leads to reduced hemoglobin production
Folate-deficiency anemia	Folate is important in DNA synthesis; inadequate folate in the diet results in a reduction in cell division and therefore a reduced number of red blood cells
Pernicious anemia	Secondary folate-deficiency anemia caused by inadequate amounts of vitamin B_{12}, which is important for folate synthesis
Hemorrhagic anemia	Results from blood loss due to trauma, ulcers, or excessive menstrual bleeding
Hemolytic anemia	Occurs when red blood cells rupture or are destroyed at an excessive rate; causes include inherited defects, exposure to certain drugs or snake venom, response to artificial heart valves, autoimmune disease, and hemolytic disease of the newborn
Aplastic anemia	Caused by an inability of the red bone marrow to produce red blood cells, usually as a result of damage to stem cells after exposure to certain drugs, chemicals, or radiation
Thalassemia	Autosomal recessive disease that results in insufficient production of globin part of hemoglobin
Leukemia	Cancers of the red bone marrow in which one or more white blood cell types is produced; cells are usually immature or abnormal and lack normal immunological functions
Thrombocytopenia	Reduction in the number of platelets that leads to chronic bleeding through small vessels and capillaries; causes include genetics, autoimmune disease, infections, and decreased platelet production resulting from pernicious anemia, drug therapy, radiation therapy, or leukemias
Clotting Disorders	
Disseminated intravascular coagulation (DIC)	Clotting throughout the vascular system, followed by bleeding; may develop when normal regulation of clotting by anticoagulants is overwhelmed, as occurs due to massive tissue damage; also caused by alteration of the lining of the blood vessels resulting from infections or snakebites
Von Willebrand disease	Most common inherited bleeding disorder; platelet plug formation and the contribution of activated platelets to blood clotting are impaired; treatments are injection of von Willebrand factor or administration of drugs that increase von Willebrand factor levels in blood, which helps platelets adhere to collagen and become activated
Hemophilia	Genetic disorder in which clotting is abnormal or absent; each of the several types results from deficiency or dysfunction of a clotting factor; most often a sex-linked trait that occurs almost exclusively in males
Infectious Diseases of Blood	
Septicemia (blood poisoning)	Spread of microorganisms and their toxins by the blood; often the result of a medical procedure, such as insertion of an intravenous tube; release of toxins by bacteria can cause septic shock, producing decreased blood pressure and possibly death
Malaria	Caused by a protozoan introduced into blood by *Anopheles* mosquito; symptoms include chills and fever produced by toxins released when the protozoan causes red blood cells to rupture
Infectious mononucleosis	Caused by Epstein-Barr virus, which infects salivary glands and lymphocytes; symptoms include fever, sore throat, and swollen lymph nodes, all probably produced by the immune system response to infected lymphocytes
Acquired immunodeficiency syndrome (AIDS)	Caused by human immunodeficiency virus (HIV), which infects lymphocytes and suppresses immune system

White Blood Count

A **white blood count (WBC)** measures the total number of white blood cells in the blood. Normally, 4500–11,000 white blood cells are present in each microliter of blood. **Leukopenia** (loo-kō-pē′nē-ă) is a lower-than-normal WBC resulting from depression or destruction of the red marrow. Viral infections, radiation, drugs, tumors, and vitamin deficiencies (B_{12} or folate) can cause leukopenia. **Leukocytosis** (loo′kō-sī-tō′sis) is an abnormally high WBC. **Leukemia** (loo-kē′mē-ă), a cancer of the red marrow, often results in leukocytosis, but the white blood cells have an abnormal structure and function as well. Bacterial infections can also cause leukocytosis by stimulating neutrophils to increase in number.

Differential White Blood Count

A **differential white blood count** determines the percentage of each of the five kinds of white blood cells. Normally, neutrophils account for 55–70%; lymphocytes, 20–40%; monocytes, 2–8%; eosinophils, 1–4%; and basophils, 0.5–1%. A differential WBC can provide insight into a patient's condition. For example, in patients with bacterial infections the neutrophil count is often greatly increased, whereas in patients with allergic reactions the eosinophil and basophil counts are elevated.

Clotting

The blood's ability to clot can be assessed by the platelet count and the prothrombin time measurement.

Platelet Count

A normal **platelet count** is 150,000–400,000 platelets per microliter of blood. In the condition called **thrombocytopenia** (throm′bō-sī-tō-pē′nē-ă), the platelet count is greatly reduced, resulting in chronic bleeding through small vessels and capillaries. It can be caused by decreased platelet production as a result of hereditary disorders, lack of vitamin B_{12}, drug therapy, or radiation therapy.

Prothrombin Time Measurement

Prothrombin time measurement expresses how long it takes for the blood to start clotting, which is normally 9–12 seconds. Prothrombin time is determined by adding thromboplastin to whole plasma. Thromboplastin is a chemical released from injured tissues that starts the process of clotting (see figure 19.12). Prothrombin time is officially reported as the International Normalized Ratio (INR), which standardizes the time blood takes to clot based on the slightly different thromboplastins used by different labs. Because many clotting factors must be activated to form fibrin, a deficiency of any one of them can cause the prothrombin time to be abnormal. Vitamin K deficiency, certain liver diseases, and drug therapy can increase prothrombin time.

Blood Chemistry

The composition of materials dissolved or suspended in the plasma can be used to assess the functioning of many of the body's systems. For example, high blood glucose levels can indicate that the pancreas is not producing enough insulin; high blood urea nitrogen (BUN) can be a sign of reduced kidney function; increased bilirubin can indicate liver dysfunction or hemolysis; and high cholesterol levels can signify an increased risk for cardiovascular disease. A number of blood chemistry tests are routinely done when a blood sample is taken, and additional tests are available.

Predict 8

When a patient complains of acute pain in the abdomen, the physician suspects appendicitis, which is often caused by a bacterial infection of the appendix. What blood test should be done to support the diagnosis?

ASSESS YOUR PROGRESS

45. *What occurs in a type and crossmatch?*
46. *What tests are included in a CBC? Give the normal value, and name a disorder that would cause an abnormal test result for each.*
47. *What are the normal values for a platelet count and a prothrombin time measurement? Name a disorder that would cause an abnormal result for each test.*
48. *What are some examples of blood chemistry tests?*

Answer

Learn to Predict

Frankie's feeling of fatigue and her blood test results are consistent with anemia. A low red blood cell count with microcytic cells, low hemoglobin, and a low hematocrit are all indicators of iron deficiency anemia.

The increased reticulocyte count indicated an increased rate of red blood cell production. But if red blood cell production was increased, why was Frankie's red blood cell count still low? We learned in this chapter that red blood cell production is regulated by the hormone erythropoietin. Specifically, reduced red blood cell numbers, as indicated by Frankie's blood test, caused less oxygen to be transported to her kidneys. Consequently, her kidneys secreted more erythropoietin, which resulted in increased red blood cell production in the red bone marrow. Because of Frankie's iron deficiency, which caused hemoglobin synthesis to slow, the newly synthesized red blood cells were smaller than normal, or microcytic. Remember, Frankie also complained of intense abdominal pain. The evidence of hemoglobin in her feces suggested that Frankie is losing blood into her digestive tract, which, considering her abdominal pain, would be consistent with having an ulcer. Frankie's doctor would need to order additional tests to confirm the presence of ulcers before determining treatment.

Answers to the odd-numbered Predict questions from this chapter appear in appendix E.

Summary

19.1 Functions of Blood

1. Blood transports gases, nutrients, waste products, processed molecules, and regulatory molecules.
2. Blood is involved in the regulation of pH, osmosis, and body temperature.
3. Blood protects against disease and initiates tissue repair.

19.2 Composition of Blood

Blood is a type of connective tissue that consists of plasma and formed elements.

19.3 Plasma

1. Plasma is mostly water (91%) and contains proteins, such as albumin (maintains osmotic pressure), globulins (function in transport and immunity), fibrinogen (involved in clot formation), and hormones and enzymes (involved in regulation).
2. Plasma contains ions, nutrients, waste products, and gases.

19.4 Formed Elements

The formed elements are red blood cells (erythrocytes), white blood cells (leukocytes), and platelets (cell fragments).

Production of Formed Elements

1. In the embryo and fetus, the formed elements are produced in a number of locations.
2. After birth, red bone marrow becomes the source of the formed elements.
3. All formed elements are derived from hemocytoblast, which gives rise to two intermediate stem cells: myeloid stem cells and lymphoid stem cells. Myeloid stem cells give rise to red blood cells, platelets, and most of the white blood cells. Lymphoid stem cells give rise to lymphocytes.

Red Blood Cells

1. Red blood cells are biconcave discs containing hemoglobin and carbonic anhydrase.
   - A hemoglobin molecule consists of four heme and four globin molecules. The heme molecules transport oxygen, and the globin molecules transport carbon dioxide and nitric oxide. Iron is required for oxygen transport.
   - Carbonic anhydrase is involved with the transport of carbon dioxide.
2. Erythropoiesis is the production of red blood cells.
   - Stem cells in red bone marrow eventually give rise to late erythroblasts, which lose their nuclei and are released into the blood as reticulocytes. Loss of the endoplasmic reticulum by a reticulocyte produces a red blood cell.
   - In response to low blood oxygen, the kidneys produce erythropoietin, which stimulates erythropoiesis.
3. Hemoglobin from ruptured red blood cells is phagocytized by macrophages. The hemoglobin is broken down, and heme becomes bilirubin, which is secreted in bile.

White Blood Cells

1. White blood cells protect the body against microorganisms and remove dead cells and debris.
2. Five types of white blood cells exist.
   - Neutrophils are small, phagocytic cells.
   - Eosinophils attack certain worm parasites and modulate inflammation.
   - Basophils release histamine and are involved with increasing the inflammatory response.
   - Lymphocytes are important in immunity, including the production of antibodies.
   - Monocytes leave the blood, enter tissues, and become large, phagocytic cells called macrophages.

Platelets

Platelets, or thrombocytes, are cell fragments pinched off from megakaryocytes in the red bone marrow.

19.5 Hemostasis

Hemostasis, the cessation of bleeding, is very important to the maintenance of homeostasis.

Vascular Spasm

Vasoconstriction of damaged blood vessels reduces blood loss.

Platelet Plug Formation

1. Platelets repair minor damage to blood vessels by forming platelet plugs.
   - In platelet adhesion, platelets bind to collagen in damaged tissues.
   - In the platelet release reaction, platelets release chemicals that activate additional platelets.
   - In platelet aggregation, platelets bind to one another to form a platelet plug.
2. Platelets also release chemicals involved with coagulation.

Coagulation

1. Coagulation is the formation of a blood clot.
2. The first stage of coagulation occurs through the extrinsic or intrinsic pathway. Both pathways end with the production of activated factor X.
   - The extrinsic pathway begins with the release of thromboplastin from damaged tissues.
   - The intrinsic pathway begins with the activation of factor XII.
3. Activated factor X, factor V, phospholipids, and Ca^{2+} form prothrombinase.
4. Prothrombinase converts prothrombin to thrombin.
5. Thrombin converts fibrinogen to fibrin. The insoluble fibrin forms the clot.

Control of Clot Formation

1. Heparin and antithrombin inhibit thrombin activity. Therefore, fibrinogen is not converted to fibrin, and clot formation is inhibited.
2. Prostacyclin counteracts the effects of thrombin.

Clot Retraction and Dissolution

1. Clot retraction results from the contraction of platelets, which pull the edges of damaged tissue closer together.
2. Serum, which is plasma minus fibrinogen and some clotting factors, is squeezed out of the clot.
3. Factor XII, thrombin, tissue plasminogen activator, and urokinase activate plasmin, which dissolves fibrin (the clot).

19.6 Blood Grouping

1. Blood groups are determined by antigens on the surface of red blood cells.
2. Antibodies can bind to red blood cell antigens, resulting in agglutination or hemolysis of red blood cells.

ABO Blood Group

1. Type A blood has A antigens, type B blood has B antigens, type AB blood has A and B antigens, and type O blood has neither A nor B antigens.
2. Type A blood has anti-B antibodies, type B blood has anti-A antibodies, type AB blood has neither anti-A nor anti-B antibodies, and type O blood has both anti-A and anti-B antibodies.
3. Mismatching the ABO blood group results in a transfusion reaction.

Rh Blood Group

1. Rh-positive blood has the D antigen, whereas Rh-negative blood does not.
2. Antibodies against the D antigen are produced by an Rh-negative person when the person is exposed to Rh-positive blood.
3. The Rh blood group is responsible for hemolytic disease of the newborn.

19.7 Diagnostic Blood Tests

Type and Crossmatch

Blood typing determines the ABO and Rh blood groups of a blood sample. A crossmatch tests for agglutination reactions between donor and recipient blood.

Complete Blood Count

A complete blood count consists of the following: red blood count, hemoglobin measurement (grams of hemoglobin per 100 mL of blood), hematocrit measurement (percent volume of red blood cells), white blood count, and differential white blood count (the percentage of each type of white blood cell).

Clotting

Platelet count and prothrombin time measurement assess the blood's ability to clot.

Blood Chemistry

The composition of materials dissolved or suspended in plasma (e.g., glucose, urea nitrogen, bilirubin, and cholesterol) can be used to assess the functioning and status of the body's systems.

REVIEW AND COMPREHENSION

1. Which of these is a function of blood?
   a. clot formation
   b. protection against foreign substances
   c. maintenance of body temperature
   d. regulation of pH and osmosis
   e. All of these are correct.

2. Which of these is *not* a component of plasma?
   a. nitrogen c. platelets e. urea
   b. sodium ions d. water

3. Which of these proteins is normally found in the plasma and plays an important role in maintaining the osmotic concentration of the blood?
   a. albumin c. platelets e. globulins
   b. fibrinogen d. hemoglobin

4. Red blood cells
   a. are the least numerous formed element in the blood.
   b. are phagocytic cells.
   c. are produced in the yellow marrow.
   d. do not have a nucleus.
   e. All of these are correct.

5. Given these ways of transporting carbon dioxide in the blood:
   (1) bicarbonate ions
   (2) combined with blood proteins
   (3) dissolved in plasma

   Choose the arrangement that lists them in the correct order from largest to smallest percentage of carbon dioxide transported.
   a. 1,2,3 c. 2,3,1 e. 3,1,2
   b. 1,3,2 d. 2,1,3

6. Each hemoglobin molecule can become associated with _____ oxygen molecule(s).
   a. one d. four
   b. two e. an unlimited number of
   c. three

7. Erythropoietin
   a. is produced mainly by the heart.
   b. inhibits the production of red blood cells.
   c. production increases when blood oxygen decreases.
   d. production is inhibited by testosterone.
   e. All of these are correct.

8. Which of these changes occur(s) in the blood in response to the initiation of a vigorous exercise program?
   a. increased erythropoietin production
   b. increased concentration of reticulocytes
   c. decreased bilirubin formation
   d. Both a and b are correct.
   e. All of these are correct.

9. Which of the components of hemoglobin is correctly matched with its fate following the destruction of a red blood cell?
   a. heme—reused to form a new hemoglobin molecule
   b. globin—broken down into amino acids
   c. iron—mostly secreted in bile
   d. All of these are correct.

10. The blood cells that protect against worm parasites are
    a. eosinophils. c. neutrophils. e. lymphocytes.
    b. basophils. d. monocytes.

11. The most numerous type of white blood cell, whose primary function is phagocytosis, is
    a. eosinophils. c. neutrophils. e. lymphocytes.
    b. basophils. d. monocytes.

12. Monocytes
    a. are the smallest white blood cells.
    b. increase in number during chronic infections.
    c. give rise to neutrophils.
    d. produce antibodies.

13. The smallest white blood cells, which include B cells and T cells, are
    a. eosinophils. c. neutrophils. e. lymphocytes.
    b. basophils. d. monocytes.
14. Platelets
    a. are derived from megakaryocytes.
    b. are cell fragments.
    c. have surface molecules that attach to collagen.
    d. play an important role in clot formation.
    e. All of these are correct.
15. Given these processes in platelet plug formation:
    (1) platelet adhesion (3) platelet release reaction
    (2) platelet aggregation

    Choose the arrangement that lists the processes in the correct order after a blood vessel is damaged.
    a. 1,2,3 c. 3,1,2 e. 2,3,1
    b. 1,3,2 d. 3,2,1
16. A constituent of plasma that forms the network of fibers in a clot is
    a. fibrinogen. c. platelets. e. prothrombinase.
    b. tissue factor. d. thrombin.
17. Given these chemicals:
    (1) activated factor XII (3) prothrombinase
    (2) fibrinogen (4) thrombin

    Choose the arrangement that lists the chemicals in the order they are used during clot formation.
    a. 1,3,4,2 c. 3,2,1,4 e. 3,4,2,1
    b. 2,3,4,1 d. 3,1,2,4
18. The extrinsic pathway
    a. begins with the release of thromboplastin (tissue factor).
    b. leads to the production of activated factor X.
    c. requires Ca^{2+}.
    d. All of these are correct.
19. The chemical involved in the breakdown of a clot (fibrinolysis) is
    a. antithrombin. d. plasmin.
    b. fibrinogen. e. sodium citrate.
    c. heparin
20. A person with type A blood
    a. has anti-A antibodies.
    b. has type B antigens.
    c. will have a transfusion reaction if given type B blood.
    d. All of these are correct.
21. In the United States, the most common blood type is
    a. A positive. c. O positive. e. AB negative.
    b. B positive. d. O negative.

Answers appear in appendix F.

CRITICAL THINKING

1. In hereditary hemolytic anemia, massive destruction of red blood cells occurs. Would you expect the reticulocyte count to be above or below normal? Explain why one of the symptoms of the disease is jaundice. In 1910, physicians discovered that hereditary hemolytic anemia can be treated successfully by removing the spleen. Explain why this treatment is effective.
2. Joseph, a physical education major, wanted to improve his performance in an upcoming marathon race. About 6 weeks before the race, 500 mL of blood was removed from his body, and the formed elements were separated from the plasma. The formed elements were frozen, and the plasma was reinfused into his body. Just before the competition, the formed elements were thawed and injected into his body. Explain why this procedure, called blood doping or blood boosting, would help Joseph's performance. Suggest any possible bad effects.
3. Ben has an infected prostate. His physician prescribed several antibiotics before finding one that was effective. Results of the most recent blood tests indicate that Ben is anemic. After analyzing the following measurements of Ben's blood, identify the type of anemia he has.

	Ben's Values	Normal Values
Red blood count	3.1 million RBCs/mm^3	4.6–6.2 million RBCs/mm^3
Reticulocyte count	0.4%	1–3%
Red blood cells	Normocytic, 7.5 mm	Normocytic, 7.5 mm
White blood count	2800 WBCs/mm^3	5000–10,000 WBCs/mm^3
Hemoglobin	9.0 g/100 mL	14–16.5 g/100 mL
Hematocrit	27%	40–54%
Prothrombin time	20 seconds	11–15 seconds
Platelets	200,000/mm^3	250,000–400,000 platelets/mm^3

Which of the following conclusions is most consistent with the results? Explain.
a. pernicious anemia
b. iron-deficiency anemia
c. aplastic anemia
d. hemorrhagic anemia
e. vitamin B_{12} deficiency

4. Some people habitually use barbiturates to depress feelings of anxiety. Barbiturates cause hypoventilation, a slower-than-normal rate of breathing, because they suppress the respiratory centers in the brain. What happens to the red blood count of a habitual user of barbiturates? Explain.
5. According to an old saying, "good food makes good blood." Name three substances in the diet that are essential for "good blood." What blood disorders develop if these substances are absent from the diet?
6. Grace has a plasma membrane defect in her red blood cells that makes them more susceptible to rupturing. Her red blood cells are destroyed faster than they can be replaced. Are her RBC, hemoglobin, hematocrit, and bilirubin levels below normal, normal, or above normal? Explain.
7. Pam lives in Los Angeles, not far from the beach. She traveled by plane with her fiance, Alex, to Jackson Hole, which is approximately 6000 feet above sea level. They took hikes of increasing length for each of 4 days and rested on the fifth day. On the sixth day, she and Alex hiked to the top of Table Mountain, which is approximately 11,000 feet above sea level. Which of the following was (were) apparent in Pam on the day they climbed Table Mountain? Explain.
   (1) Pam's rate of erythropoietin secretion was increasing.
   (2) Pam's erythrocyte count was increasing.
   (3) Pam's reticulocyte count was increasing.
   (4) Pam's platelet count was increasing.
   a. 1,2,3,4 c. 1,2 e. 1
   b. 1,2,3 d. 2,3

Answers to odd-numbered questions appear in appendix G.

Design Elements: EKG: ©McGraw-Hill Education; Bacteria: Source: CDC/Janice Haney Carr; Male doctor: ©Digital Vision/PunchStock; Twins: ©Barbara Penoyar/Getty Images; Fetus: ©Janis Christie/Getty Images; Female doctor: ©Stockbyte/Getty Images

Photo: Photograph of the chordae tendineae attached to the papillary muscles of a ventricle. ©Frieder Michler/Science Source

20

Cardiovascular System

THE HEART

Most of us have a general understanding of heart function—it "beats" and pumps the blood through the body. And that is true; the heart is a muscular pump that generates the forces that move blood through the blood vessels. Our overall health is dependent on the proper function of the heart and the medical field has invested much time and effort in the development of treatments for heart disease.

The heart of a healthy adult beats about 60 to 100 times each minute under resting conditions. Of course, that rate varies depending on the level of physical activity and emotional state. For most people, the heart continues to function for more than 75 years. During periods of vigorous exercise, heart rate can increase dramatically, but a person's life is in danger if the heart loses its ability to pump blood for even a few minutes. **Cardiology** (kar-dē-ol′ō-jē) is the medical specialty concerned with diagnosing and treating heart disease.

Learn to Predict

Grandpa Stan never missed watching his grandson pitch. One day, while climbing into the bleachers, he had difficulty breathing and knew he'd better see a doctor. Using a stethoscope, Stan's regular physician could hear an irregular swooshing after the first heart sound, so he referred Stan to a cardiologist. The cardiologist conducted a series of exams and determined that Stan had an incompetent bicuspid valve. **After reading chapter 20, identify the major functional changes in the heart that result from an incompetent valve, and explain how these changes led to Stan's symptoms.**

20.1 Functions of the Heart

LEARNING OUTCOME

After reading this section, you should be able to

A. **List the major functions of the heart.**

Though we may think of the heart as a single structure, it is actually two pumps in one. The right side of the heart pumps blood through the **pulmonary** (pŭl′mō-nār-ē) **circulation,** which carries blood to the lungs, where CO_2 diffuses from the blood into the lungs and O_2 diffuses from the lungs into the blood. The pulmonary circulation returns the blood to the left side of the heart. The left side of the heart then pumps blood through the **systemic circulation,** which delivers O_2 and nutrients to all the remaining tissues of the body. From those tissues, CO_2 and other waste products are carried back to the right side of the heart (figure 20.1).

The following are the functions of the heart:

1. *Generating blood pressure*. Contractions of the heart generate blood pressure, which is responsible for moving blood through the blood vessels.
2. *Routing blood*. The heart separates the pulmonary and systemic circulations and ensures that the blood flowing to the tissues has adequate levels of O_2.
3. *Ensuring one-way blood flow*. The valves of the heart ensure a one-way flow of blood through the heart and blood vessels.
4. *Regulating blood supply*. The rate and force of heart contractions change to meet the metabolic needs of the tissues, which vary depending on such conditions as rest, exercise, and changes in body position.

ASSESS YOUR PROGRESS

Answers to these questions are found in the section you have just completed. Re-read the section if you need help in answering these questions.

1. *State the four functions of the heart.*

FUNDAMENTAL **Figure**

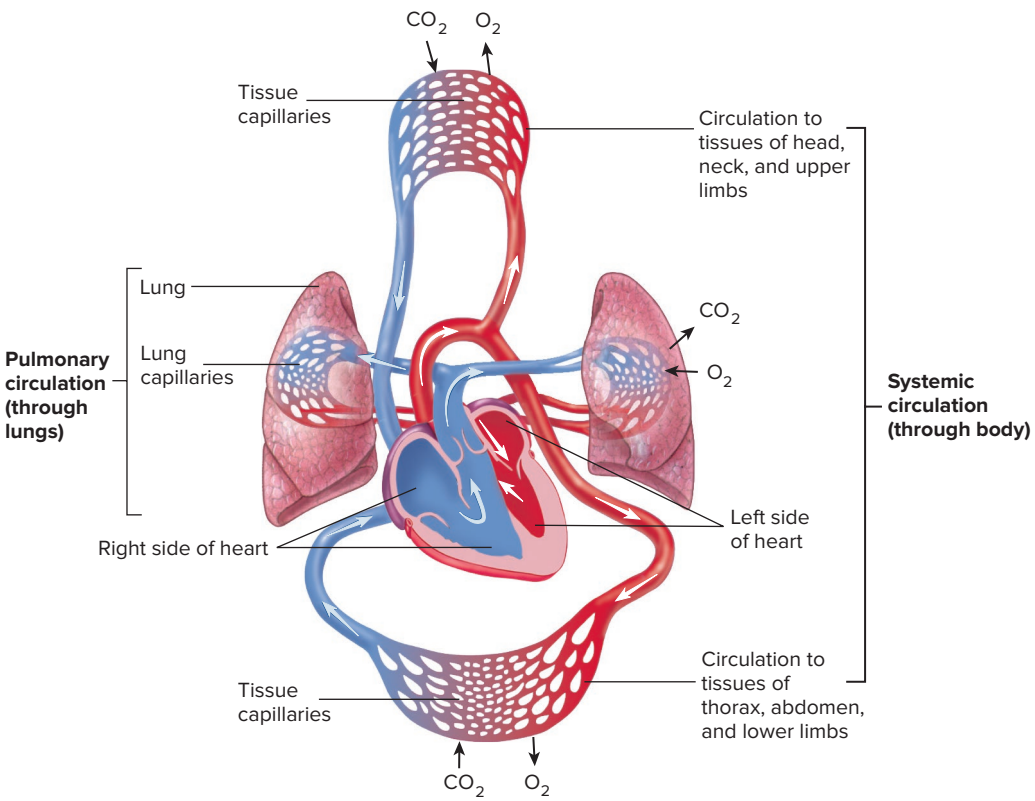


FIGURE 20.1 Systemic and Pulmonary Circulation

The circulatory system consists of the pulmonary and systemic circulations. The right side of the heart pumps blood through vessels to the lungs and back to the left side of the heart through the pulmonary circulation. The left side of the heart pumps blood through vessels to the tissues of the body and back to the right side of the heart through the systemic circulation. AP|R

20.2 Size, Shape, and Location of the Heart

LEARNING OUTCOMES

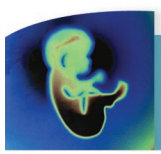
After reading this section, you should be able to

A. **Cite the size, shape, and location of the heart.**
B. **Explain why knowing the heart's location is important.**

The adult heart is shaped like a blunt cone and is approximately the size of a closed fist, with an average mass of 250 g in females and 300 g in males. It is larger in physically active adults compared with other healthy adults. The heart generally decreases in size after approximately age 65, especially in people who are not physically active. The blunt, rounded point of the heart is the **apex;** the larger, flat part at the opposite end of the heart is the **base.**

The heart is located in the **mediastinum** (me′dē-as-tī′nŭm; see figure 1.14), a midline partition of the thoracic cavity that also contains the trachea, the esophagus, the thymus, and associated structures.

It is important for health professionals to know the location of the heart in the thoracic cavity. Positioning a stethoscope to hear the heart sounds and positioning electrodes to record an electrocardiogram from chest leads depend on this knowledge. Effective **cardiopulmonary resuscitation** (kar′dē-ō-pŭl′mo-nār-ē rē-sŭs′i-tā-shŭn; **CPR**) also depends on a reasonable knowledge of the position of the heart.



Clinical IMPACT 20.1

Cardiopulmonary Resuscitation (CPR)

CPR is an emergency procedure that maintains blood flow in the body if a person's heart stops. CPR consists of firm and rhythmic compression of the chest combined with artificial ventilation of the lungs. This is a life-saving process, but it requires training for correct execution. The American Heart Association (AHA) has developed different guidelines for the specific CPR practice for infants, children or teens, and adults. Guidelines released in 2010 emphasize the importance of beginning with chest compressions. Individuals properly trained in CPR can then administer artificial ventilation. However, in an emergency situation involving a teen or an adult, an untrained individual may use the "hands-only" CPR method until emergency medical help arrives. The person firmly presses down on the sternum at a rate of at least 100 compressions per minute (about the tempo of the Bee Gees song "Staying Alive"). Applying pressure to the sternum compresses the chest wall, which also compresses the heart, causing it to pump blood. Hands-only CPR can provide an adequate blood supply to the heart wall and brain until emergency medical assistance arrives.

The heart lies obliquely in the mediastinum, with its base directed posteriorly and slightly superiorly and its apex directed anteriorly and slightly inferiorly. The apex is also directed to the left, so that approximately two-thirds of the heart's mass lies to the left of the midline of the sternum (figure 20.2). The base of the heart is located deep to the sternum and extends to the second intercostal space. The apex is located deep to the fifth intercostal space, approximately 7–9 centimeters (cm) to the left of the sternum and medial to the midclavicular line, a perpendicular line that extends down from the middle of the clavicle.

ASSESS YOUR PROGRESS

2. *What is the approximate size and shape of the heart?*
3. *Where is the heart located? How does this knowledge assist medical professionals during routine physical exams?*

20.3 Anatomy of the Heart

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Describe the structure of the pericardium.**
B. **List the layers of the heart wall and describe the structure and function of each.**
C. **Relate the large veins and arteries that enter and exit the heart.**
D. **Describe the location and blood flow through the coronary arteries and cardiac veins.**
E. **Review the structure and functions of the chambers of the heart.**
F. **Name the valves of the heart and state their locations and functions.**

Pericardium

The **pericardium** (per-i-kar′dē-ŭm), or *pericardial sac,* is a double-layered, closed sac that surrounds the heart (figure 20.3). It consists of two layers: (1) the outer **fibrous pericardium** and (2) inner **serous pericardium.** The fibrous pericardium is a tough, fibrous connective tissue layer that prevents overdistension of the heart and anchors it within the mediastinum. Superiorly, the fibrous pericardium is continuous with the connective tissue coverings of the great vessels, such as the aorta, and inferiorly it is attached to the surface of the diaphragm (see figure 20.2*a*). The serous pericardium is a layer of simple squamous epithelium.

The serous pericardium is further divided into two parts: (1) the **parietal pericardium** and (2) the **visceral pericardium.** The parietal pericardium is the part lining the fibrous pericardium. The visceral pericardium, also called the *epicardium,* is the part covering the heart surface (figure 20.3). The parietal and visceral portions of the serous pericardium are continuous with each other where the great vessels enter or leave the heart. The space between the visceral and parietal pericardia is the **pericardial cavity** and it is

filled with a thin layer of serous **pericardial fluid.** This fluid helps reduce friction as the heart moves within the pericardial sac.

Even though the pericardium contains fibrous connective tissue, it can accommodate changes in heart size by gradually enlarging. The pericardial cavity can also increase in volume to hold a significant volume of pericardial fluid, such as with certain illnesses.

Predict 1

Over the weekend, Tony, 22 years old, developed severe chest pains that became worse with deep inhalations and when lying down. As his condition worsened over the next day, Tony became anxious and feared that he might be having a heart attack, so he had a friend drive him to the emergency room. The ER physician identified a low-grade fever, tachycardia (increased heart rate), and a weak and rapid pulse. A chest x-ray showed distension of the jugular veins and pericardial space. The ER physician diagnosed pericarditis, which was probably due to a viral infection. The physician performed pericardiocentesis to drain the excess fluid from the pericardium. Explain the manifestations that the physician observed, describe how she drained the excess fluid with a needle, and name the body layers the needle penetrated.

Heart Wall

The heart wall is composed of three layers of tissue: the epicardium, myocardium, and endocardium (figure 20.4).

1. The **epicardium** (ep-i-kar′dē-ŭm), or *visceral pericardium,* is the superficial layer of the heart wall. It is a thin serous membrane that constitutes the smooth, outer surface of the heart. The serous pericardium is called the epicardium when considered a part of the heart and the visceral pericardium when considered a part of the pericardium.

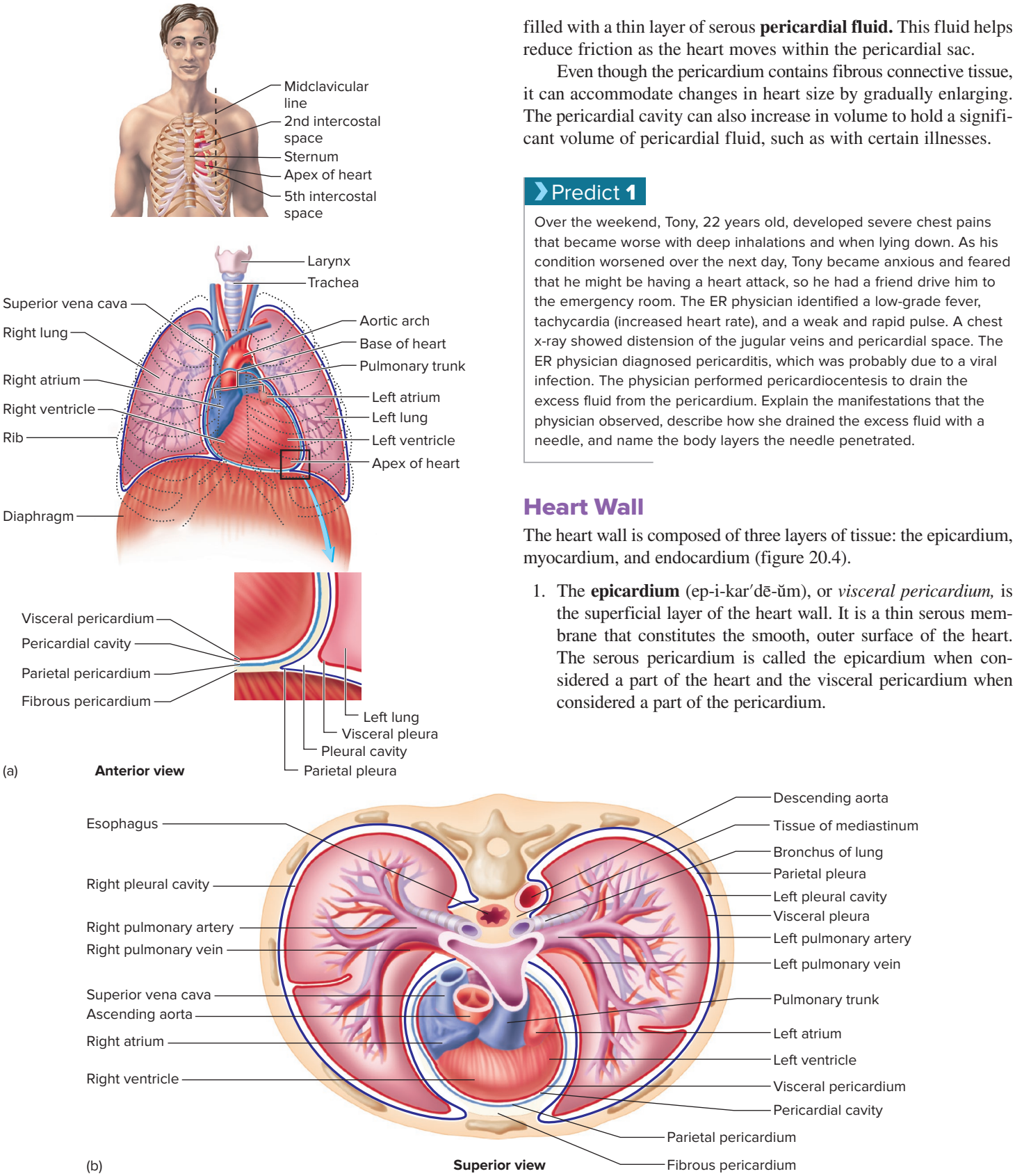


FIGURE 20.2 Location of the Heart in the Thorax

(*a*) The heart lies in the thoracic cavity between the lungs, deep to and slightly to the left of the sternum. The base of the heart, located deep to the sternum, extends to the second intercostal space, and the apex of the heart is deep to the fifth intercostal space, approximately 7–9 cm to the left of the sternum, or where the midclavicular line intersects with the fifth intercostal space (see inset). (*b*) Cross section of the thorax, showing the position of the heart in the mediastinum and its relationship to other structures. AP|R

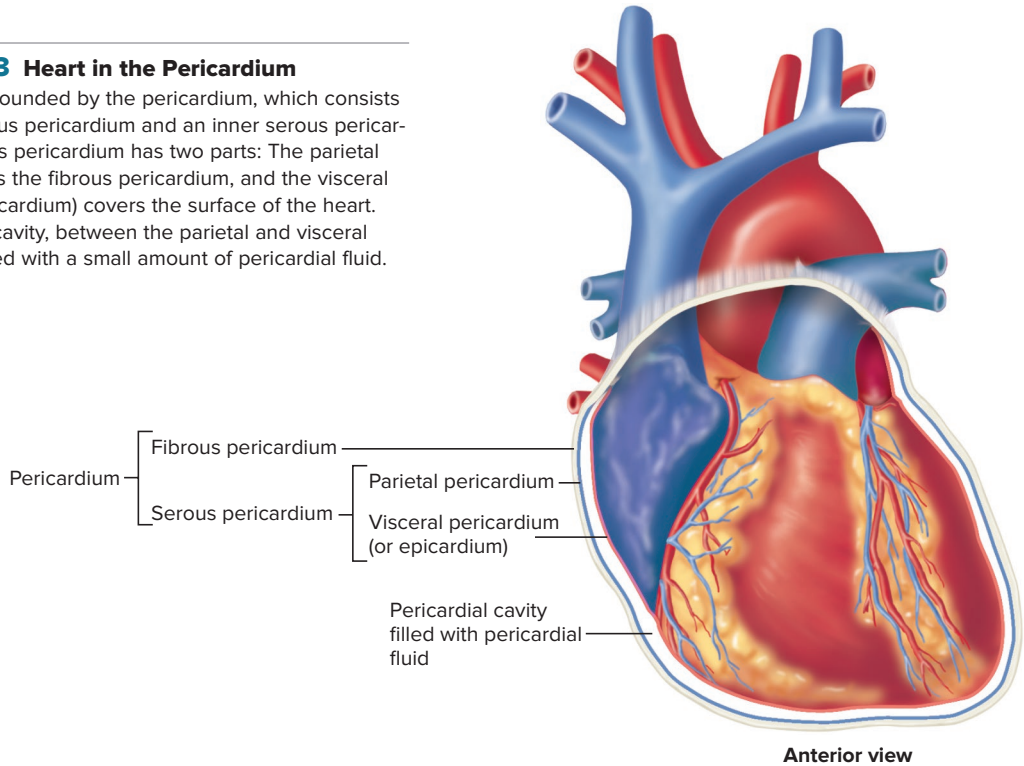


FIGURE 20.3 Heart in the Pericardium
The heart is surrounded by the pericardium, which consists of an outer fibrous pericardium and an inner serous pericardium. The serous pericardium has two parts: The parietal pericardium lines the fibrous pericardium, and the visceral pericardium (epicardium) covers the surface of the heart. The pericardial cavity, between the parietal and visceral pericardia, is filled with a small amount of pericardial fluid.

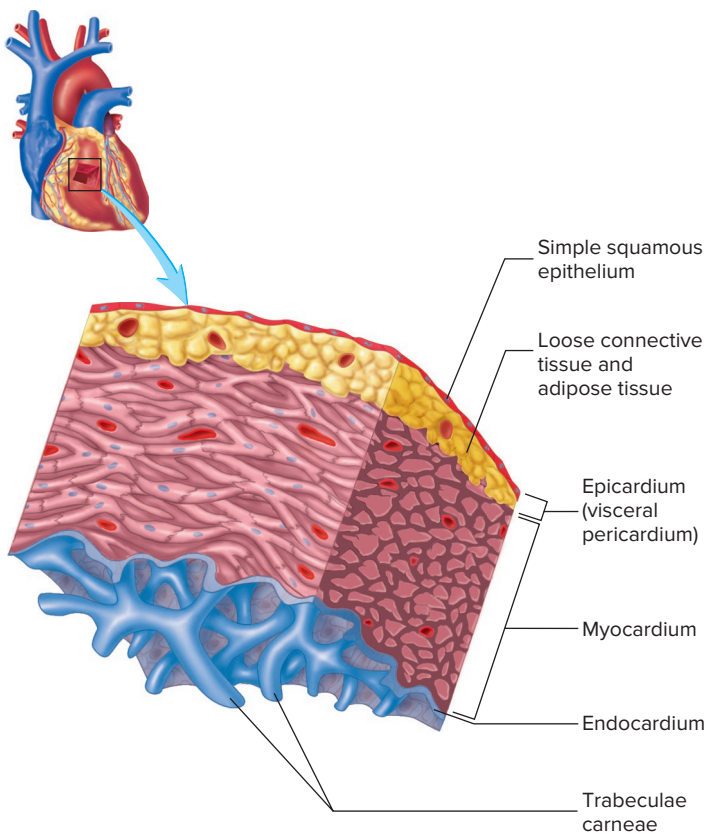


FIGURE 20.4 Heart Wall
Part of the wall of the heart has been removed, enlarged, and rotated, so that its inner surface is visible. The enlarged section illustrates the epicardium (visceral pericardium), myocardium, and endocardium. AP|R

2. The **myocardium** (mī-ō-kar′dē-ŭm) is the thick, middle layer of the heart. It is composed of cardiac muscle cells and is responsible for the heart's ability to contract.
3. The **endocardium** (en-dō-kar′dē-ŭm) is deep to the myocardium. It consists of simple squamous epithelium over a layer of connective tissue. The endocardium forms the smooth, inner surface of the heart chambers, which allows blood to move easily through the heart. The endocardium also covers the surfaces of the heart valves.

Ridges formed by the myocardium can be seen on the internal surfaces of the heart chambers. Though the interior surfaces of the atria are mainly flat, the interior of both auricles and a part of the right atrial wall contain muscular ridges called **pectinate** (pek′ti-nāt) **muscles.** The pectinate muscles of the right atrium are separated from the larger, smooth portions of the atrial wall by a ridge called the **crista terminalis** (kris′tă ter′mi-nal′is; terminal crest). The interior walls of the ventricles contain larger, muscular ridges and columns called **trabeculae** (tră-bek′ū-lē; beams) **carneae** (kar′nē-ē; flesh). These ridges help with forceful ejection of blood from the ventricles.

External Anatomy and Coronary Circulation

The heart consists of four chambers: two **atria** (ā′trē-ă; sing. *atrium*) and two **ventricles** (ven′tri-klz). The thin-walled atria form the superior and posterior parts of the heart, and the thick-walled ventricles form the anterior and inferior portions (figure 20.5). **Auricles** (aw′ri-klz; ears) are flaplike extensions of the atria that can be seen anteriorly between each atrium and ventricle. It is interesting to note that the entire atrium used to be called the auricle, and some medical personnel still refer to it as such.

Blood enters the atria of the heart through several large veins. The **superior vena cava** (vē′nă kā′vă) and the **inferior vena cava** carry blood from the body to the right atrium. In addition, the smaller coronary sinus carries blood from the walls of the heart to the right atrium. Four **pulmonary veins** carry blood from the lungs to the left atrium.

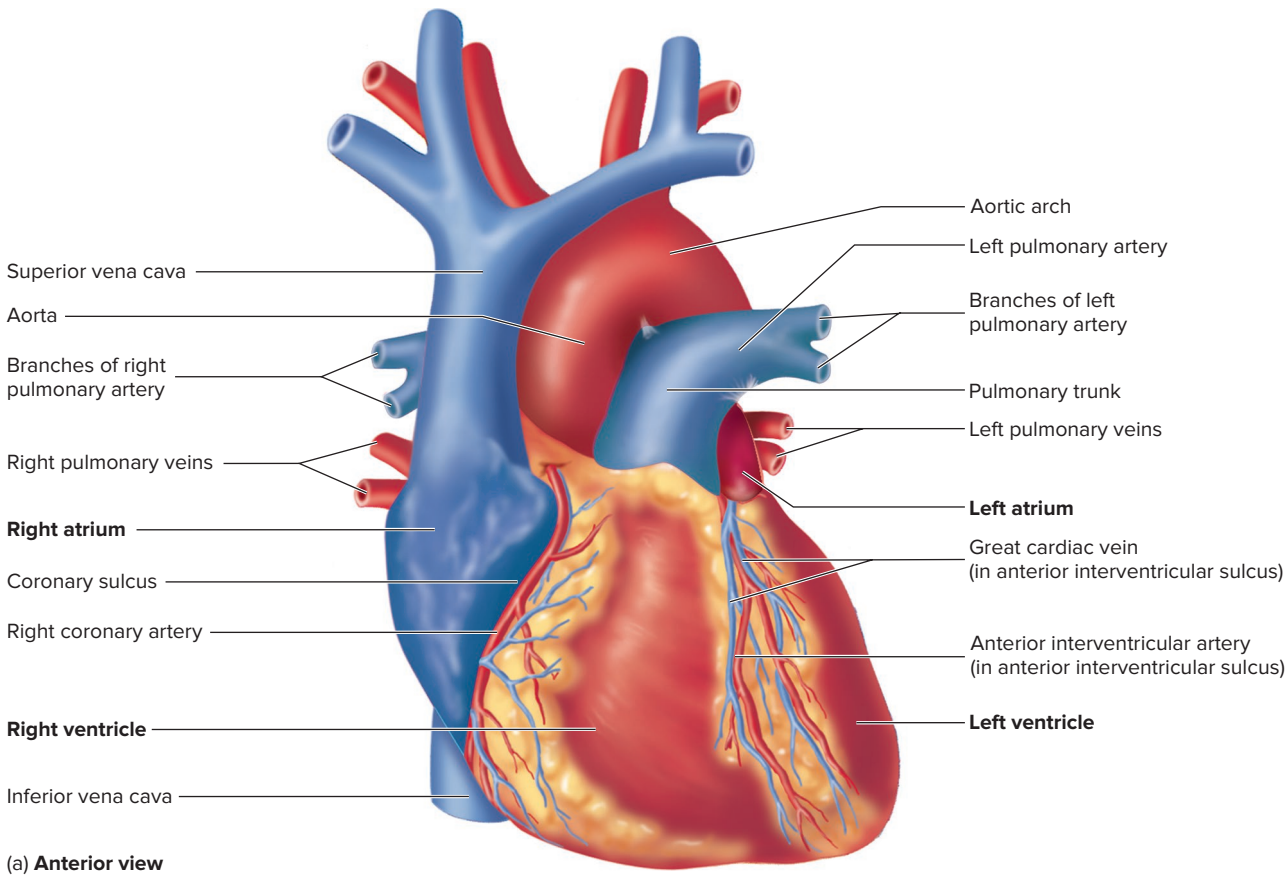
Blood leaves the ventricles of the heart through two arteries: the **pulmonary trunk** and the **aorta.** The pulmonary trunk carries blood from the right ventricle to the lungs. The aorta carries blood from the left ventricle to the body. Because of their large size, the pulmonary trunk and aorta are often called the great arteries.

The coronary circulation consists of blood vessels that carry blood to and from the tissues of the heart wall. The major vessels of the coronary circulation lie in several grooves, or sulci, on the surface of the heart. A large groove called the **coronary** (kōr′o-nār-ē; circling like a crown) **sulcus** (sool′kŭs; ditch) runs obliquely around the heart, separating the atria from the ventricles. Two more grooves extend inferiorly from the coronary sulcus, indicating the division between the right and left ventricles. (1) The **anterior interventricular sulcus** is on the anterior surface of the heart, extending from the coronary sulcus toward the apex of the heart (figure 20.5*a,b*). (2) The **posterior interventricular sulcus** is on the posterior surface of the heart, extending from the coronary sulcus toward the apex of the heart (figure 20.5*c*). In a healthy, intact heart, the grooves are covered by adipose tissue, and only after this tissue is removed can they be seen.

The major arteries supplying blood to the tissue of the heart lie within the coronary sulcus and interventricular grooves on the surface of the heart. The **right** and **left coronary arteries** exit the aorta just above the point where the aorta leaves the heart. These vessels lie within the coronary sulcus (figure 20.6*a*). The right coronary artery is usually smaller in diameter than the left one, and it does not carry as much blood as the left coronary artery.

The left coronary artery has three major branches.

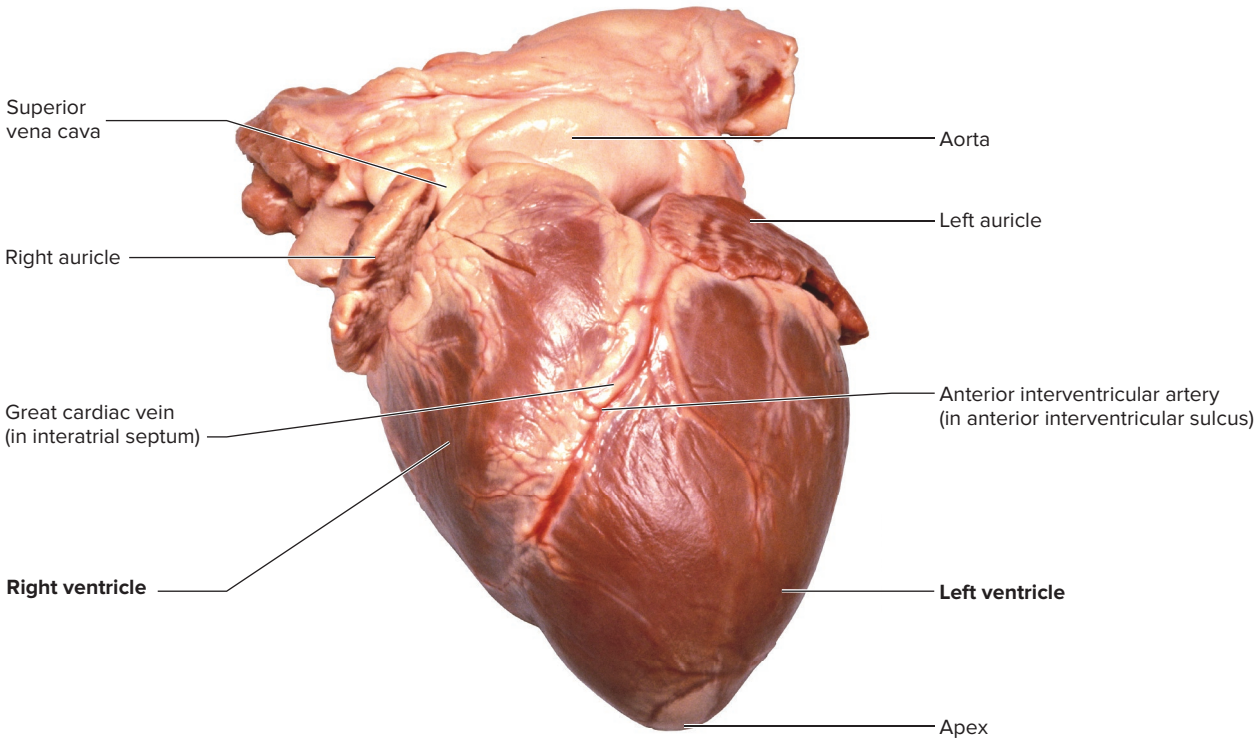
1. The first major branch of the left coronary artery is the **anterior interventricular artery,** or the *left anterior descending artery*. It extends inferiorly in the anterior interventricular sulcus and supplies blood to most of the anterior part of the heart.
2. The second major branch of the left coronary artery is the **left marginal artery,** which supplies blood to the lateral wall of the left ventricle.
3. The third major branch of the left coronary artery is the **circumflex** (ser′kŭm-fleks) **artery,** which extends around to the posterior side of the heart in the coronary sulcus. Branches of the circumflex artery supply blood to much of the posterior wall of the heart.



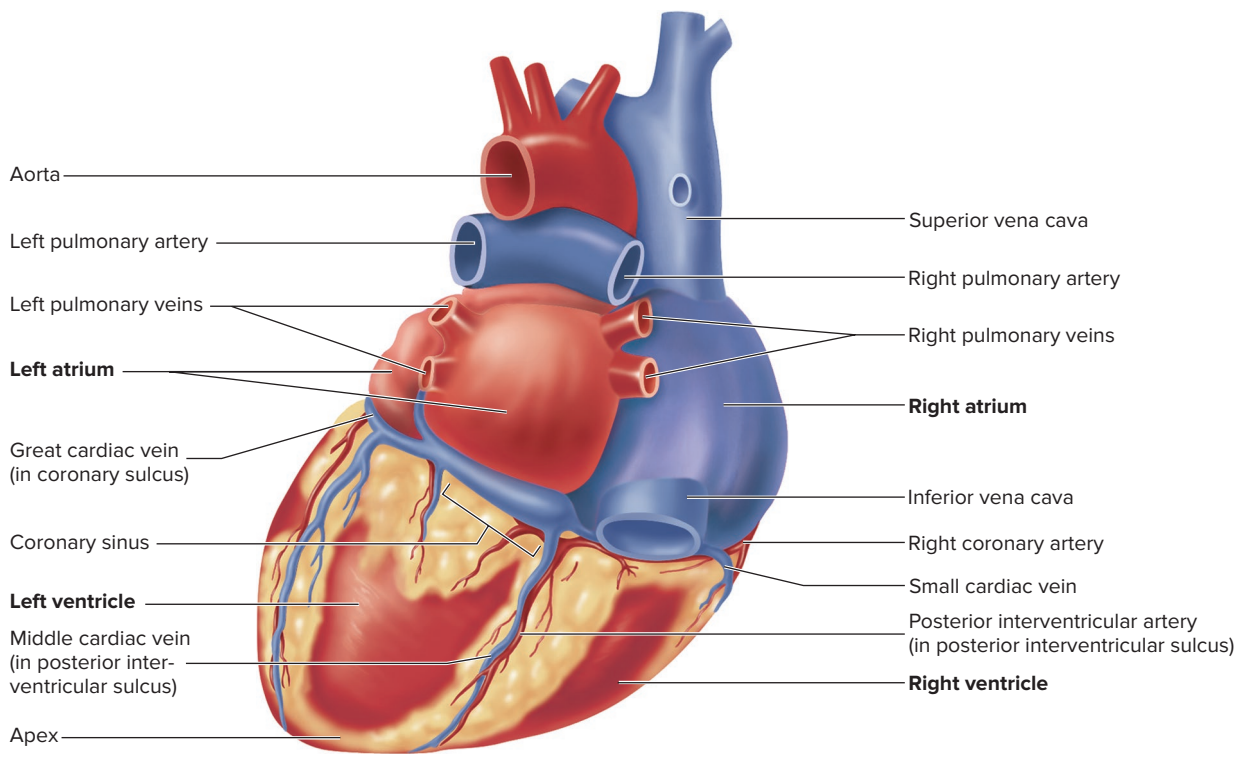
(a) **Anterior view**

FIGURE 20.5 Surface View of the Heart

(*a*) The two atria (right and left) are located superiorly, and the two ventricles (right and left) are located inferiorly. The superior and inferior venae cavae enter the right atrium. The pulmonary veins enter the left atrium. The pulmonary trunk exits the right ventricle, and the aorta exits the left ventricle. AP|R



(b) **Anterior view**



(c) **Posterior view**

FIGURE 20.5 (continued)

(*b*) Photograph of the anterior surface of the heart. (c) The two atria (right and left) are located superiorly, and the two ventricles (right and left) are located inferiorly. The superior and inferior venae cavae enter the right atrium, and the four pulmonary veins enter the left atrium. The pulmonary trunk divides, forming the left and right pulmonary arteries. (b) ©A. & F. Michler/Getty Images

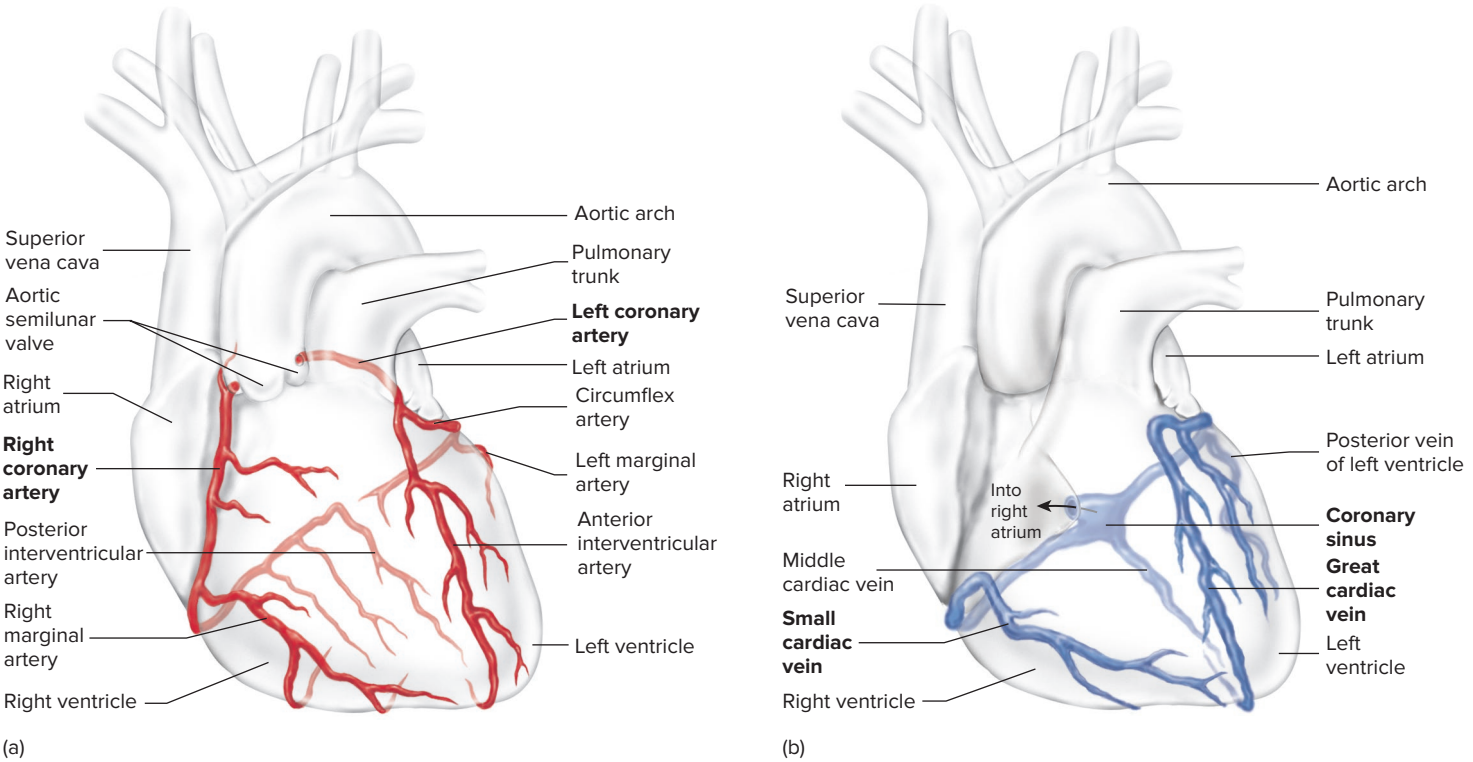


FIGURE 20.6 Coronary Circulation

(*a*) Arteries supplying blood to the heart. The arteries of the anterior surface are seen directly and are darker in color; the arteries of the posterior surface are seen through the heart and are lighter in color. (*b*) Veins draining blood from the heart. The veins of the anterior surface are seen directly and are darker in color; the veins of the posterior surface are seen through the heart and are lighter in color. APR

The right coronary artery lies within the coronary sulcus and extends from the aorta around to the posterior part of the heart. There are two major branches of the right coronary artery. (1) A larger branch of the right coronary artery, called the **right marginal artery,** and other branches supply blood to the lateral wall of the right ventricle. (2) A second branch of the right coronary artery, called the **posterior interventricular artery,** lies in the posterior interventricular sulcus and supplies blood to the posterior and inferior part of the heart.

Most of the myocardium receives blood from more than one arterial branch. In addition, the coronary circulation includes many **anastamoses,** or direct connections between arteries. These anastamoses may form either between branches of a given artery or between branches of different arteries. As a result of these many connections among the coronary arteries, if one artery becomes blocked, the areas primarily supplied by that artery may still receive some blood through other arterial branches and anastamoses. The density of blood vessels supplying blood to the myocardium increases with aerobic exercise, as do the number and extent of the anastamoses. Consequently, aerobic exercise increases the chance that a person will survive the blockage of a small coronary artery. The blockage of larger coronary blood vessels still has the potential to permanently damage large areas of the heart wall.

The coronary circulation also includes veins that carry the blood from the heart walls to the right atrium. There are two major veins draining the blood from the heart wall tissue: (1) The **great cardiac vein** drains blood from the left side of the heart, and (2) a **small cardiac vein** drains the right margin of the heart (figure 20.6*b*). These veins converge toward the posterior part of the coronary sulcus and empty into a large venous cavity called the **coronary sinus,** which in turn empties into the right atrium. A number of smaller veins empty into the cardiac veins, into the coronary sinus, or directly into the right atrium.

Blood flow through the coronary blood circulation is not continuous. When the cardiac muscle contracts, blood vessels in the wall of the heart are compressed so blood does not readily flow through them. When the cardiac muscle relaxes, the blood vessels are not compressed, and blood flow through the coronary blood vessels resumes.

As blood flows through tissues, O_2 is released from the blood and moves into the tissues. The amount of O_2 released varies from one tissue to another, even in the case of the different muscle tissue types. In a resting person, blood flowing through the coronary arteries gives up approximately 70% of its O_2. In comparison, blood flowing through arteries to skeletal muscle gives up only about 25% of its O_2. The percentage of O_2 the blood releases to skeletal muscle can increase to 70% or more during exercise. Because the percentage of O_2 delivered to cardiac muscle is near its maximum at rest, it cannot increase substantially during exercise. Therefore, cardiac muscle requires blood to flow through the coronary arteries at a higher rate than its resting level in order to provide an adequate O_2 supply during exercise.

ASSESS YOUR PROGRESS

4. *Describe the parts of the pericardium and their functions.*
5. *Describe the three layers of the heart wall, and state their functions.*
6. *Name the chambers of the heart, and describe their structures. What is an auricle?*
7. *List the major blood vessels that enter and leave the heart. Which chambers do they enter or exit?*
8. *Describe the flow of blood through the coronary arteries and their branches.*
9. *Trace the flow of blood through the cardiac veins.*

Heart Chambers and Valves

Right and Left Atria

The **right atrium** has three major openings: (1) an opening from the superior vena cava, (2) an opening from the inferior vena cava, and (3) an opening from the coronary sinus. The openings from the superior vena cava and the inferior vena cava receive blood from the body, and the opening of the coronary sinus receives blood from the heart itself (figure 20.7). The **left atrium** has four relatively uniform openings from the four pulmonary veins that receive blood from the lungs.

The right and left atria are separated from each other by the wall of tissue called the **interatrial septum.** The **fossa ovalis** (fos′ă ō-va′lis) is a slight, oval depression on the right side of the interatrial septum marking the former location of the **foramen ovale** (ō-va′lē), an opening between the right and left atria in the embryonic and fetal heart. In the fetal heart, this opening allows blood to flow from the right to the left atrium and bypass the pulmonary circulation (see chapter 29).

Right and Left Ventricles

The atria open into the ventricles through **atrioventricular canals** (figure 20.7). Each ventricle has one large, superiorly placed outflow route near the midline of the heart. Blood flows from the **right ventricle** into the pulmonary trunk. Blood flows from the **left ventricle** into the aorta. The two ventricles are separated from each other by the **interventricular septum,** which has a thick, muscular part toward the apex and a thin, membranous part toward the atria. The wall of the left ventricle is much thicker than the wall of the right ventricle (figure 20.7). The thicker wall of the left ventricle allows for stronger contractions to pump blood through the systemic circulation.

Atrioventricular Valves

An **atrioventricular valve** is in each atrioventricular canal and is composed of cusps, or flaps. Atrioventricular valves ensure blood flows from the atria into the ventricles, preventing blood from flowing back into the atria. The atrioventricular valve between the right atrium and the right ventricle is called the **tricuspid** (trī-kŭs′pid) **valve** because it consists of three cusps (figures 20.7 and 20.8*a*). The atrioventricular valve between the left atrium and the left ventricle is called the **bicuspid** (bī-kŭs′pid) **valve** because it has two cusps. Another common term for the bicuspid valve is the *mitral* (mī′trăl) *valve* (figures 20.7 and 20.8*b*).

Each ventricle contains cone-shaped, muscular pillars called **papillary** (pap′i-lār-ē; nipple) **muscles.** These muscles are attached to the cusps of the atrioventricular valves by thin, strong connective tissue

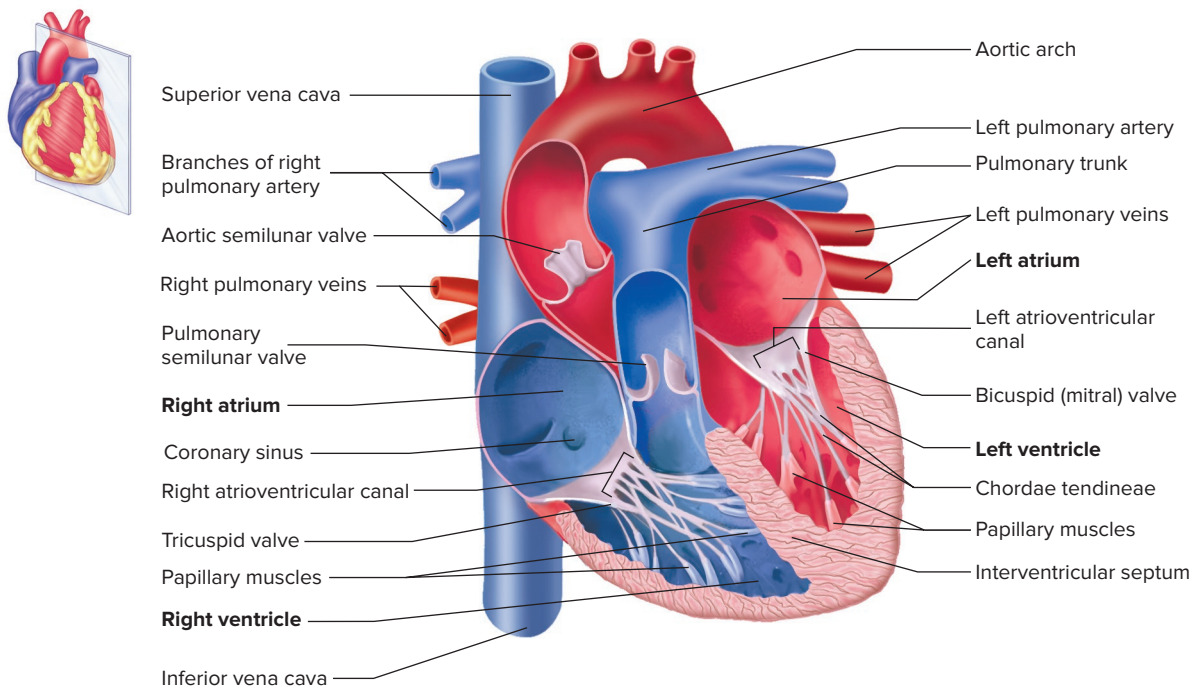


FIGURE 20.7 Internal Anatomy of the Heart
The heart is cut in a frontal plane to show the internal anatomy. AP|R

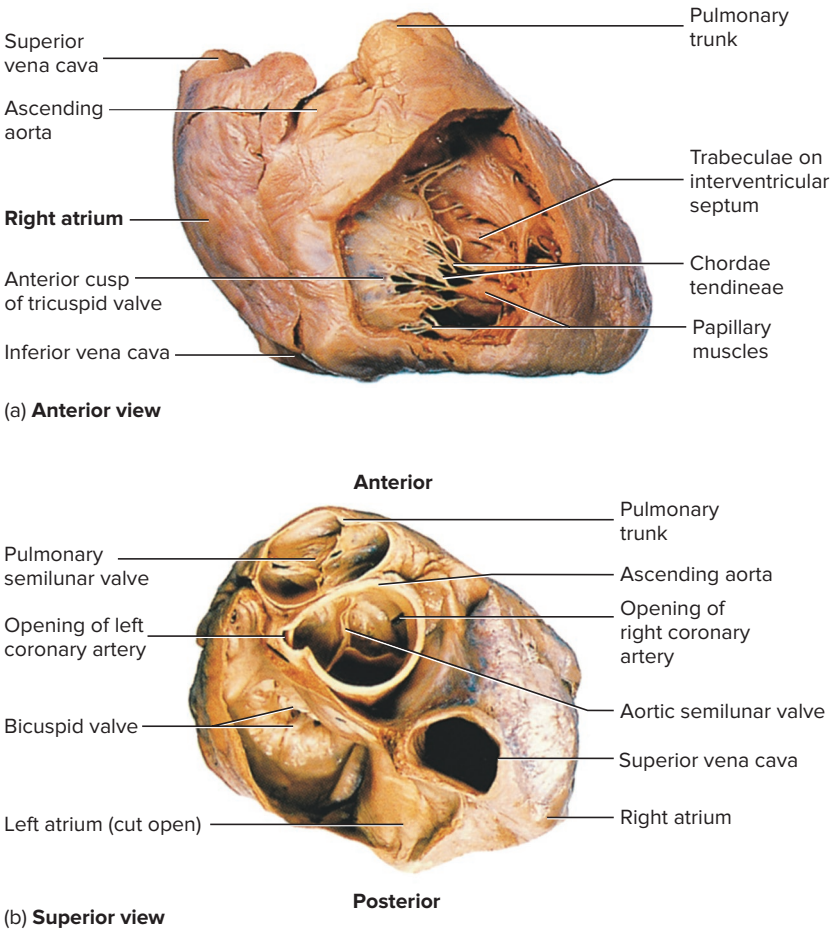


FIGURE 20.8 Heart Valves

(*a*) Tricuspid valve, chordae tendineae, and papillary muscles. (*b*) Heart valves. Note the three cusps of each semilunar valve meeting to prevent the backflow of blood.

strings called **chordae tendineae** (kōr′dē ten′di-nē-ē; heart strings) (figures 20.7 and 20.8*a*). The papillary muscles contract when the ventricles contract and prevent the valves from opening into the atria by pulling on the chordae tendineae attached to the valve cusps, similar to the way parachute cords hold a parachute in place when a skydiver is airborne. Blood flowing from the atrium into the ventricle pushes the valve open into the ventricle; however, when the ventricle contracts, blood pushes the valve back toward the atrium. The atrioventricular canal is closed as the valve cusps meet (figure 20.9).

Semilunar Valves

A semilunar (sem-ē-loo′năr; half-moon-shaped) valve is positioned between each ventricle and its associated great artery. The semilunar valves are identified by the great artery in which each is located and include the **aortic semilunar valve** and **pulmonary semilunar valve.** Each valve consists of three pocketlike, semilunar cusps, the free inner borders of which meet in the center of the artery to block blood flow (see figures 20.7 and 20.8*b*). Contraction of the ventricles pushes blood against the semilunar valves, forcing them to open. Blood can then enter the great arteries. However, when blood flows back from the aorta or pulmonary trunk toward the ventricles, it enters the pockets of the cusps, causing the cusps to meet in the center of the aorta or pulmonary trunk. This effectively closes the semilunar valves and prevents blood from flowing back into the ventricles (figure 20.9*a*).

ASSESS YOUR PROGRESS

10. *Why is the wall of the left ventricle thicker than the wall of the right ventricle?*
11. *Describe the openings of the right and left atria. What structure separates the atria from each other?*
12. *Describe the openings of the right and left ventricles. What structure separates the ventricles from each other?*
13. *Name the valves that separate the atria from the ventricles. What are the functions of the papillary muscles and the chordae tendineae?*
14. *Where are the semilunar valves found?*

20.4 Route of Blood Flow Through the Heart

LEARNING OUTCOME

After reading this section, you should be able to

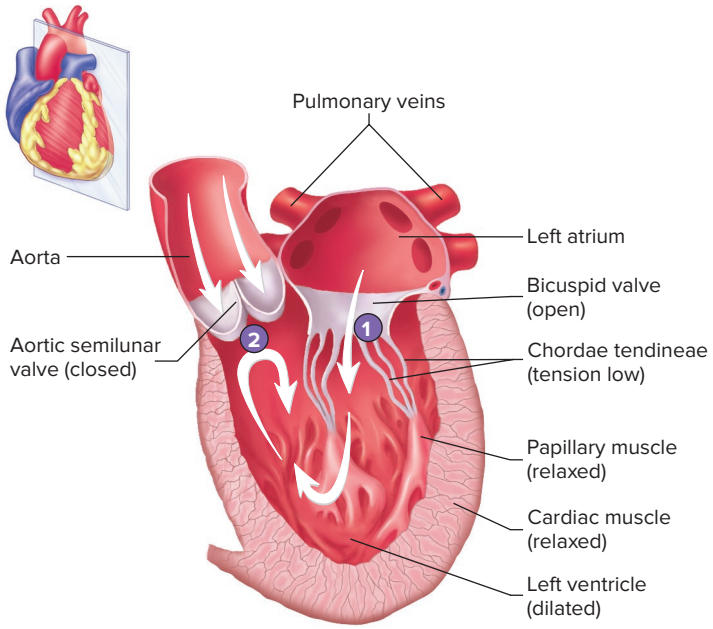
A. **Relate the flow of blood through the heart, naming the chambers, valves, and vessels in the correct order.**

Blood flow through the heart is depicted in figure 20.10. Even though it is more convenient to discuss blood flow through the heart one side at a time, it is important to understand that blood flows through both sides simultaneously. Both atria contract at about the same time and both ventricles contract at about the same time, therefore blood is moving through both the pulmonary and the systemic circulations with each heartbeat. This concept is particularly important when electrical activity, pressure changes, and heart sounds are discussed later in this chapter.

Blood enters the relaxed right atrium from the systemic circulation, which returns blood from all the tissues of the body. Most of the blood in the right atrium then passes into the relaxed right ventricle. The right atrium then contracts, pushing most of the remaining blood in the atrium into the right ventricle to complete right ventricular filling.

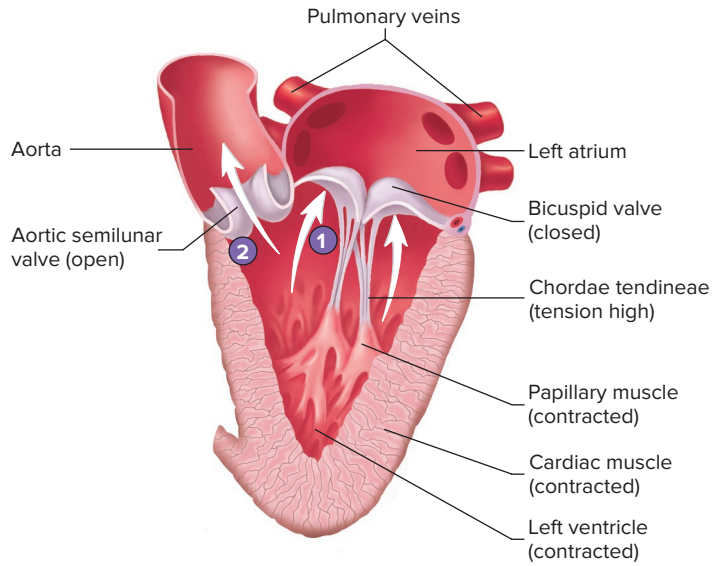
Contraction of the right ventricle pushes blood against the tricuspid valve, forcing it closed. Closing of the tricuspid valve prevents blood from moving back into the right atrium. Blood also pushes against the pulmonary semilunar valve, forcing it open. Blood then flows into the pulmonary trunk.

The pulmonary trunk branches to form the **pulmonary arteries** (see figure 20.5), which carry blood to the lungs, where CO_2 is released and O_2 is picked up (see chapters 21 and 23).



(a) **Valve positions when blood is flowing into the left ventricle.**

1. The bicuspid valve is open. The cusps of the valve are pushed by the blood into the ventricle.
2. The aortic semilunar valve is closed. The cusps of the valve overlap as they are pushed by the blood in the aorta toward the ventricle.



(b) **Valve positions when blood is flowing out of the left ventricle.**

1. The bicuspid valve is closed. The cusps of the valves overlap as they are pushed by the blood toward the left atrium.
2. The aortic semilunar valve is open. The cusps of the valve are pushed by the blood toward the aorta.

PROCESS FIGURE 20.9 Function of the Heart Valves

(*a*) Valve positions when blood is flowing into the left ventricle. (*b*) Valve positions when blood is flowing out of the left ventricle. Numbered steps show the functions of the bicuspid and aortic semilunar valves. The tricuspid and pulmonary semilunar valves (not shown) open and close in a similar pattern.

? *Considering that valves open and close based on pressure differences on either side of a valve, what is the result of abnormally high blood pressure in the aorta?*

Blood returning from the lungs enters the left atrium through the four pulmonary veins. Most of the blood passes from the left atrium into the relaxed left ventricle. Contraction of the left atrium completes left ventricular filling.

Contraction of the left ventricle pushes blood against the bicuspid valve, closing it and preventing blood from moving back into the left atrium. Blood is also pushed against the aortic semilunar valve, opening it and allowing blood to enter the aorta. Blood flowing through the aorta is distributed to all parts of the body, except to the parts of the lungs supplied by the pulmonary blood vessels (see chapter 23).

Recall that in the embryonic and fetal heart the foramen ovale allows for blood to flow between the two atria. This hole closes at birth, separating the right and left sides of the heart. For a more detailed discussion of blood flow through the fetal heart, see section 29.3 and figure 29.22.

ASSESS YOUR PROGRESS

15. *Starting at the venae cavae and ending at the aorta, trace the flow of blood through the heart.*

20.5 Histology

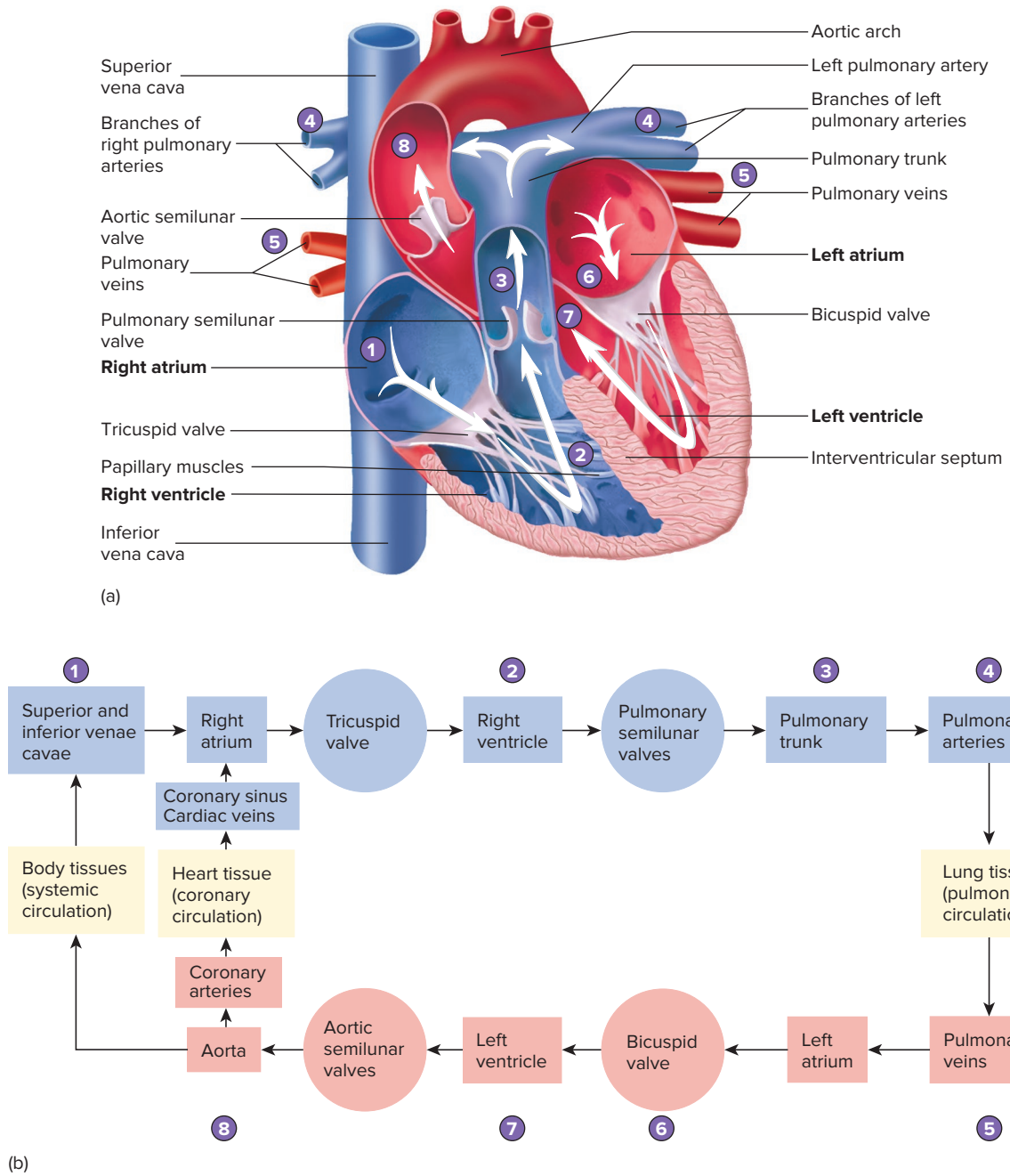
LEARNING OUTCOMES

After reading this section, you should be able to

A. **Describe the structure and functions of the heart skeleton.**
B. **Relate the structural and functional characteristics of cardiac muscle cells.**
C. **Compare and contrast cardiac muscle and skeletal muscle.**
D. **Explain the structure and function of the conducting system of the heart.**

Heart Skeleton

The **heart skeleton** consists of a plate of fibrous connective tissue between the atria and the ventricles. This connective tissue plate forms **fibrous rings** around the atrioventricular and semilunar valves and provides solid support for them, reinforcing the valve openings (figure 20.11). The fibrous connective tissue plate also serves as electrical insulation between the atria and the ventricles and provides a rigid site for attachment of the cardiac muscles.



PROCESS FIGURE 20.10 Blood Flow Through the Heart

(*a*) Frontal section of the heart revealing the four chambers and the direction of blood flow (*purple numbers*). (*b*) Diagram listing, in order, the structures through which blood flows in the systemic, pulmonary, and coronary circulations. The heart valves are indicated by *circles;* deoxygenated blood appears *blue,* and oxygenated blood appears *red*.

? *Imagine that you are a red blood cell moving through the circulation. After moving into the right atrium, how many heart valves will you pass through before you first enter the circulation of the lungs? How many heart valves will you pass through before entering the circulation of the brain?*

Cardiac Muscle

Cardiac muscle cells are elongated, branching cells that have one, or occasionally two, centrally located nuclei. Cardiac muscle cells contain actin and myosin myofilaments organized to form sarcomeres, which join end-to-end to form myofibrils (see chapter 9). As is the case in skeletal muscle, the actin and myosin myofilaments are responsible for cardiac muscle contraction, and their organization gives cardiac muscle a striated (banded)

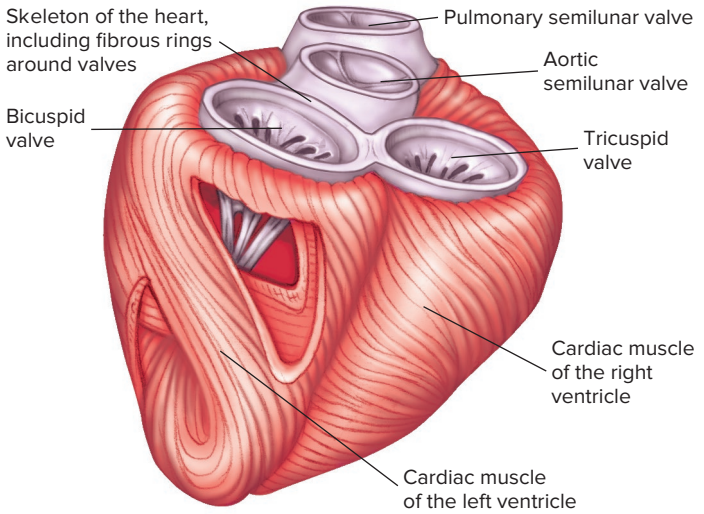


FIGURE 20.11 Heart Skeleton

The skeleton of the heart consists of fibrous connective tissue rings, which surround the heart valves and separate the atria from the ventricles. Cardiac muscle attaches to the fibrous connective tissue. The muscle fibers are arranged so that contraction of the ventricles produces a wringing motion and the distance between the apex and the base of the heart shortens.

appearance. However, the striations are less regularly arranged and less numerous than in skeletal muscle (figure 20.12).

Cardiac muscle cell contraction is very similar to that of skeletal muscle; however, the onset of contraction is longer and prolonged in cardiac muscle. These differences in contraction are partially due to differences in cell anatomy. Cardiac muscle has a smooth **sarcoplasmic reticulum,** which stores Ca^{2+}, similar to skeletal muscle. But the sarcoplasmic reticulum is not as regularly arranged as in skeletal muscle fibers, and there are no dilated cisternae, as in skeletal muscle.

We learned in chapter 9 that stimulations of the skeletal muscle at the sarcolemma, or plasma membrane, are carried deep into the cell by transverse tubules. Similarly, cardiac muscles have transverse tubules that are in close association with the sarcoplasmic reticulum. However, the T tubules in cardiac muscle are larger in diameter than in skeletal muscle, and extensions of T tubules are not as closely associated with the sarcoplasmic reticulum as in skeletal muscle. Also, the T tubules of cardiac muscle are found near the Z disks of the sarcomeres, instead of where the actin and myosin overlap, as in skeletal muscle. Given these structural differences,

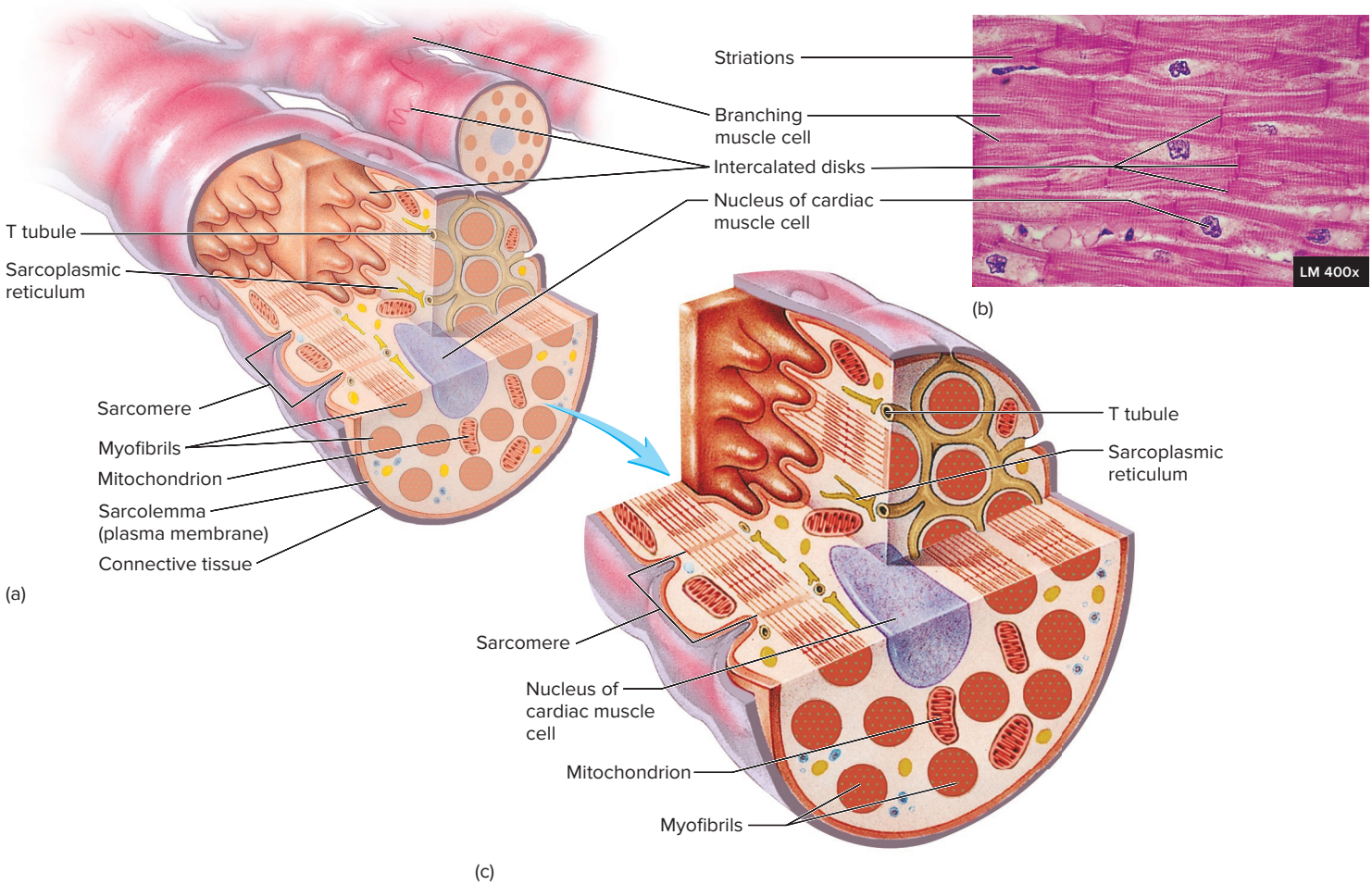


FIGURE 20.12 Histology of the Heart

(*a*) Cardiac muscle cells are branching cells with centrally located nuclei. The cells are joined to one another by intercalated disks. Gap junctions in the intercalated disks allow action potentials to pass from one cardiac muscle cell to the next. (*b*) A light micrograph of cardiac muscle tissue. The cardiac muscle cells appear striated because of the arrangement of the individual myofilaments. (c) As in skeletal muscle, sarcomeres join end-to-end to form myofibrils, and mitochondria provide ATP for contraction. Sarcoplasmic reticulum and T tubules are visible but are not as numerous as they are in skeletal muscle. (b) ©Ed Reschke AP|R

depolarizations of the cardiac muscle plasma membrane are not carried from the surface of the cell to the sarcoplasmic reticulum as efficiently as they are in skeletal muscle, and Ca^{2+} must diffuse a greater distance from the sarcoplasmic reticulum to the actin myofilaments. Another important difference between cardiac muscle and skeletal muscle is the sources for Ca^{2+} necessary for contraction. In skeletal muscle, adequate Ca^{2+} for contraction is stored in the sarcoplasmic reticulum, but cardiac muscle requires some Ca^{2+} from the extracellular fluid and from the T tubules.

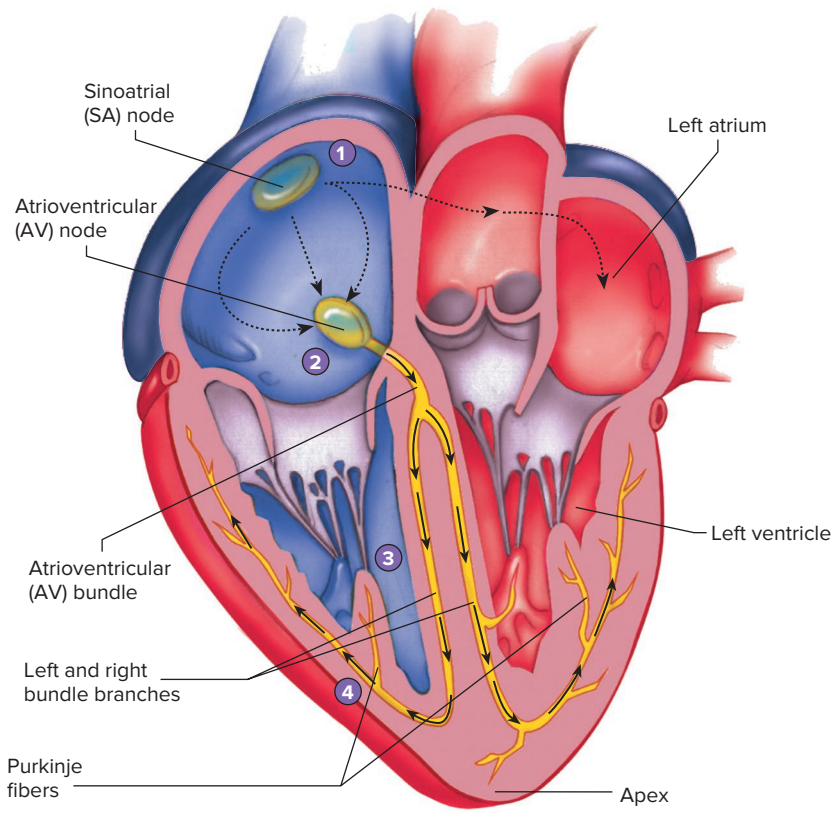
Cardiac muscle is specialized to meet the high energy requirements needed for proper myocardial function. Adenosine triphosphate (ATP) provides the energy for cardiac muscle contraction. ATP production depends on O_2 availability. Because cardiac muscle must continue to contract and relax in a relatively steady rhythm to maintain life, it cannot develop a large oxygen deficit, which is often seen in skeletal muscle. Cardiac muscle cells are rich in mitochondria, which perform oxidative metabolism at a rate rapid enough to sustain normal myocardial energy requirements. Also, the myocardium has an extensive capillary network that provides an adequate O_2 supply to the cardiac muscle cells.

Another unique characteristic of cardiac muscle is that cardiac muscle cells are organized in spiral bundles or sheets. Additionally, cardiac cells are bound to adjacent cells by specialized cell-to-cell contacts called **intercalated** (in-ter′kă-lā-ted) **disks** (figure 20.12). Intercalated disks are located at the ends of cells, connecting them end-to-end; however, intercalated disks can also connect cells laterally. At intercalated disks, the plasma membranes are folded, and the adjacent cells fit together, thus greatly increasing contact between them. In addition, specialized plasma membrane structures at the intercalated disks increase physical and electrical connections between cells. These plasma membrane structures include desmosomes and gap junctions. **Desmosomes** (dez′mō-sōmz) hold the cells together, and **gap junctions** allow cytoplasm to flow freely between cells, resulting in areas of low electrical resistance between the cells. This enables action potentials to pass easily from one cell to the next (see figure 4.2). Electrically, the cardiac muscle cells behave as a single unit, and the heart's highly coordinated contractions depend on this functional characteristic.

Conducting System

A conducting system relays action potentials through the heart. This system consists of modified cardiac muscle cells that form two nodes (knots or lumps) and a conducting bundle (figure 20.13). The two nodes are contained within the walls of the right atrium and are named according to their position in the atrium. The **sinoatrial (SA) node** is medial to the opening of the superior vena cava, and the **atrioventricular (AV) node** is medial to the right atrioventricular valve. The AV node gives rise to a conducting bundle of the heart, the **atrioventricular (AV) bundle** (bundle of His).

1. Action potentials originate in the sinoatrial (SA) node (the pacemaker) and travel across the wall of the atrium (*arrows*) from the SA node to the atrioventricular (AV) node.
2. Action potentials pass through the AV node and along the atrioventricular (AV) bundle, which extends from the AV node, through the fibrous skeleton, into the interventricular septum.
3. The AV bundle divides into right and left bundle branches, and action potentials descend to the apex of each ventricle along the bundle branches.
4. Action potentials are carried by the Purkinje fibers from the bundle branches to the ventricular walls and papillary muscles.



PROCESS FIGURE 20.13 Conducting System of the Heart

The conduction system of the heart is composed of specialized cardiac muscle cells that produce spontaneous action potentials. The organization of the conduction system ensures the proper pattern of contractions of the atria and ventricle, maintaining normal blood flow. AP|R

? *Why is it important for stimulation of the ventricles to begin at the apex and spread toward the base?*

This bundle passes through a small opening in the fibrous skeleton to reach the interventricular septum, where it divides to form the **right** and **left bundle branches,** which extend beneath the endocardium on each side of the interventricular septum to the apex of both the right and the left ventricles.

The inferior terminal branches of the bundles are called **Purkinje** (per-kin′jē) **fibers.** These fibers are large-diameter cardiac muscle fibers. They have fewer myofibrils than most cardiac muscle cells and do not contract as forcefully. Intercalated disks are well developed between the Purkinje fibers and contain numerous gap junctions. As a result of these structural modifications, action potentials travel along the Purkinje fibers much more rapidly than through other cardiac muscle tissue.

Unlike skeletal muscle cells that require neural stimulation for contraction, cardiac muscle cells have the intrinsic capacity to spontaneously generate action potentials for contraction. Because cells of the SA node spontaneously generate action potentials at a greater frequency than other cardiac muscle cells, these cells are called the **pacemaker** of the heart. The SA node is made up of specialized, small-diameter cardiac muscle cells that merge with the other cardiac muscle cells of the right atrium. Once action potentials are produced, they spread from the SA node to adjacent cardiac muscle cells of the atrium. Preferential pathways conduct action potentials from the SA node to the AV node at a greater velocity than they are transmitted in the remainder of the atrial muscle cells. However, such pathways cannot be distinguished structurally from the remainder of the atrium. It is the activity of the SA node that causes the heart to contract spontaneously and rhythmically.

When the heart beats under resting conditions, approximately 0.04 second is required for action potentials to travel from the SA node to the AV node. Action potentials are propagated slowly through the AV node, compared with the remainder of the conducting system. The slow rate of action potential conduction in the AV node is due, in part, to the smaller-diameter muscle cells and fewer gap junctions in their intercalated disks. Like the other specialized conducting cells in the heart, they have fewer myofibrils than most cardiac muscle cells. As a consequence, a delay of 0.11 second occurs from the time action potentials reach the AV node until they pass to the AV bundle. The delay of action potentials at the AV node allows for completion of the atrial contraction before ventricular contraction begins.

After action potentials pass from the AV node to the highly specialized conducting bundles, the velocity of conduction increases dramatically. The action potentials pass through the left and right bundle branches and through the individual Purkinje fibers that penetrate the myocardium of the ventricles (figure 20.13).

Because of the arrangement of the conducting system in the ventricles, the first part of the ventricular myocardium that is stimulated is the inner wall of the ventricles near the apex. Thus, ventricular contraction begins at the apex and progresses throughout the ventricles toward the base of the heart. The spiral arrangement of muscle layers in the wall of the heart results in a wringing action. During the process, the distance between the apex and the base of the heart decreases and blood is forced upward from the apex toward the great vessels at the base of the heart (see figure 20.10).

Predict 2

Because of a reduced blood supply to the AV node, the delay in the conduction of action potentials from the SA node to the AV node is increased slightly. All other areas of the conducting system of the heart are functioning normally. Predict how this affects the normal rhythm of the heart.

ASSESS YOUR PROGRESS

16. *What is the heart skeleton composed of? What are its functions?*
17. *Compare and contrast cardiac muscle and skeletal muscle.*
18. *Why does cardiac muscle have slow onset of contraction and prolonged contraction?*
19. *What anatomical features are responsible for the ability of cardiac muscle cells to contract as a unit?*
20. *Identify the parts of the conducting system of the heart. Explain how the conducting system coordinates contraction of the atria and ventricles.*
21. *Explain why Purkinje fibers conduct action potentials more rapidly than other cardiac muscle cells.*
22. *Relate why the SA node is the pacemaker of the heart.*

20.6 Electrical Properties

LEARNING OUTCOMES

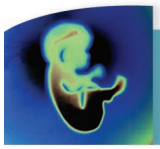
After reading this section, you should be able to

A. **Summarize the characteristics of action potentials in cardiac muscle.**
B. **Explain what is meant by the autorhythmicity of cardiac muscle and relate it to the pacemaker potential.**
C. **Explain the importance of a long refractory period in cardiac muscle.**
D. **Describe the waves and intervals of an electrocardiogram.**

In chapter 3, we defined the membrane potential of a cell as the electrical charge difference across the plasma membrane. This charge difference is the result of a cell's regulation of ion movement into and out of the cell. Cardiac muscle cells—like other electrically excitable cells, such as neurons and skeletal muscle fibers—have a **resting membrane potential,** the membrane potential when the cell is relaxed. The resting membrane potential depends on a low permeability of the plasma membrane to Na^+ and Ca^{2+} and a higher permeability to K^+. When neurons, skeletal muscle fibers, and cardiac muscle cells are depolarized to their threshold level, action potentials result (see chapter 11).

Action Potentials

Like action potentials in skeletal muscle, those in cardiac muscle exhibit depolarization followed by repolarization of the resting



Clinical IMPACT 20.2 Angina, Infarctions, and the Treatment of Blocked Coronary Arteries

Angina pectoris (an′ji-nă, an-jī′nă pek′tō-ris) is chest pain that results from a reduced blood supply to cardiac muscle. The pain is temporary and, if blood flow is restored, little permanent change or damage results. Angina pectoris is characterized by chest discomfort deep to the sternum, often described as heaviness, pressure, or moderately severe pain. It is often mistaken for indigestion. The pain can also be referred to the neck, lower jaw, left arm, and left shoulder (see chapter 14).

Most often, angina pectoris results from narrowed and hardened coronary arterial walls. The reduced blood flow results in a reduced supply of O_2 to cardiac muscle cells. As a consequence, the limited anaerobic respiration of cardiac muscle results in a reduced pH in affected areas of the heart, which stimulates pain receptors. The pain is predictably associated with exercise because the increased pumping of the heart requires more O_2, and the narrowed blood vessels cannot supply it.

Rest and drugs, such as nitroglycerin, frequently relieve angina pectoris. Nitroglycerin dilates the blood vessels, including the coronary arteries. Consequently, the drug increases the O_2 supply to cardiac muscle and reduces the heart's workload. Because peripheral arteries are dilated, the heart has to pump blood against a lower pressure, and the need for O_2 decreases. The heart also pumps less blood because blood tends to remain in the dilated blood vessels and less blood is returned to the heart.

Myocardial infarction (mī-ō-kar′dē-ăl in-fark′shŭn) results when a prolonged lack of blood flow to a part of the cardiac muscle leads to a lack of O_2 and ultimately cellular death. Symptoms of myocardial infarction include chest pain that radiates into the left shoulder and arm, shortness of breath, nausea, vomiting, and sweating. Interestingly, these symptoms are common in men, but women may experience very different symptoms. Over 40% of women who have suffered a myocardial infarction did not experience chest pain. Symptoms for women include sudden fatigue, dizziness, and abdominal pain.

Myocardial infarctions vary in severity, depending on the amount of cardiac muscle and the part of the heart that is affected. If blood supply to cardiac muscle is reestablished within 20 minutes, no permanent damage occurs. If the oxygen deficiency lasts longer, cell death results. However, within 30–60 seconds after blockage of a coronary blood vessel, functional changes are obvious. The electrical properties of the cardiac muscle are altered, and the heart's ability to function properly is lost.

The most common cause of myocardial infarction is thrombus formation that blocks a coronary artery. Coronary arteries narrowed by **atherosclerotic** (ath′er-ō-skler-ot′ik) **lesions** increase the risk for myocardial infarction. Atherosclerotic lesions partially block blood vessels, resulting in turbulent blood flow, and the surfaces of the lesions are rough. These changes increase the probability of thrombus formation.

Blocked blood vessels can be treated using various medical techniques. **Angioplasty** (an′jē-ō-plas-tē) is a process whereby a surgeon threads a small balloon, usually into the femoral artery (see chapter 21), through the aorta and into a coronary artery. After entering the partially occluded coronary artery, the balloon is inflated, flattening the atherosclerotic deposits against the vessel walls and opening the occluded blood vessel. This technique improves the function of cardiac muscle in patients experiencing inadequate blood flow to the cardiac muscle through the coronary arteries. However, some controversy exists about its effectiveness. At least in some patients, dilation of the coronary arteries can reverse within a few weeks or months, and blood clots can form in coronary arteries following angioplasty. To help prevent future blockage, a metal-mesh tube called a **stent** is inserted into the vessel. Although the stent is better able to hold the vessel open, it, too, can eventually become blocked. Small, rotating blades and lasers are also used to remove lesions from coronary vessels.

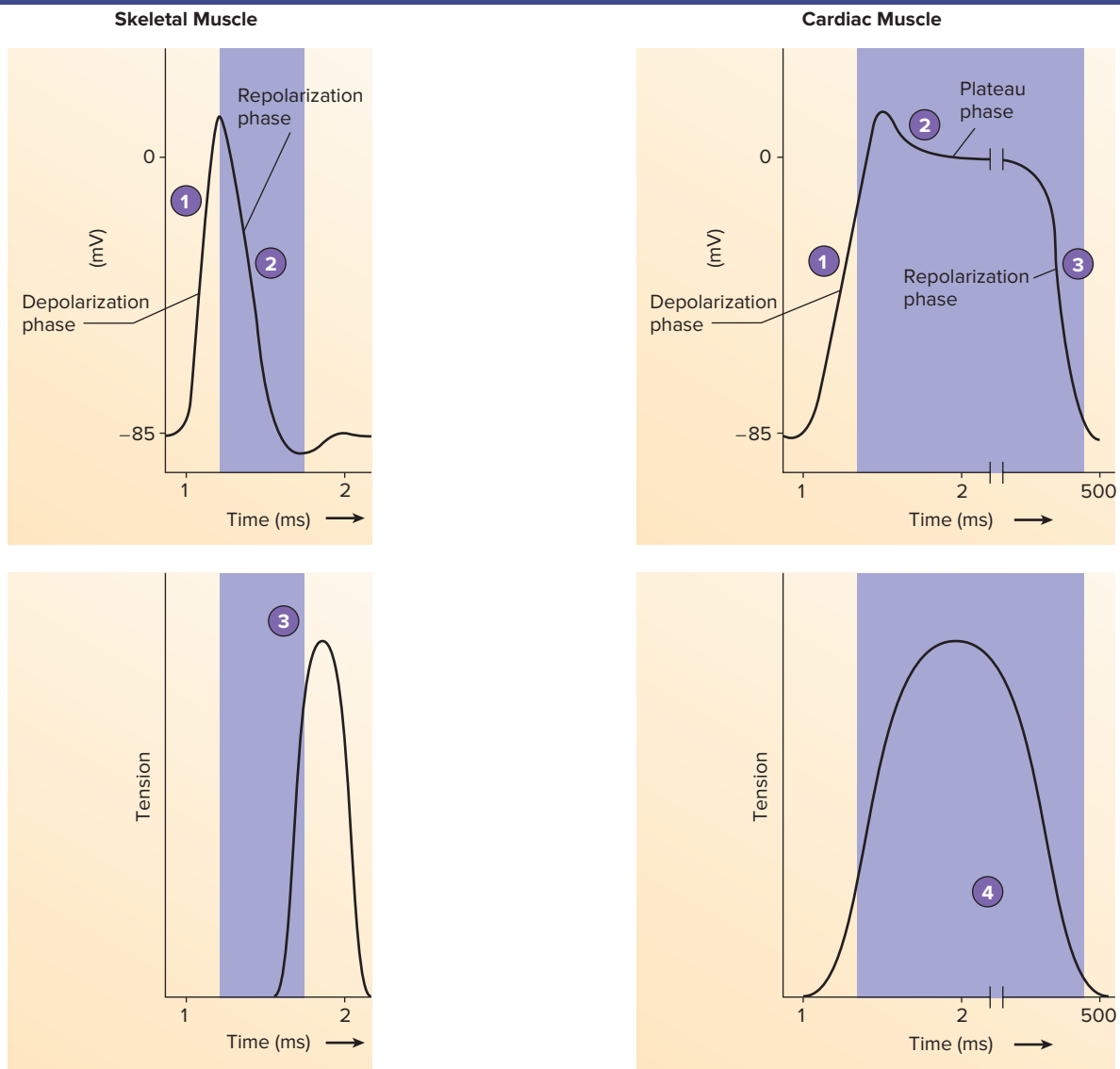
Coronary bypass is a surgical procedure that relieves the effects of obstructed coronary arteries. This technique involves taking healthy segments of blood vessels from other parts of the patient's body and using them to bypass obstructions in the coronary arteries. The technique is common in cases of severe occlusion in specific parts of coronary arteries.

Enzymes are used to break down blood clots that form in the coronary arteries and cause myocardial infarctions. The major enzyme used is **tissue plasminogen** (plaz-min′ō-jen) **activator (t-PA).** This enzyme activates plasminogen, an inactive form of an enzyme in the body that breaks down the fibrin of clots. The strategy calls for administering t-PA to people suffering from myocardial infarctions as soon as possible following the onset of symptoms. Removal of the occlusions produced by clots reestablishes blood flow to the cardiac muscle and reduces the amount of cardiac muscle permanently damaged by the occlusions.

membrane potential. Alterations in membrane channels are responsible for the changes in the permeability of the plasma membrane that produce the action potentials. Action potentials in cardiac muscle last longer than those in skeletal muscle, and the membrane channels differ somewhat from those in skeletal muscle. In contrast to action potentials in skeletal muscle, which take less than 2 milliseconds (ms) to complete, action potentials in cardiac muscle take approximately 200–500 ms to complete (figure 20.14).

The longer action potentials in cardiac muscle can be divided into four phases, each associated with specific changes in ion movement across the membrane. In cardiac muscle, the action potential consists of

1. a rapid **depolarization phase** during which the membrane potential quickly becomes more positive,
2. a rapid but partial **early repolarization phase,**
3. a prolonged period of slow repolarization, the **plateau phase,**
4. a more rapid **final repolarization phase,** during which the membrane potential returns to its resting level (figure 20.14).



(a)

1 **Depolarization phase**
- Voltage-gated Na^+ channels open.
- Voltage-gated K^+ channels begin to open.

2 **Repolarization phase**
- Voltage-gated Na^+ channels close.
- Voltage-gated K^+ channels continue to open.
- Voltage-gated K^+ channels close at the end of repolarization and return the membrane potential to its resting value.

3 **Refractory period effect on tension**
- Maximum tension is obtained after the refractory period (purple shaded area) is completed allowing for increased tension with additional stimulation.

(b)

1 **Depolarization phase**
- Voltage-gated Na^+ channels open.
- Voltage-gated K^+ channels close.
- Voltage-gated Ca^{2+} channels begin to open.

2 **Early repolarization and plateau phases**
- Voltage-gated Na^+ channels close.
- Some voltage-gated K^+ channels open, causing early repolarization.
- Voltage-gated Ca^{2+} channels are open, producing the plateau by slowing further repolarization.

3 **Final repolarization phase**
- Voltage-gated Ca^{2+} channels close.
- Many voltage-gated K^+ channels open.

4 **Refractory period effect on tension**
- Cardiac muscle contracts and relaxes almost completely during the refractory period (purple shaded area).

PROCESS FIGURE 20.14 Comparison of Action Potentials in Skeletal and Cardiac Muscle

(*a*) An action potential in skeletal muscle consists of depolarization and repolarization phases. (*b*) An action potential in cardiac muscle consists of depolarization, early repolarization, plateau, and final repolarization phases. Cardiac muscle does not repolarize as rapidly as skeletal muscle (indicated by the *break in the curve*) because of the plateau phase.

? *Using the tension graph, explain why skeletal muscle can exhibit tetany (sustained contraction) but cardiac muscle cannot.*

Rapid depolarization is the result of changes in membrane permeability to Na^+, K^+, and Ca^{2+}; however, membrane permeability to Na^+ is the primary determinant of this phase. Membrane channels, called **voltage-gated Na^+ channels,** open, bringing about the depolarization phase of the action potential. As the voltage-gated Na^+ channels open, Na^+ diffuses into the cell, causing rapid depolarization until the cell is depolarized to approximately +20 millivolts (mV).

The voltage change occurring during depolarization affects other ion channels in the plasma membrane. Several types of **voltage-gated K^+ channels** exist, each of which opens and closes at different membrane potentials, causing changes in membrane permeability to K^+. For example, at rest, the movement of K^+ through open voltage-gated K^+ channels is primarily responsible for establishing the resting membrane potential in cardiac muscle cells. Depolarization causes these voltage-gated K^+ channels to close, thereby decreasing membrane permeability to K^+. Depolarization also causes **voltage-gated Ca^{2+}** channels to begin to open. These changes contribute to depolarization. Compared with Na^+ channels, the Ca^{2+} channels open and close slowly.

Repolarization is also the result of changes in membrane permeability to Na^+, K^+, and Ca^{2+}. Early repolarization occurs when the voltage-gated Na^+ channels and some voltage-gated Ca^{2+} channels close, and a small number of voltage-gated K^+ channels open. Sodium ion movement into the cell slows, and some K^+ moves out of the cell. At this point, repolarization begins, but in cardiac muscle early repolarization is slow due to the influx of Ca^{2+}, resulting in a plateau phase. The plateau phase occurs as voltage-gated Ca^{2+} channels remain open, and Ca^{2+} and some Na^+ move into the cell through the voltage-gated Ca^{2+} channels. The influx of these ions counteracts the potential change produced by the movement of K^+ out of the cell. The plateau phase ends, and final repolarization begins as the voltage-gated Ca^{2+} channels close and many more voltage-gated K^+ channels open. Thus, Ca^{2+} and Na^+ stop diffusing into the cell, and the tendency for K^+ to diffuse out of the cell increases. These permeability changes cause the membrane potential to return to its resting level.

Action potential propagation in cardiac muscle differs from that in skeletal muscle. First, action potentials in cardiac muscle are conducted from cell to cell through the gap junctions of the intercalated disks, whereas action potentials in skeletal muscle fibers are conducted along the length of a single muscle fiber (cell), but not from fiber to fiber. Second, action potential propagation is slower in cardiac muscle than in skeletal muscle because cardiac muscle cells are smaller in diameter and much shorter than skeletal muscle fibers. Although the gap junctions allow the transfer of action potentials between cardiac muscle cells, they slow the rate of action potential conduction between the cardiac muscle cells.

Another interesting characteristic of cardiac muscle contraction is the need for extracellular Ca^{2+} for contraction to occur. The movement of Ca^{2+} through the plasma membrane, including the membranes of the T tubules, into cardiac muscle cells stimulates the release of Ca^{2+} from the sarcoplasmic reticulum, a process called **calcium-induced calcium release (CICR).** When an action potential occurs in a cardiac muscle cell, Ca^{2+} enters the cell and binds to receptors in the membranes of the sarcoplasmic reticulum, resulting in the opening of Ca^{2+} channels on the membrane of the sarcoplasmic reticulum. Calcium ions then move out of the sarcoplasmic reticulum and activate the interaction between actin and myosin to produce contraction of the cardiac muscle cells. Skeletal muscle contraction does not depend on this mechanism and relies only on intracellular Ca^{2+} for contraction.

Autorhythmicity of Cardiac Muscle

The heart is said to be **autorhythmic** (aw′tō-rith′mik) because it stimulates itself (*auto*) to contract at regular intervals (*rhythmic*). If the heart is removed from the body and maintained under physiological conditions with the proper nutrients and temperature, it will continue to beat autorhythmically for a long time.

In the SA node, pacemaker cells generate action potentials spontaneously and at regular intervals. These action potentials spread through the conducting system of the heart to other cardiac muscle cells, causing voltage-gated Na^+ channels to open. As a result, action potentials are produced and the cardiac muscle cells contract.

Depolarization of pacemaker cells is dependent on Na^+, K^+, and Ca^{2+}; however, the ways that these ions affect the membrane potential are very different. When a spontaneously developing local potential, called the **pacemaker potential,** reaches threshold, then action potentials are generated in the SA node (figure 20.15). Changes in ion movement into and out of the pacemaker cells cause the pacemaker potential. Sodium ions cause depolarization by moving into the cells through specialized nongated Na^+ channels. A decreasing permeability to K^+ also causes depolarization as less K^+ moves out of the cells. The decreasing K^+ permeability occurs due to the voltage changes at the end of the previous action potential. As a result of the depolarization, voltage-gated Ca^{2+} channels open, and the movement of Ca^{2+} into the pacemaker cells causes further depolarization. When the pacemaker potential reaches threshold, many voltage-gated Ca^{2+} channels open. In pacemaker cells, the movement of Ca^{2+} into the cells is primarily responsible for the depolarization phase of the action potential. This is different from other cardiac muscle cells, where the movement of Na^+ into the cells is primarily responsible for depolarization. Repolarization occurs, as in other cardiac muscle cells, when the voltage-gated Ca^{2+} channels close and the voltage-gated K^+ channels open. After the resting membrane potential is reestablished, production of another pacemaker potential starts the generation of the next action potential.

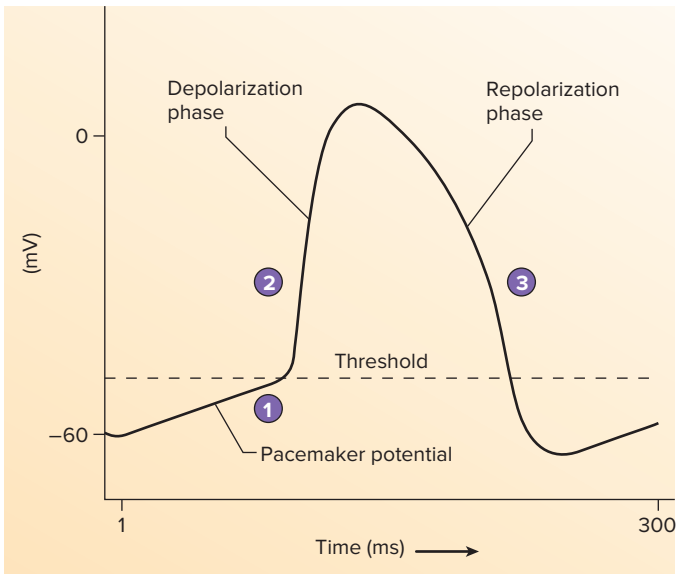
Although most cardiac muscle cells respond to action potentials produced by the SA node, some cardiac muscle cells in the conducting system can also generate spontaneous action potentials. Normally, the SA node controls the rhythm of the heart because its pacemaker cells generate action potentials at a faster rate than other potential pacemaker cells. The SA node produces a heart rate of 70–80 beats per minute (bpm). In some conditions, another area of the conducting system may generate a heartbeat. An **ectopic focus** (ek-top′ik fō′kŭs; pl. *foci*, fō′sī) is any part of the heart other than the SA node that generates a heartbeat. For example, if the SA node does not function properly, the part of the heart that can produce action potentials at the next highest frequency is the AV node, which produces a heart rate of 40–60 bpm. Another cause of an ectopic focus is blockage of the conducting pathways between the SA node and other parts of the heart. For example, if action

Permeability changes in pacemaker cells

1 Pacemaker potential
- A small number of Na^+ channels are open.
- Voltage-gated K^+ channels that opened in the repolarization phase of the previous action potential are closing.
- Voltage-gated Ca^{2+} channels begin to open.

2 Depolarization phase
- Voltage-gated Ca^{2+} channels are open.
- Voltage-gated K^+ channels are closed.

3 Repolarization phase
- Voltage-gated Ca^{2+} channels close.
- Voltage-gated K^+ channels open.



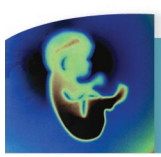
PROCESS FIGURE 20.15 Pacemaker Potential

The production of action potentials by the pacemaker cells of the SA node is responsible for the autorhythmicity of the heart.

? *When studying action potentials, it is important to recognize not only the major ions involved but also the direction those ions move across the membrane. When the appropriate ion channel is open, which ion(s) is(are) moving into the cell and which ion(s) is(are) moving out the cell?*

potentials do not pass through the AV node, an ectopic focus can develop in an AV bundle, resulting in a heart rate of only 30 bpm.

Ectopic foci can also appear when the rate of action potential generation in cardiac muscle cells outside the SA node becomes enhanced. For example, when cells are injured, their plasma membranes become more permeable, resulting in depolarization. Inflammation or lack of adequate blood flow to cardiac muscle tissue can injure cardiac muscle cells. These injured cells can be the source of ectopic action potentials. Also, alterations in blood levels of K^+ and Ca^{2+} can change the cardiac muscle membrane potential, and certain drugs, such as those that mimic the effect of epinephrine on the heart, can alter cardiac muscle membrane permeability. Changes in cardiac muscle cells' membrane potentials or permeability can produce ectopic foci.



Clinical IMPACT 20.3

Drugs That Block Calcium Channels

Various chemical agents, such as nifedipine and verapamil (ver-ap′ă-mil), block voltage-gated Ca^{2+} channels. Voltage-gated Ca^{2+} channel–blocking agents prevent the movement of Ca^{2+} through voltage-gated Ca^{2+} channels into the cell; for that reason, they are called **calcium channel blockers.** Some calcium channel blockers are widely used to treat various cardiac disorders, including tachycardia and certain arrhythmias (table 20.1). Calcium channel blockers slow the development of the pacemaker potential and thus reduce the heart rate. If action potentials arise prematurely within the SA node or other areas of the heart, calcium channel blockers reduce that tendency. Calcium channel blockers also reduce the amount of work performed by the heart because less Ca^{2+} enters cardiac muscle cells to activate the contractile mechanism. On the other hand, epinephrine and norepinephrine increase the heart rate and its force of contraction by opening voltage-gated Ca^{2+} channels.

Refractory Periods of Cardiac Muscle

Cardiac muscle, like skeletal muscle, has **refractory** (rē-frak′tōr-ē) **periods** associated with its action potentials. The refractory period can be subdivided into the absolute refractory period and the relative refractory period. During the **absolute refractory period,** the cardiac muscle cell is completely insensitive to further stimulation. During the **relative refractory period,** the cell is sensitive to stimulation, but a greater stimulation than normal is required to cause an action potential. Because the plateau phase of the action potential in cardiac muscle delays repolarization to the resting membrane potential, the refractory period is prolonged. The long refractory period ensures that contraction and most of relaxation are complete before another action potential can be initiated (see figure 20.14*b, step 4*). This prevents tetanic contractions in cardiac muscle and is responsible for rhythmic contractions.

Predict 3

Predict the consequences if cardiac muscle could undergo tetanic contraction.

TABLE 20.1 **Major Cardiac Arrhythmias**

Conditions	Symptoms	Possible Causes
Abnormal Heart Rhythms		
Tachycardia	Heart rate in excess of 100 beats per minute (bpm)	Elevated body temperature; excessive sympathetic stimulation; toxic conditions
Paroxysmal atrial tachycardia	Sudden increase in heart rate to 95–150 bpm for a few seconds or even for several hours; P wave precedes every QRS complex; P wave inverted and superimposed on T wave	Excessive sympathetic stimulation; abnormally elevated permeability of slow channels
Ventricular tachycardia	Frequently causes fibrillation	Often associated with damage to AV node or ventricular muscle
Abnormal Rhythms Resulting from Ectopic Action Potentials		
Atrial flutter	300 P waves/min; 125 QRS complexes/min, resulting in two or three P waves (atrial contraction) for every QRS complex (ventricular contraction)	Ectopic action potentials in the atria
Atrial fibrillation	No P waves; normal QRS complexes; irregular timing; ventricles constantly stimulated by atria; reduced pumping effectiveness and filling time	Ectopic action potentials in the atria
Ventricular fibrillation	No QRS complexes; no rhythmic contraction of the myocardium; many patches of asynchronously contracting ventricular muscle	Ectopic action potentials in the ventricles
Bradycardia	Heart rate less than 60 bpm	Elevated stroke volume in athletes; excessive vagal stimulation; carotid sinus syndrome
Sinus Arrhythmia	Heart rate varies 5% during respiratory cycle and up to 30% during deep respiration	Cause not always known; occasionally caused by ischemia or inflammation or associated with cardiac failure
SA Node Block	Cessation of P wave; new low heart rate due to AV node acting as pacemaker; normal QRS complex and T wave	Ischemia; tissue damage due to infarction; causes unknown
AV Node Block		
First-degree	PR interval greater than 0.2 second	Inflammation of AV bundle
Second-degree	PR interval 0.25–0.45 second; some P waves trigger QRS complexes and others do not; 2:1, 3:1, and 3:2 P wave/QRS complex ratios may occur	Excessive vagal stimulation
Third-degree (complete heart block)	P wave dissociated from QRS complex; atrial rhythm approximately 100 bpm; ventricular rhythm less than 40 bpm	Ischemia of AV nodal fibers or compression of AV bundle
Premature Atrial Contractions	Occasional shortened intervals between contractions; frequently occurs in healthy people P wave superimposed on QRS complex	Excessive smoking; lack of sleep; too much caffeine; alcoholism
Premature Ventricular Contractions (PVCs)	Prolonged QRS complex; exaggerated voltage because only one ventricle may depolarize; inverted T wave; increased probability of fibrillation	Ectopic foci in ventricles; lack of sleep; too much caffeine, irritability; occasionally occurs with coronary thrombosis

Note: SA = sinoatrial; AV = atrioventricular.

Electrocardiogram

Action potentials conducted through the myocardium during the cardiac cycle produce electrical currents that can be measured at the body surface. Electrodes placed on the body surface and attached to an appropriate recording device can detect small voltage changes resulting from action potentials in the cardiac muscle. The electrodes do not detect individual action potentials; rather, they detect a summation of all the action potentials transmitted by the cardiac muscle cells through the heart at a given time. The summated record of the cardiac action potentials is an **electrocardiogram** (**ECG** or **EKG;** figure 20.16).

The ECG is a record of the electrical activity of the heart. It, however, is not a direct measurement of mechanical events in the heart, and neither the force of contraction nor blood pressure can be determined from it. However, each deflection in the ECG record indicates an electrical event within the heart that is correlated with a subsequent mechanical event. Consequently, electrocardiography is extremely valuable in diagnosing a number of abnormal cardiac rhythms (arrhythmias; table 20.1) and other abnormalities, particularly because it is painless, easy to record, and noninvasive (does not require surgery). In addition to abnormal heart rates and rhythms, ECG analysis can reveal abnormal conduction pathways, hypertrophy or atrophy of portions of the heart, and the approximate location of damaged cardiac muscle (table 20.1).

Figure 20.16 represents a typical ECG tracing of a single heartbeat. The normal ECG consists of a P wave, a QRS complex, and a

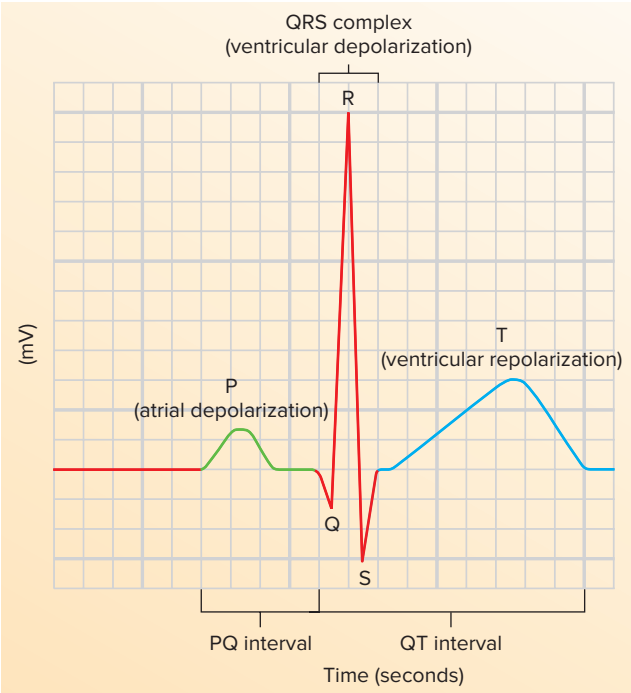


FIGURE 20.16 Electrocardiogram
The major waves and intervals of an electrocardiogram. Each thin, horizontal line on the ECG recording represents 1 mV, and each thin, vertical line represents 0.04 second.

T wave, each representing important electrical changes of the myocardium of the heart (figure 20.16).

- The **P wave,** which is the result of action potentials that cause depolarization of the atrial myocardium, signals the onset of atrial contraction.
- The **QRS complex,** composed of three individual waves—the Q, R, and S waves—results from ventricular depolarization and signals the onset of ventricular contraction.
- The **T wave** represents repolarization of the ventricles and precedes ventricular relaxation. A wave representing repolarization of the atria cannot be seen because it occurs during the QRS complex.

In addition to the different waves that can be detected on an ECG, time intervals can also be determined. The time between the beginning of the P wave and the beginning of the QRS complex is the **PQ interval,** commonly called the **PR interval** because the Q wave is often very small. During the PR interval, which lasts approximately 0.16 second, the atria contract and begin to relax. The ventricles begin to depolarize at the end of the PR interval. The **QT interval** extends from the beginning of the QRS complex to the end of the T wave, lasting approximately 0.36 second. The QT interval represents the approximate length of time required for the ventricles to contract and begin to relax.

Elongation of the PR interval can result from three events: (1) a delay in action potential conduction through the atrial muscle because of damage, such as that caused by **ischemia** (is-kē′mē-ă), which is obstruction of the blood supply to the walls of the heart; (2) a delay in action potential conduction through atrial muscle because of a dilated atrium; or (3) a delay in action potential conduction through the AV node and bundle because of ischemia, compression, or necrosis of the AV node or bundle. These conditions result in slow conduction of action potentials through the bundle branches. An unusually long QT interval reflects the abnormal conduction of action potentials through the ventricles, which can result from myocardial infarctions or from an abnormally enlarged left or right ventricle.

MICROBES In Your Body 20.1 How Bacteria Affect Cardiac Muscle

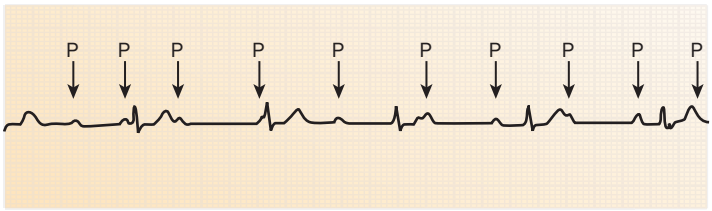
You've learned that the majority of bacteria are either harmless or an integral part of our well-being. Unfortunately, there are a handful of pathogenic bacteria that can interfere with the body's homeostasis.

Most people associate bacterial pneumonia with the lungs only. However, in the medical community, it is well known that pneumonia can cause serious heart problems. In fact, cardiac problems cause 70% of the deaths in individuals with other types of severe bacterial infections. Most bacterial pneumonia is caused by the bacterium *Streptococcus pneumoniae,* but until recently the mechanism by which this pathogen damages the heart had not been well understood. It seems that these bacteria induce the cells lining blood vessels to endocytose them and deposit them in cardiac muscle tissue. There, the bacteria release a toxin, called pneumolysin, which kills the cardiac muscle cells. These areas of dead cardiac muscle are called microlesions. In addition, during recovery from the infection, scars may form within the myocardium. Thus, the bacteria physically damage the heart, which interrupts the electrical signal necessary for cardiac muscle contraction. In addition, simply treating pneumonia with the traditional antibiotic, ampicillin, may actually worsen damage to the heart. Ampicillin causes the bacterial cell walls to burst, which releases a surge of pneumolysin, creating even more microlesions. Use of an antibiotic that does not destroy the bacterial cell walls will help reduce cardiac muscle death. Further, a vaccine against the bacterial molecule that induces the bacterial transport and against pneumolysin has shown great promise in minimizing the tissue damage caused by these bacteria.

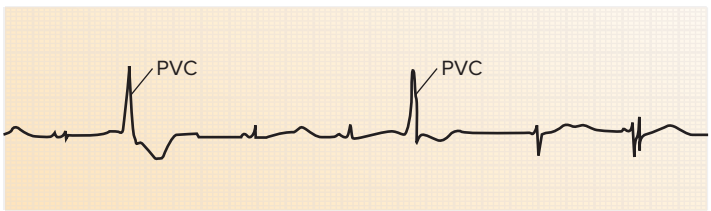
Although pathogenic bacteria exist, modern medicine continues to make great strides to reduce their damaging effects on our bodies. In addition, the more we learn about our microbiome, the more effectively we may be able to prevent bacterial infections from occurring in the first place.

Predict 4

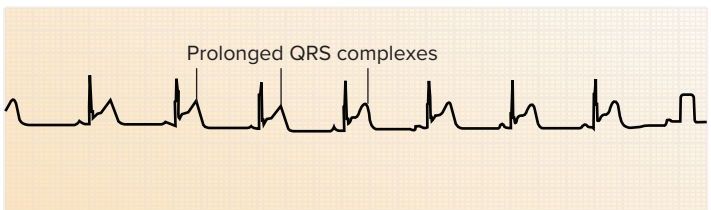
Given that *Streptococcus pneumoniae* microlesions interrupt the electrical activity that flows between cardiac muscle cells, the heart can experience severe stress and may malfunction or stop contracting altogether. Using what you learned about skeletal muscle contraction, would microlesions in skeletal muscle cause the same type of reaction as in cardiac muscle?



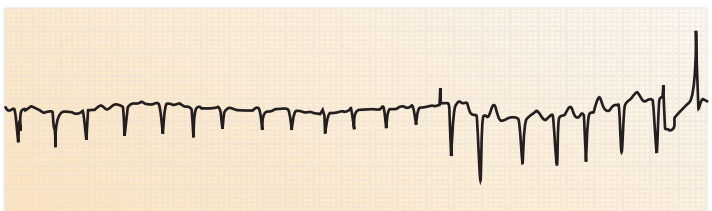
Complete heart block (P waves and QRS complexes are not coordinated)



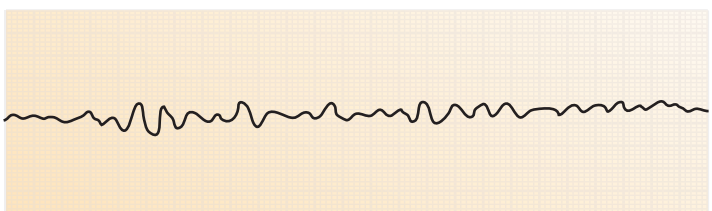
Premature ventricular contraction (PVC) (no P waves precede PVCs)



Bundle branch block



Atrial fibrillation (no clear P waves and rapid QRS complexes)



Ventricular fibrillation (no P, QRS, or T waves)

FIGURE 20.17 Alterations in an Electrocardiogram
Abnormal conduction of action potentials through the conducting system and the myocardium leads to alterations of patterns of an ECG.

Altered forms of the electrocardiogram due to cardiac abnormalities include complete heart block, premature ventricular contraction, bundle branch block, atrial fibrillation, and ventricular fibrillation (figure 20.17).

ASSESS YOUR PROGRESS

23. *For cardiac muscle action potentials, describe ion movement during the depolarization, early repolarization, plateau, and final repolarization phases.*

24. *Why is cardiac muscle referred to as autorhythmic? What are ectopic foci?*

25. *How does the depolarization of pacemaker cells differ from the depolarization of other cardiac cells? What is the pacemaker potential?*

26. *How is the prolonged refractory period generated in cardiac muscle? What is the advantage of a prolonged refractory period?*

27. *What does an ECG measure? Name the waves and intervals produced by an ECG, and state what events occur during each wave and interval.*

20.7 Cardiac Cycle

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Describe the cardiac cycle and the relationship among the contraction of each of the chambers, the opening and closing of valves, the pressure in each of the chambers, the phases of the electrocardiogram, and the heart sounds.**

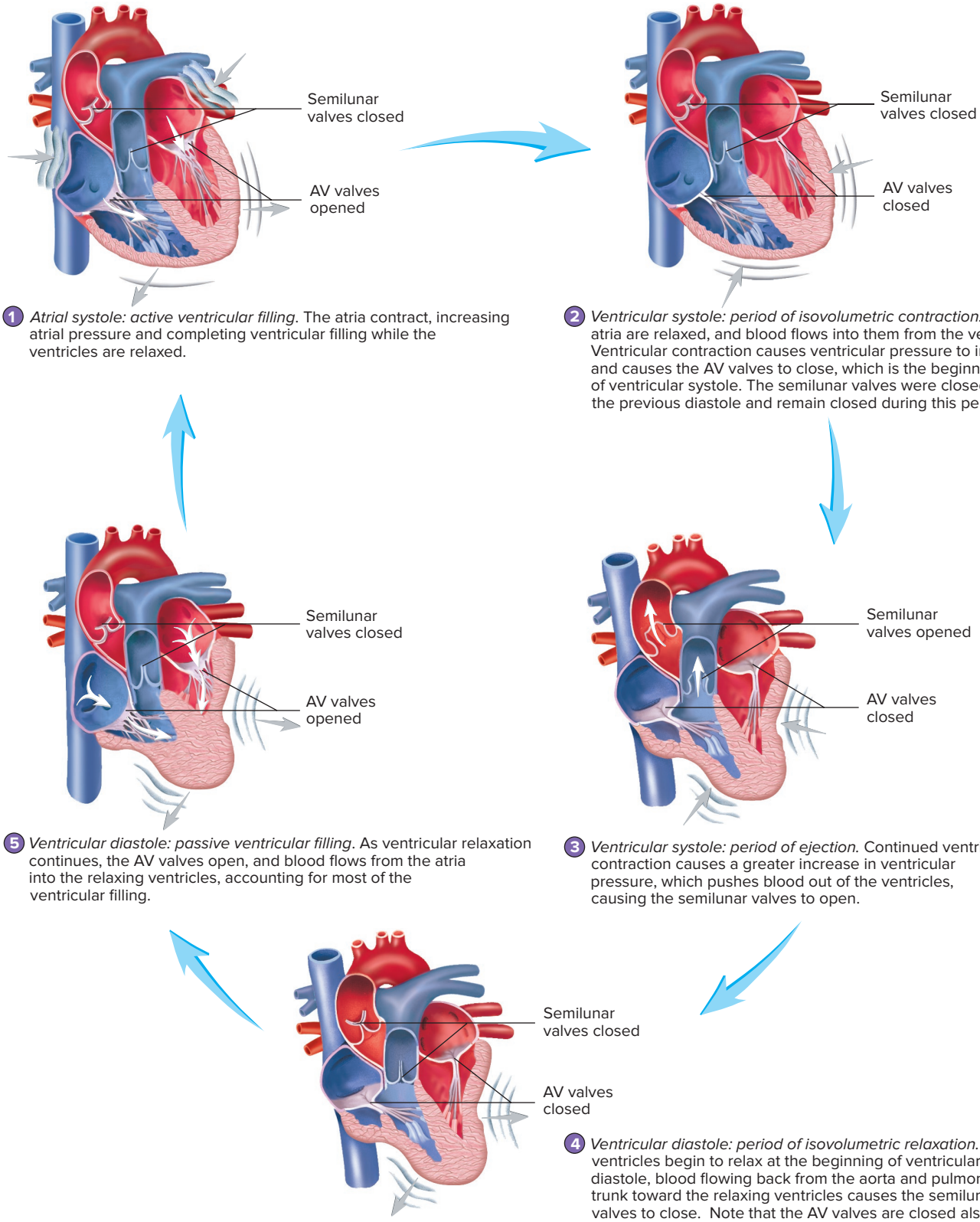
B. **Discuss the heart sounds and their significance.**

The right and left halves of the heart can be viewed as two separate pumps that work together. Each pump consists of a "primer pump" (the atrium) and a "power pump" (the ventricle). Both atrial primer pumps complete the filling of the ventricles with blood, and both ventricular power pumps produce the major force that causes blood to flow through the pulmonary and systemic arteries. The term **cardiac cycle** refers to the repetitive pumping process that begins with the onset of cardiac muscle contraction and ends with the beginning of the next contraction (figure 20.18). Blood moves from an area of higher pressure to an area of lower pressure. Pressure changes produced within the heart chambers as a result of cardiac muscle contraction and relaxation move blood along the previously described routes of the pulmonary and systemic circulations.

The duration of the cardiac cycle varies considerably among humans and during an individual's lifetime. It can be as short as 0.25–0.3 second in a newborn or as long as 1 or more seconds in a well-trained athlete. The normal cardiac cycle of 0.7–0.8 second depends on the capability of cardiac muscle to contract and on the functional integrity of the conducting system.

The cardiac cycle involves a predictable pattern of contraction and relaxation of the heart chambers. As you study the events of the cardiac cycle described in this section, keep in mind that the term **systole** (sis′tō-lē) means to contract, and **diastole** (dī-as′tō-lē) means to dilate. Therefore, **atrial systole** is contraction of the atrial myocardium, and **atrial diastole** is relaxation of the atrial myocardium. Similarly, **ventricular systole** is contraction of the ventricular myocardium, and **ventricular diastole** is relaxation of the ventricular myocardium. When the terms *systole* and *diastole* are used alone, they refer to ventricular systole and diastole.

Before we begin our discussion of the cardiac cycle, it is important to have a clear image of the state of the heart. At the



1 *Atrial systole: active ventricular filling.* The atria contract, increasing atrial pressure and completing ventricular filling while the ventricles are relaxed.

2 *Ventricular systole: period of isovolumetric contraction.* The atria are relaxed, and blood flows into them from the veins. Ventricular contraction causes ventricular pressure to increase and causes the AV valves to close, which is the beginning of ventricular systole. The semilunar valves were closed in the previous diastole and remain closed during this period.

3 *Ventricular systole: period of ejection.* Continued ventricular contraction causes a greater increase in ventricular pressure, which pushes blood out of the ventricles, causing the semilunar valves to open.

4 *Ventricular diastole: period of isovolumetric relaxation.* As the ventricles begin to relax at the beginning of ventricular diastole, blood flowing back from the aorta and pulmonary trunk toward the relaxing ventricles causes the semilunar valves to close. Note that the AV valves are closed also.

5 *Ventricular diastole: passive ventricular filling.* As ventricular relaxation continues, the AV valves open, and blood flows from the atria into the relaxing ventricles, accounting for most of the ventricular filling.

PROCESS FIGURE 20.18 Cardiac Cycle

The cardiac cycle is a repeating series of contraction and relaxation that moves blood through the heart (*AV* = atrioventricular).

? *Ventricular systole is divided into two phases: the isovolumetric (same volume) phase and the ventricular ejection phase. Explain the differences between these two phases.*

beginning of the cardiac cycle, the atria and ventricles are relaxed, the AV valves are open, and the semilunar valves are closed. During the cardiac cycle, changes in chamber pressure and the opening and closing of the heart valves determine the direction of blood movement. As the cardiac cycle is described, it is important to focus on these pressure changes and heart valve movements.

At rest, most of the blood movement into the chambers is a passive process resulting from the greater blood pressure in the veins than in the heart chambers. As the blood moves into the atria, much of it flows into the ventricles for two reasons: (1) The AV valves are open and (2) atrial pressure is slightly greater than ventricular pressure. This time period when blood is passively moving into the ventricles is called *passive ventricular filling*.

The following is a detailed description of the cardiac cycle describing the stimulation of the heart chambers, changes in pressure, and opening and closing of the heart valves:

1. The SA node generates an action potential that stimulates atrial contraction. This P wave of an ECG represents this electrical activity. Atrial contraction begins the cardiac cycle. As the atria contract, they carry out the primer pump function by forcing more blood into the ventricles. This period is referred to as *active ventricular filling* (figure 20.18, *step 1*).
2. The action potential passes to the AV node, down the AV bundle, bundle branches, and Purkinje fibers, stimulating ventricular systole. This electrical activity is represented as the QRS complex of an ECG. As the ventricles contract, ventricular pressures increase, causing blood to flow toward the atria and close the AV valves. Recall that the semilunar valves are closed at this point as well. Ventricular contraction continues and ventricular pressures rise; however, because all the valves are closed, no blood flows from the ventricles at this time. This brief interval is called the *period of isovolumetric (iso,* same*) contraction* because the volume of blood in the ventricles does not change, even though the ventricles are contracting (figure 20.18, *step 2*).
3. Ventricular contraction continues, and ventricular pressure builds until it overcomes the pressures in the pulmonary trunk and aorta. As a result, the semilunar valves are pushed open, and blood flows from the ventricles into those arteries. This time period, when blood moves from the ventricles into the arteries, is called the *period of ejection* (figure 20.18, *step 3*).
4. Ventricular repolarization, represented by the T wave of an ECG, leads to ventricular diastole. As ventricular diastole begins, the ventricles relax, and ventricular pressures decrease below the pressures in the pulmonary trunk and aorta. Consequently, blood begins to flow back toward the ventricles, causing the semilunar valves to close (figure 20.18, *step 4*). With closure of the semilunar valves, all the heart valves are closed, and no blood flows into the relaxing ventricles during the *period of isovolumetric relaxation*.
5. Atrial diastole began during ventricular systole, and as the atria relaxed, blood flowed into them from the veins. As the ventricles continue to relax, ventricular pressures drop below atrial pressures, and the AV valves open. Passive ventricular filling begins again (figure 20.18, *step 5*).

Note that once the ventricles have fully relaxed, the state of the heart is the same as when the cardiac cycle began, all chambers are relaxed, the AV valves are open, and the semilunar valves are closed. With the next stimulus from the SA node, another cardiac cycle will begin (figure 20.18, *step 1*).

Events Occurring During the Cardiac Cycle

Figure 20.19 graphs the main events of the cardiac cycle and should be examined from top to bottom:

- Panel 1: An ECG indicates the electrical events that cause contraction and relaxation of the atria and ventricles.
- Panel 2: The pressure graph shows the pressure changes within the left atrium, left ventricle, and aorta resulting from atrial and ventricular contraction and relaxation. Although pressure changes in the right side of the heart are not shown, they are similar to those in the left side, only lower.
- Panel 3: The volume graph presents the changes in left ventricular volume as blood flows into and out of the left ventricle as a result of the pressure changes.
- Panel 4: The sound graph records the closing of valves caused by blood flow.

After reviewing figure 20.19, correlate the events with the steps illustrated in figure 20.18. In the remainder of this section, we will discuss changes in blood volume and pressure in the heart chambers.

Atrial Systole and Active Ventricular Filling

Before the cardiac cycle begins, all chambers are relaxed and blood is flowing from the veins into the atria and passively into the ventricles. Most of ventricular filling occurs during this time (see figure 20.19, *panel 3*). When the atria contract, active ventricular filling occurs as the force of atrial contraction "tops off" the ventricles.

Under most conditions, the atria function primarily as reservoirs, and the ventricles can pump sufficient blood to maintain homeostasis even if the atria do not contract at all. During exercise, however, the heart pumps 300–400% more blood than during rest. As heart rate increases during exercise, atrial contraction is important for ventricular filling because less time is available for passive ventricular filling. Therefore, it is during exercise that the pumping action of the atria becomes important for maintaining the pumping efficiency of the heart.

Ventricular Systole: Period of Isovolumetric Contraction

During the previous ventricular diastole, the ventricles were filled with 120–130 mL of blood. The volume of blood in the ventricles at this point is the **end-diastolic volume (EDV).** As the ventricles begin to contract, ventricular pressure rapidly increases, resulting in closure of the AV valves. Ventricular volume does not change during the period of isovolumetric contraction because all the heart valves are closed.

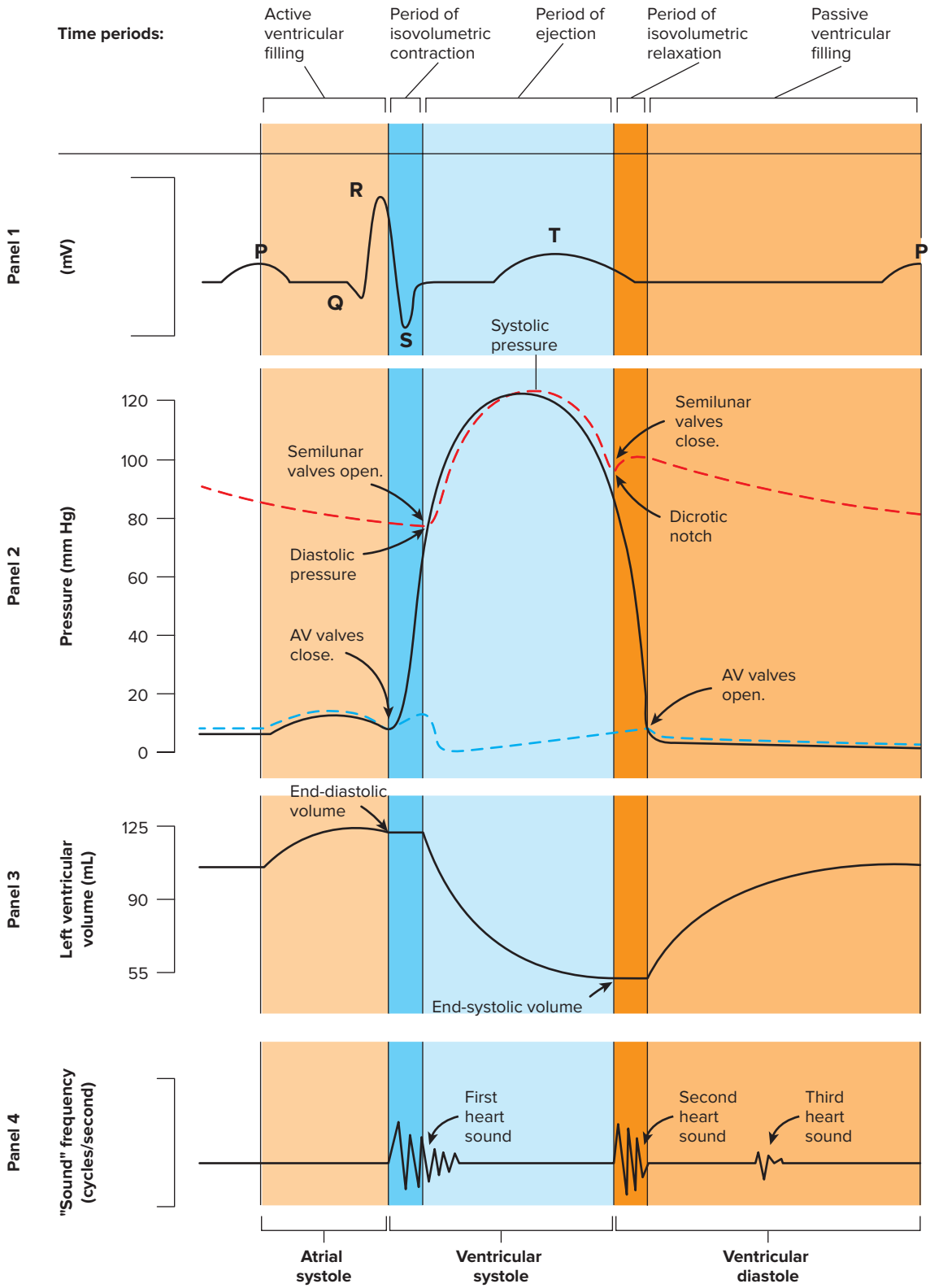


FIGURE 20.19 Events Occurring During the Cardiac Cycle

The cardiac cycle is divided into five time periods (top). This graph represents several events that occur during the cardiac cycle. Each panel represents a different aspect of cardiac function. From top to bottom: Panel 1 represents the electrocardiogram; panel 2 represents pressure changes for the left atrium (*blue line*), left ventricle (*black line*), and aorta (*red line*); panel 3 represents the left ventricular volume curve; and panel 4 represents heart sounds. AP|R

Ventricular Systole: Period of Ejection

As soon as ventricular pressures exceed the pressures in the aorta and pulmonary trunk, the semilunar valves open. The aortic semilunar valve opens at approximately 80 mm Hg ventricular pressure, whereas the pulmonary semilunar valve opens at approximately 8 mm Hg. Although the pressures are different, both valves open at nearly the same time.

As blood flows from the ventricles during the period of ejection, the left ventricular pressure continues to climb to approximately 120 mm Hg, and the right ventricular pressure increases to approximately 25 mm Hg. The larger left ventricular pressure causes blood to flow throughout the body (systemic circulation), whereas the lower right ventricular pressure causes blood to flow through the lungs (pulmonary circulation). It is important to note that even though the pressure generated by the left ventricle is much higher than that of the right ventricle, the amount of blood pumped by each is almost the same.

Predict 5

Which ventricle has the thickest wall? Why is it important for each ventricle to pump approximately the same volume of blood?

During the first part of ejection, blood flows rapidly out of the ventricles. Toward the end of ejection, ventricular pressure decreases due to reduced blood flow, despite continued ventricular contraction. By the end of ejection, the volume of blood in the ventricles has decreased to 50–60 mL. The volume of blood remaining in the ventricles at the end of ventricular systole is called the **end-systolic volume (ESV).**

Ventricular Diastole: Period of Isovolumetric Relaxation

Completion of the T wave results in ventricular repolarization and relaxation. The already decreasing ventricular pressure falls very rapidly as the ventricles suddenly relax as ventricular diastole begins. When the ventricular pressures fall below the pressures in the aorta and pulmonary trunk, the recoil of the elastic arterial walls, which were stretched during the period of ejection, forces the blood to flow back toward the ventricles, thereby closing the semilunar valves. Ventricular volume does not change during the period of isovolumetric relaxation because all the heart valves are closed at this time.

Ventricular Diastole: Passive Ventricular Filling

The relaxed atria were filling with blood during ventricular systole and the period of isovolumetric relaxation. During ventricular diastole, as ventricular pressure drops below atrial pressure, the atrioventricular valves open and allow blood to flow from the filled atria into the ventricles. At this point the atria and ventricles are relaxed. Blood flows from the area of higher pressure in the veins and atria toward the area of lower pressure in the relaxed ventricles. Remember that most ventricular filling occurs during the first one-third of ventricular diastole. At the end of passive ventricular filling, the ventricles are approximately 70% filled.

Predict 6

Fibrillation is abnormal, rapid contractions of different parts of the heart that prevent the heart muscle from contracting as a single unit. Explain why atrial fibrillation does not immediately cause death but ventricular fibrillation does.

Heart Sounds

The pumping heart produces distinct sounds, as revealed by using a stethoscope (figure 20.19, *panel 4*). These sounds are best heard by applying the stethoscope at particular sites in relation to the heart valves (figure 20.20). The **first heart sound** is a low-pitched sound, often described as "lubb." It occurs at the beginning of ventricular systole and is caused by vibration of the atrioventricular valves and surrounding fluid as the valves close. The **second heart sound** is a higher-pitched sound often described as "dupp." It occurs at the beginning of ventricular diastole and results from closure of the aortic and pulmonary semilunar valves. Systole is therefore approximately the time between the first and second heart sounds. Diastole, which lasts somewhat longer, is approximately the time between the second heart sound and the next first heart sound.

A faint **third heart sound** can be heard in some normal people, particularly those who are thin and young. It is caused by blood flowing in a turbulent fashion into the ventricles, and it can be detected near the end of the first one-third of diastole, during passive ventricular filling.

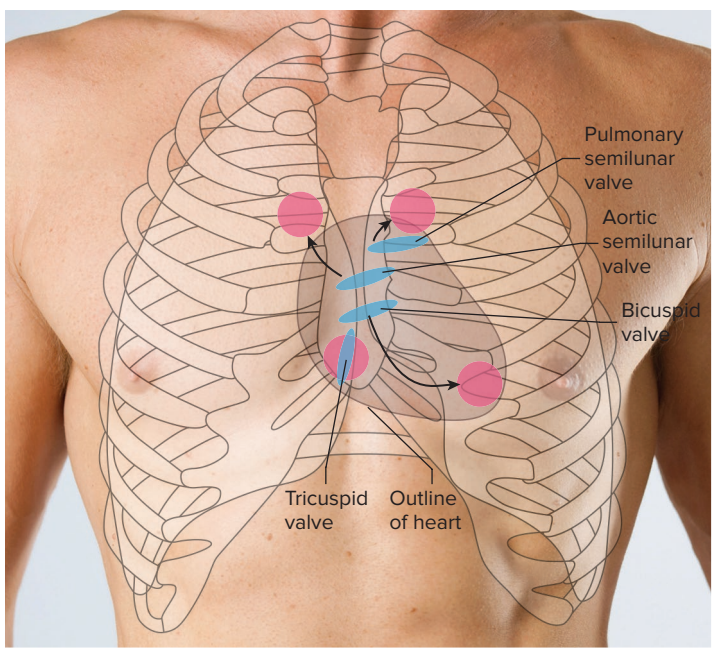
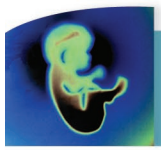


FIGURE 20.20 Location of the Heart Valves in the Thorax
Surface markings of the heart in the male. The positions of the four heart valves are indicated by *blue ellipses,* and the sites where the sounds of the valves are best heard with the stethoscope are indicated by *pink circles*.



Clinical IMPACT 20.4 Abnormal Heart Sounds

Heart sounds provide important information about the normal function of the heart and help clinicians diagnose cardiac abnormalities. Abnormal heart sounds are called **murmurs** (mer′merz), and certain murmurs are important indicators of specific cardiac abnormalities (table 20.2). For example, an **incompetent valve** (also called a valvular insufficiency) leaks significantly. After an incompetent valve closes, blood flows through it but in a reverse direction, called regurgitation. Regurgitation results in turbulence, which causes a gurgling or swishing sound immediately after the valve closes. An incompetent tricuspid valve or bicuspid valve makes a swish sound immediately after the first heart sound, and the first heart sound may be muffled. An incompetent aortic or pulmonary semilunar valve results in a swish sound immediately after the second heart sound.

Stenosed (sten′ōzd) **valves** have an abnormally narrow opening and produce abnormal heart sounds. Blood flows through stenosed valves very turbulently and produces a rushing sound before the valve closes. For example, a stenosed atrioventricular valve produces a rushing sound immediately before the first heart sound, and a stenosed semilunar valve produces a rushing sound immediately before the second heart sound.

Inflammation of the heart valves, resulting from a condition such as rheumatic fever, can cause valves to become either incompetent or stenosed. In addition, myocardial infarctions that make papillary muscles nonfunctional can cause bicuspid or tricuspid valves to be incompetent. Heart murmurs also result from congenital abnormalities in the hearts of infants. Two examples are septal defects in the heart and patent ductus arteriosus (see chapter 29).

Either incompetent or stenosed valves increase the amount of work the cardiac muscle must perform. Consequently, these conditions can lead to heart failure.

Aortic Pressure Curve

The elastic walls of the aorta are stretched as blood is ejected into the aorta from the left ventricle. Aortic pressure remains slightly below ventricular pressure during this period of ejection. Recall that as blood leaves the ventricles, the pressure in the ventricles begins to decrease, even as the ventricles continue to contract. Similarly, pressure within the aorta decreases as well (see figure 20.19, *panel 2*). As ventricular pressure drops below that in the aorta, blood flows back toward the ventricle because of the elastic recoil of the aorta. As the blood flows back toward the left ventricle, the aortic semilunar valve closes. Pressure within the aorta rises slightly at this point. This sudden change in aortic pressure results in a **dicrotic** (dī-krot′ik) **notch,** or *incisura* (in′sī-soo′ră; a cutting into) in the aortic pressure curve. The term *dicrotic* means "double-beating"; when increased pressure caused by recoil is large, a double pulse can be felt. Aortic pressure then gradually falls throughout the rest of ventricular diastole as blood flows through the peripheral vessels. When aortic pressure has fallen to approximately 80 mm Hg, the ventricles again contract, forcing blood once more into the aorta.

Many of us have had our blood pressure measured during a medical exam. Blood pressure measurements performed for clinical purposes reflect the pressure changes that occur in the aorta rather than in the left ventricle (see chapter 21). The blood pressure in the aorta fluctuates between systolic pressure, which is about 120 mm Hg, and diastolic pressure, which is about 80 mm Hg, for the average young adult at rest.

Predict 7

Predict the pressure changes that occur in the aorta, the left ventricle, and the left atrium after the second heart sound and before the first heart sound of the next cardiac cycle.

ASSESS YOUR PROGRESS

28. *Define* systole *and* diastole.

29. *List the five periods of the cardiac cycle (see figures 20.18 and 20.19). State whether the AV and semilunar valves are open or closed during each period and the phase of the electrocardiogram for each period.*

30. *Define* isovolumetric. *When does most ventricular filling occur?*

31. *Differentiate between end-diastolic volume and end-systolic volume.*

32. *What produces the first and the second heart sounds?*

33. *Explain the production of the following in the aorta: systolic pressure, diastolic pressure, and the dicrotic notch (incisura).*

20.8 Mean Arterial Blood Pressure

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Define *mean arterial pressure, cardiac output,* and *peripheral resistance.***

B. **Explain the role of MAP in causing blood flow.**

Blood pressure is necessary to move the blood and therefore is critical to the maintenance of homeostasis. Recall that blood flows from areas of higher pressure to areas of lower pressure. For example, during one cardiac cycle, blood flows from the higher pressure in the aorta, resulting from contraction of the left ventricle, through the systemic circulation, toward the lower pressure in the relaxed right atrium.

Mean arterial pressure (MAP) is slightly less than the average of the systolic and diastolic pressures in the aorta. It is proportional to cardiac output times peripheral resistance. **Cardiac output (CO),** or *minute volume,* is the amount of blood pumped by the heart per minute, and **peripheral resistance (PR)** is the total resistance against which blood must be pumped:

$$MAP = CO \times PR$$

Because mean arterial pressure is determined by both cardiac output and peripheral resistance, changes to either can alter mean arterial pressure (figure 20.21). Cardiac output is discussed in this chapter, and peripheral resistance is explained in chapter 21.

Cardiac output is equal to heart rate times stroke volume. **Heart rate (HR)** is the number of times the heart beats (contracts) per minute. **Stroke volume (SV)** is the volume of blood pumped during each heartbeat (cardiac cycle). If we consider the volumes of blood described in the cardiac cycle discussion, stroke volume is equal to end-diastolic volume minus end-systolic volume. During diastole, blood flows from the atria into the ventricles, and end-diastolic volume normally increases to approximately 125 mL. After the ventricles partially empty during systole, end-systolic volume decreases to approximately 55 mL. Because stroke volume is equal to end-diastolic volume minus end-systolic volume, we can predict that stroke volume is equal to 70 mL (125 − 55).

To better understand stroke volume, imagine that you are squeezing a sponge under a running water faucet. As you relax your fingers, the sponge fills with water; as you contract your fingers, the sponge releases water. Even after you have squeezed the sponge, some water remains in it. In this analogy, the amount of water you squeeze out of the sponge (stroke volume) is the difference between the amount of water in the sponge when your hand is relaxed (end-diastolic volume) and the amount left in the sponge after you squeeze it (end-systolic volume).

Stroke volume can be increased by increasing end-diastolic volume or by decreasing end-systolic volume (figure 20.21). During exercise, end-diastolic volume increases because of an increase in **venous return,** which is the amount of blood returning to the heart from the systemic circulation. End-systolic volume decreases because the heart contracts more forcefully. For example, stroke volume can increase from a resting value of 70 mL to an exercising value of 115 mL by increasing end-diastolic volume to 145 mL and decreasing end-systolic volume to 30 mL.

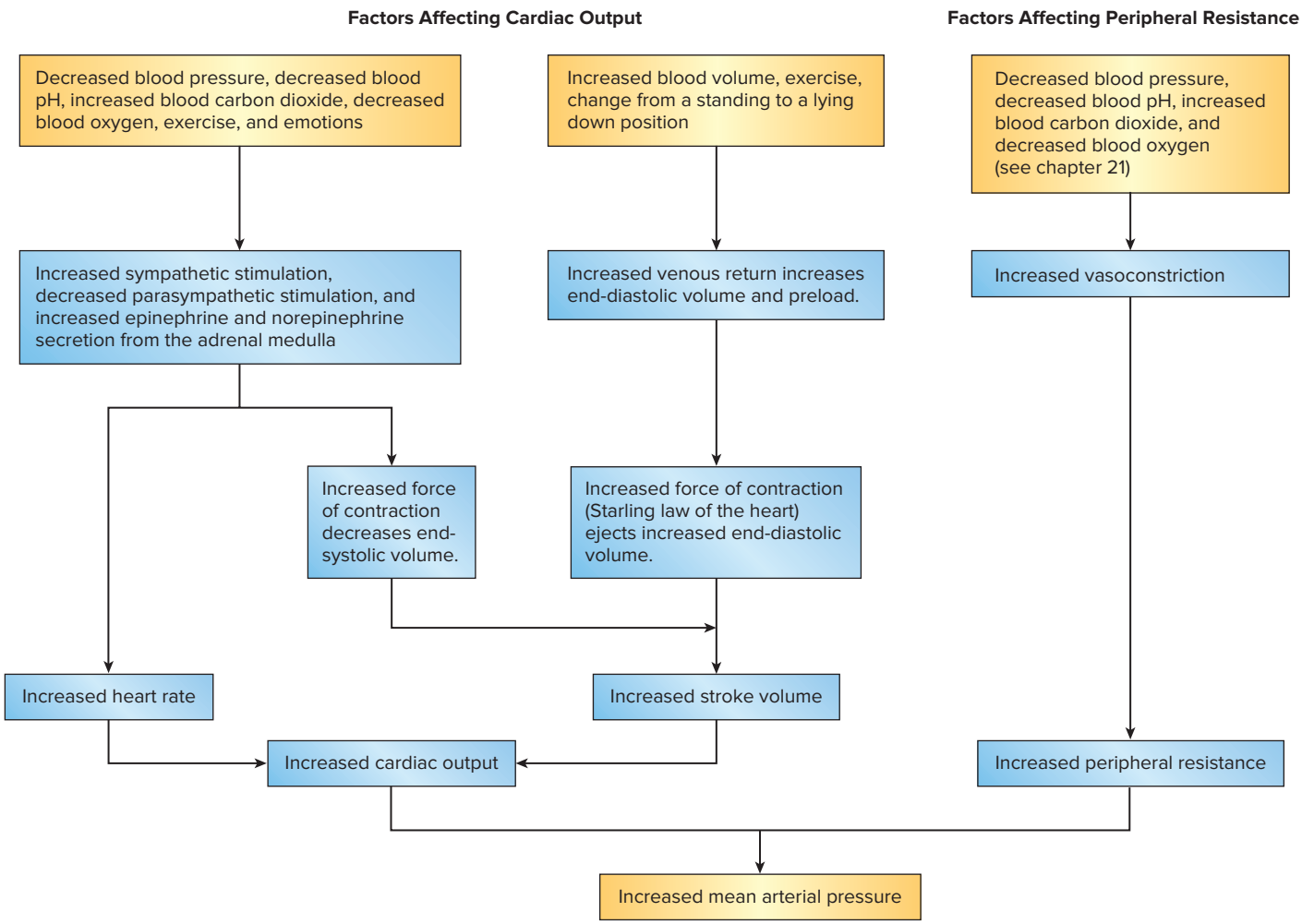


FIGURE 20.21 Factors Affecting Mean Arterial Pressure
Mean arterial pressure is regulated by controlling cardiac output and peripheral resistance.

Cardiac output is also influenced by heart rate (CO = HR × SV). Under resting conditions, the heart rate is approximately 72 bpm, and the stroke volume is approximately 70 mL/beat, although these values can vary considerably from person to person. Therefore, the cardiac output is

$$\begin{aligned} CO &= HR \times SV \\ &= 72 \text{ bpm} \times 70 \text{ mL/beat} \\ &= 5040 \text{ mL/min (approximately 5 L/min)} \end{aligned}$$

Changes in heart rate and stroke volume will result in changes in cardiac output. For example, during exercise, the heart rate can increase to 190 bpm, and the stroke volume can increase to 115 mL. Consequently, cardiac output is

$$\begin{aligned} CO &= 190 \text{ bpm} \times 115 \text{ mL/beat} \\ &= 21{,}850 \text{ mL/min (approximately 22 L/min)} \end{aligned}$$

Cardiac reserve is the difference between cardiac output when a person is at rest and maximum cardiac output. The greater a person's cardiac reserve, the greater his or her capacity for doing exercise. Cardiovascular disease and lack of exercise can reduce cardiac reserve and affect a person's quality of life. Exercise can greatly increase cardiac reserve by increasing cardiac output. In well-trained athletes, stroke volume during exercise can increase to over 200 mL/beat, resulting in cardiac outputs of 40 L/min or more.

ASSESS YOUR PROGRESS

34. *Explain the relationship among mean arterial pressure, cardiac output, and peripheral resistance. Define each.*

35. *Explain the role of MAP in causing blood flow.*

36. *What is stroke volume, and what are two ways to increase it?*

37. *What is cardiac reserve? How can exercise influence cardiac reserve?*

20.9 Regulation of the Heart

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Describe intrinsic regulation of the heart.**

B. **Relate the three types of extrinsic regulation of the heart and their effects.**

To maintain homeostasis, the amount of blood pumped by the heart must vary dramatically, depending on the level of activity and the O_2 and nutrient needs of the body tissues. For example, during exercise, cardiac output can increase several times over resting values to meet the needs of the active tissues. Intrinsic and extrinsic regulatory mechanisms control cardiac output. **Intrinsic regulation** results from the heart's normal functional characteristics and does not depend on either neural or hormonal regulation. It functions whether the heart is in place in the body or is removed and maintained outside the body under proper conditions. **Extrinsic regulation** involves neural and hormonal control. Neural regulation of the heart results from sympathetic and parasympathetic reflexes, and the major hormonal regulation comes from epinephrine and norepinephrine secreted by the adrenal medulla.

Intrinsic Regulation

The force of contraction produced by cardiac muscle is related to the degree of stretch of the cardiac muscle cells. As venous return increases, end-diastolic volume increases (figure 20.21). A greater end-diastolic volume increases the stretch of the ventricular walls. It is easy to visualize this by thinking of a balloon filling with water. As the volume of water increases in the balloon, the balloon is stretched more and more. The extent to which the ventricular walls are stretched is sometimes called the **preload.** An increased preload increases cardiac output, and a decreased preload decreases cardiac output.

The length-versus-tension relationship in cardiac muscle is similar to that in skeletal muscle. Skeletal muscle, however, is normally stretched to nearly its optimal length before contraction, whereas cardiac muscle cells are not stretched to the point at which they contract with a maximal force (see chapter 9). Thus, an increased preload causes the cardiac muscle cells to contract with a greater force and produce a greater stroke volume. This relationship between preload and stroke volume is commonly referred to as the **Starling law of the heart,** and it describes the relationship between changes in the pumping effectiveness of the heart and changes in preload (figure 20.21). Preload, or ventricular stretching, is directly related to venous return (remember our water balloon analogy). Venous return can decrease to a value as low as 2 L/min or increase to as much as 24 L/min. Such drastic changes in venous return have major effects on the preload.

Afterload is the pressure the contracting left ventricle must produce to overcome the pressure in the aorta and move blood into the aorta. Afterload can be related to the amount of force necessary to open a door. As the ventricles contract, pressure increases, eventually forcing open the semilunar valves. Although the heart's pumping effectiveness is greatly influenced by relatively small changes in the preload, it is very insensitive to large changes in afterload. Aortic blood pressure must increase to more than 170 mm Hg before it hampers the ventricles' ability to pump blood.

It is interesting to note that during exercise, skeletal muscle activity greatly influences heart activity by altering venous return and preload. During exercise, blood vessels in exercising skeletal muscles dilate and allow more blood to flow through the vessels. The increased blood flow increases O_2 and nutrient delivery to the exercising muscles. In addition, skeletal muscle contractions repeatedly compress veins and cause blood to flow more rapidly from the skeletal muscles toward the heart. As blood flows rapidly through skeletal muscles and back to the heart, venous return to the heart increases, increasing the preload. The increased preload causes an increased force of cardiac muscle contraction, which increases stroke volume. The increase in stroke volume results in increased cardiac output, and the volume of blood flowing to the exercising muscles increases. When a person rests, venous return to the heart decreases because arteries in the skeletal muscles constrict and because muscular contractions no longer repeatedly

compress the veins. As a result, blood flow through skeletal muscles decreases, and preload and cardiac output decrease.

Extrinsic Regulation

The heart is innervated by both **parasympathetic** and **sympathetic** nerve fibers (see figure 16.5). They influence the pumping action of the heart by affecting both heart rate and stroke volume. However, the influence of parasympathetic stimulation on the heart is much less than that of sympathetic stimulation. Sympathetic stimulation can increase cardiac output by 50–100% over resting values, whereas parasympathetic stimulation can cause only a 10–20% decrease.

Extrinsic regulation of the heart keeps blood pressure, blood O_2 levels, blood CO_2 levels, and blood pH within their normal ranges of values. For example, if blood pressure suddenly decreases, extrinsic mechanisms detect the decrease and initiate responses that increase cardiac output to bring blood pressure back into its normal range.

Parasympathetic Control

Parasympathetic nerve fibers that innervate the heart are in the **vagus nerves.** Preganglionic fibers of the vagus nerve extend from the brainstem to terminal ganglia within the wall of the heart, and postganglionic fibers extend from the ganglia to the SA node, AV node, coronary blood vessels, and atrial myocardium.

Parasympathetic stimulation has an inhibitory influence on the heart, primarily by decreasing the heart rate. When a person is at rest, continuous parasympathetic stimulation inhibits the heart to some degree. An increase in heart rate during exercise results, in part, from decreased parasympathetic stimulation. Strong parasympathetic stimulation can decrease the heart rate below resting levels by at least 20–30 bpm, but it has little effect on stroke volume. In fact, if venous return remains constant while the heart is inhibited by parasympathetic stimulation, stroke volume can actually increase. The longer time between heartbeats allows the heart to fill to a greater capacity, resulting in an increased preload, which in turn increases stroke volume.

Acetylcholine, the neurotransmitter produced by postganglionic parasympathetic neurons, binds to ligand-gated channels that cause plasma membranes of cardiac muscle cells to become more permeable to K^+. As a consequence, the membrane hyperpolarizes. Heart rate decreases because the hyperpolarized membrane takes longer to depolarize to the point of an action potential.

Sympathetic Control

Sympathetic innervation of the heart begins with preganglionic neurons that originate in the thoracic region of the spinal cord. These neurons synapse with postganglionic neurons of the inferior **cervical** and upper **thoracic sympathetic chain ganglia,** which project to the heart as **cardiac nerves** (figure 20.22; see chapter 16). The postganglionic sympathetic neurons innervate the SA and AV nodes, the coronary blood vessels, and the atrial and ventricular myocardia.

Sympathetic stimulation increases both the heart rate and the force of muscular contraction. In response to strong sympathetic stimulation, the heart rate can increase to 250 or, occasionally, 300 bpm. Stronger contractions can also increase stroke volume. The increased force of contraction resulting from sympathetic stimulation causes a lower end-systolic volume in the heart; therefore, the heart empties to a greater extent (see figure 20.21).

Predict 8

What effect does sympathetic stimulation have on stroke volume if the venous return remains constant? Dilation of the coronary blood vessels occurs in response to an increased heart rate and stroke volume. Explain the functional advantage of that effect.

The relationship between increased heart rate and cardiac output is limited. If the heart rate becomes too fast, ventricular diastole does not last long enough to allow complete ventricular filling, end-diastolic volume decreases, and stroke volume actually decreases. In addition, if the heart rate increases beyond a critical level, the strength of contraction decreases, probably because metabolites accumulate in cardiac muscle cells. The heart's ability to increase the cardiac output is limited to heart rates of 170–250 bpm in response to intense sympathetic stimulation.

Sympathetic stimulation of the ventricular myocardium plays a significant role in regulating its contraction force when a person is at rest. Sympathetic stimulation maintains the strength of ventricular contraction at a level approximately 20% greater than it would be without sympathetic stimulation.

Norepinephrine, the postganglionic sympathetic neurotransmitter, increases the rate and degree of cardiac muscle depolarization, so that the frequency of the action potentials increases. The effect of norepinephrine on the heart involves its association with cell surface β-adrenergic receptors. This combination causes a G protein–mediated synthesis and accumulation of cAMP in the cytoplasm of cardiac muscle cells. Cyclic-AMP increases the permeability of the plasma membrane to Ca^{2+}, primarily by opening calcium channels in the plasma membrane.

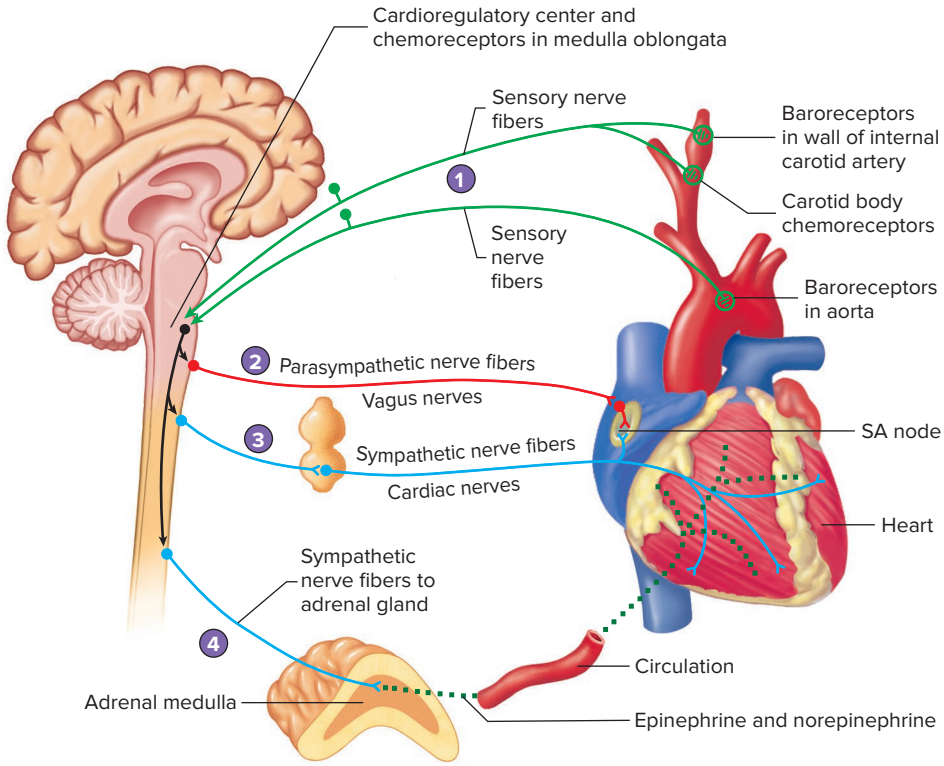
Increased sympathetic stimulation causes coronary arteries to constrict to some degree. However, increased metabolism of cardiac muscle, in response to sympathetic stimulation, allows metabolic by-products to accumulate in cardiac muscle, which causes coronary blood vessels to dilate. The dilation effect of these metabolites predominates (see chapter 21).

Hormonal Control

Epinephrine and norepinephrine released from the adrenal medulla can markedly influence the heart's pumping effectiveness. Epinephrine has essentially the same effect on cardiac muscle as norepinephrine, increasing the rate and force of heart contractions (see figure 20.21).

The secretion of epinephrine and norepinephrine is controlled by sympathetic stimulation of the adrenal medulla; it occurs in response to increased physical activity, emotional excitement, or other stressful conditions. Many stimuli that increase sympathetic stimulation of the heart also increase the release of epinephrine and norepinephrine from the adrenal medulla (see chapter 18). Epinephrine and norepinephrine travel in the blood through the vessels

1. Sensory neurons (*green*) carry action potentials from baroreceptors and carotid body chemoreceptors to the cardioregulatory center. Chemoreceptors in the medulla oblongata also influence the cardioregulatory center.
2. The cardioregulatory center controls the frequency of action potentials in the parasympathetic neurons (*red*) extending to the heart through the vagus nerves. The parasympathetic neurons decrease the heart rate.
3. The cardioregulatory center controls the frequency of action potentials in the sympathetic neurons (*blue*). The sympathetic neurons extend through the cardiac nerves and increase the heart rate and the stroke volume.
4. The cardioregulatory center influences the frequency of action potentials in the sympathetic neurons (*blue*) extending to the adrenal medulla. The sympathetic neurons increase the secretion of epinephrine and some norepinephrine into the systemic circulation. Epinephrine and norepinephrine (*dotted green line*) increase the heart rate and stroke volume.



PROCESS FIGURE 20.22 Baroreceptor and Chemoreceptor Reflexes

Reflexes in response to changes in blood pressure, pH, blood O_2, and blood CO_2 levels help regulate the activity of the heart to maintain homeostasis. Sensory neurons (*green*) carry action potentials from sensory receptors to the medulla oblongata. Sympathetic (*blue*) and parasympathetic (*red*) neurons exit the spinal cord or medulla oblongata and extend to the heart to regulate its function. Epinephrine and norepinephrine (*dotted green line*) from the adrenal gland also help regulate the heart's action (*SA* = sinoatrial). AP|R

? *Cardiac muscle is described as being under involuntary control. Why is it that some individuals can seemingly "control" their heart rate through meditation?*

of the heart to the cardiac muscle cells, where they bind to β-adrenergic receptors and stimulate cAMP synthesis. Epinephrine takes a longer time to act on the heart than sympathetic stimulation does, but the effect lasts longer.

ASSESS YOUR PROGRESS

38. *What is venous return? Explain how it affects preload. How does preload affect cardiac output? State the Starling law of the heart.*

39. *Define* afterload, *and describe its effect on the pumping effectiveness of the heart.*

40. *What part of the brain regulates the heart? Describe the autonomic nerve supply to the heart.*

41. *What effects do parasympathetic stimulation and sympathetic stimulation have on heart rate, force of contraction, and stroke volume?*

42. *What neurotransmitters are released by the parasympathetic and sympathetic postganglionic neurons of the heart? What effects do they have on membrane permeability and excitability?*

43. *Name the two main hormones that affect the heart. Where are they produced, what causes their release, and what effects do they have on the heart?*

20.10 The Heart and Homeostasis

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Describe how changes in blood pressure, pH, carbon dioxide, and oxygen affect the function of the heart.**

B. **Explain how extracellular ion concentration and body temperature affect the function of the heart.**

The pumping efficiency of the heart plays an important role in maintaining homeostasis. Blood pressure in the systemic vessels must be high enough to allow nutrient and waste product exchange across the walls of the capillaries and to meet metabolic demands. In addition, the heart's activity must be regulated because the metabolic activities of the tissues change under such conditions as

exercise and rest. Reflexes help regulate the activity of the heart to maintain homeostasis. Baroreceptor reflexes regulate blood pressure, and chemoreceptor reflexes help regulate the heart's activity.

Effect of Blood Pressure

Baroreceptor (bar′ō-rē-sep′ter, bar′ō-rē-sep′tōr) **reflexes** detect changes in blood pressure and lead to changes in heart rate and force of contraction. Stretch receptors, the sensory receptors of the baroreceptor reflexes, are in the walls of certain large arteries, such as the internal carotid arteries and the aorta. Baroreceptors measure blood pressure by detecting the degree of stretch of blood vessel walls (figure 20.22). The anatomy of these sensory structures and their afferent pathways are described in chapter 21.

Changes in blood pressure stimulate baroreceptors, which then communicate with control centers in the medulla oblongata. Sensory neurons, which are primarily found in the glossopharyngeal (cranial nerve IX) and vagus (cranial nerve X) nerves, carry action potentials from the baroreceptors to an area in the medulla oblongata called the **cardioregulatory center,** where sensory action potentials are integrated (figure 20.22). There are two parts to the cardioregulatory center: (1) the **cardioacceleratory center** increases heart rate, and (2) the **cardioinhibitory center** decreases heart rate. Action potentials then travel from the cardioregulatory center to the heart through both the sympathetic and the parasympathetic divisions of the autonomic nervous system.

At normal blood pressures (80–120 mm Hg), action potentials are sent from the baroreceptors in the internal carotid arteries and aorta to the medulla oblongata at a relatively constant frequency. When blood pressure rises, the arterial walls are stretched farther, and the action potential frequency at the baroreceptors increases (figure 20.23). When blood pressure decreases, the arterial walls are stretched to a lesser extent, and the action potential frequency decreases. In response to elevated blood pressure, the baroreceptor reflexes reduce sympathetic stimulation and increase parasympathetic stimulation of the heart, causing the heart rate to slow. Decreased blood pressure causes decreased parasympathetic and increased sympathetic stimulation of the heart, resulting in an increased heart rate and force of contraction. Withdrawal of parasympathetic stimulation is primarily responsible for increases in heart rate up to approximately 100 bpm. Larger increases in heart rate, especially during exercise, result from sympathetic stimulation. The baroreceptor reflexes are homeostatic because they keep the blood pressure within a narrow range of values that is adequate to maintain blood flow to the tissues.

Effect of pH, Carbon Dioxide, and Oxygen

Chemoreceptor (kē′mō-rē-sep′tor) **reflexes** help regulate the heart's activity. Chemoreceptors sensitive to changes in blood pH and CO_2 levels are found in the medulla oblongata. A drop in blood pH, which is often due to a rise in CO_2 decrease parasympathetic and increase sympathetic stimulation of the heart, resulting in increased heart rate and force of contraction (figure 20.24).

The increased cardiac output causes greater blood flow through the lungs, where CO_2 is eliminated from the body. This helps lower the blood CO_2 level to within its normal range, which increases blood pH.

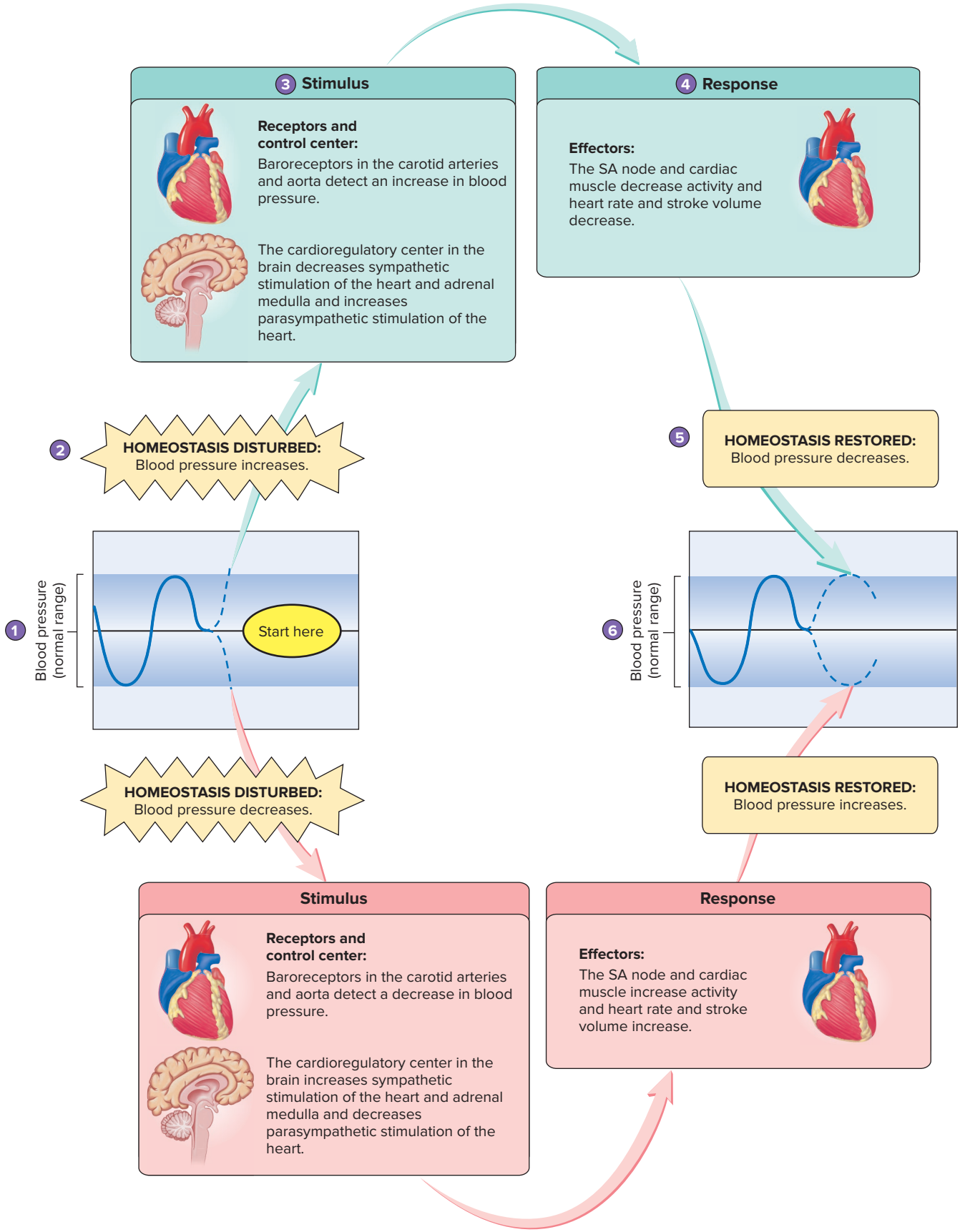
Chemoreceptors primarily sensitive to blood O_2 levels are found in the carotid and aortic bodies. These small structures are located near large arteries close to the brain and heart, and they monitor blood flowing to the brain and the rest of the body. A dramatic decrease in blood O_2 levels, as occurs during asphyxiation, activates the carotid and aortic body chemoreceptor reflexes. In carefully controlled experiments, it is possible to isolate the effects of the carotid and aortic body chemoreceptor reflexes from other reflexes, such as the medullary chemoreceptor reflexes. These experiments indicate that a reduction in blood O_2 results in decreased heart rate and increased vasoconstriction. The vasoconstriction causes blood pressure to rise, which promotes blood delivery despite the decrease in heart rate. The carotid and aortic body chemoreceptor reflexes may protect the heart for a short time by slowing the heart rate, thereby reducing its need for O_2. The carotid and aortic body chemoreceptor reflexes normally do not function independently of other regulatory mechanisms. When all the regulatory mechanisms function together, large, prolonged decreases in blood O_2 levels increase the heart rate. Low blood O_2 levels also increase stimulation of respiratory movements (see chapter 23). Increased inflation of the lungs stimulates stretch receptors in the lungs. Action potentials from these stretch receptors influence the cardioregulatory center, which causes the heart rate to increase. The reduced O_2 levels that exist at high altitudes can cause an increase in heart rate even when blood CO_2 levels remain low. However, the carotid and aortic body chemoreceptor reflexes are more important in regulating respiration (see chapter 23) and blood vessel constriction (see chapter 21) than heart rate.

Effect of Extracellular Ion Concentration

The ions that affect cardiac muscle function are the same ions that influence membrane potentials in other electrically excitable tissues, K^+, Ca^{2+}, and Na^+. However, cardiac muscle responds to these ions differently than nerve or skeletal muscle tissue does. For example, the extracellular levels of Na^+ rarely deviate enough from normal to significantly affect cardiac muscle function.

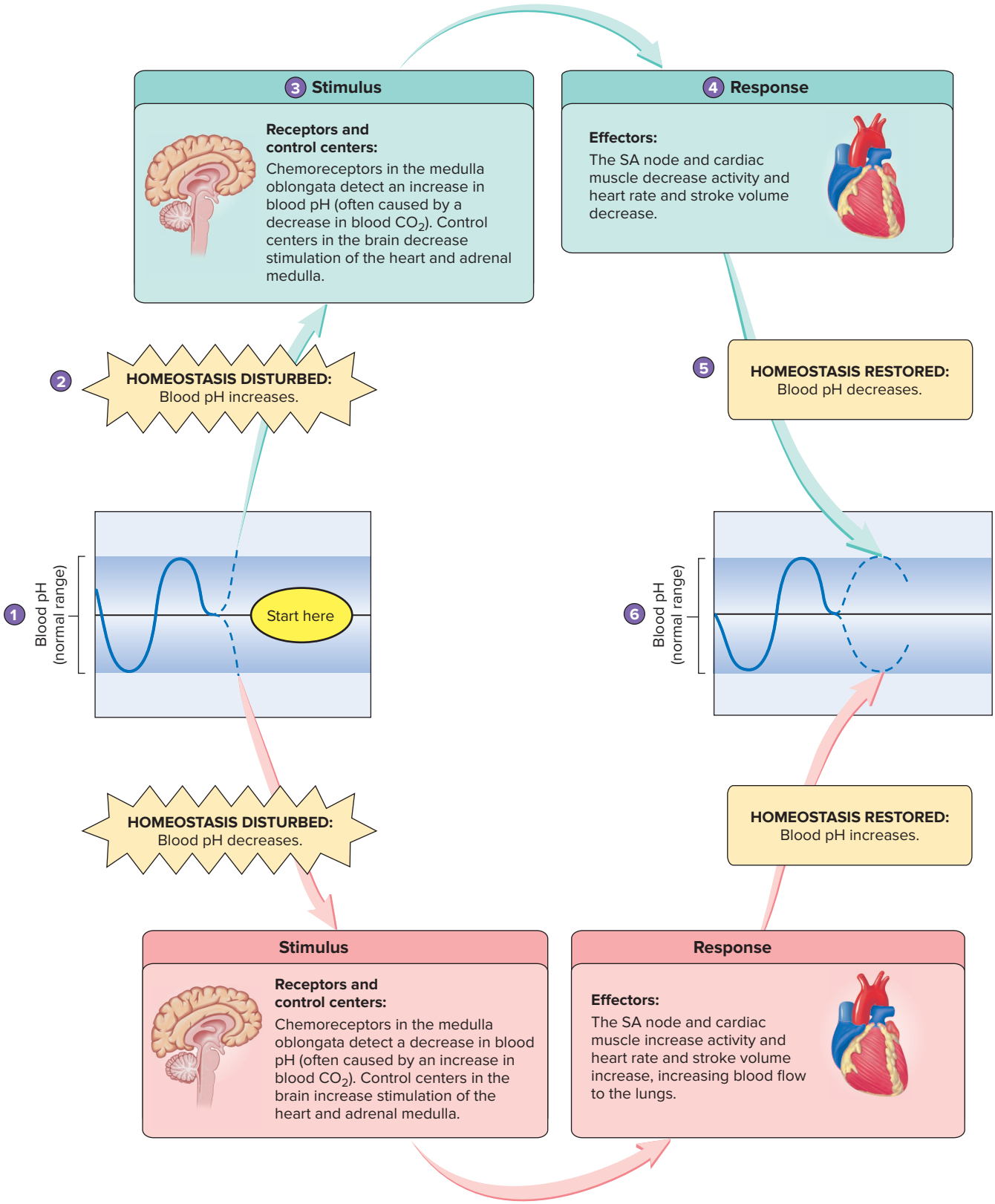
Excess extracellular K^+ in cardiac tissue causes the heart rate and stroke volume to decrease. A twofold increase in extracellular K^+ results in **heart block,** which is the loss of action potential conduction through the heart. The excess K^+ in the extracellular fluid causes changes in the membrane potential that lead to a decreased rate at which action potentials are conducted along cardiac muscle cells. As the conduction rates decrease, ectopic action potentials can occur. Elevated blood levels of K^+ can produce enough ectopic action potentials to cause fibrillation. The membrane potential changes also results in less Ca^{2+} entering the sarcoplasm of the cell; thus, the strength of cardiac muscle contraction lessens. Overall, excess extracellular K^+ results in drastic loss of heart function.

Although the extracellular concentration of K^+ is normally small, a reduction in extracellular K^+ causes the resting membrane potential to become hyperpolarized; as a consequence, it takes longer for the membrane to depolarize to threshold. Ultimately, the reduction in extracellular K^+ results in a decrease in heart rate. The force of contraction is not affected, however.



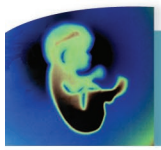
HOMEOSTASIS FIGURE 20.23 Summary of the Baroreceptor Reflex

The baroreceptor reflex maintains homeostasis in response to changes in blood pressure. (1) Blood pressure is within its normal range. (2) Blood pressure increases outside the normal range, which causes homeostasis to be disturbed. (3) Baroreceptors in the carotid arteries and aorta detect the increase in blood pressure, and the cardioregulatory center in the brain alters autonomic stimulation of the heart. (4) Heart rate and stroke volume decrease. (5) These changes cause blood pressure to decrease. (6) Blood pressure returns to its normal range; homeostasis is restored. Observe the responses to a decrease in blood pressure outside its normal range by following the *red arrows*.



HOMEOSTASIS FIGURE 20.24 Summary of the Chemoreceptor Reflex

The chemoreceptor reflex maintains homeostasis in response to changes in blood CO_2 and H^+ concentrations (pH). (1) Blood pH is within its normal range. (2) Blood pH increases outside the normal range. (3) Chemoreceptors in the medulla oblongata detect increased blood pH. Control centers in the brain decrease sympathetic stimulation of the heart and adrenal medulla. (4) Heart rate and stroke volume decrease, reducing blood flow to the lungs. (5) These changes cause blood pH to decrease (as a result of increase in blood CO_2). (6) Blood pH returns to its normal range; homeostasis is restored. Observe the responses to a decrease in blood pH outside its normal range by following the *red arrows*.



Clinical IMPACT 20.5 Treatment and Prevention of Heart Disease

Heart disease is a life-threatening condition that affects people of all walks of life. Fortunately, medications and surgical procedures are available to treat many forms of heart disease. Preventive measures have also been identified to help people reduce their chance of developing heart disease.

Heart Medications

Digitalis (dij-i-tal′is, dij-i-ta′lis) slows and strengthens contractions of the heart muscle by increasing the amount of Ca^{2+} that enters cardiac muscle cells and by prolonging the action potentials' refractory period. This drug is frequently given to people who have heart failure, although it also can be used to treat atrial tachycardia.

Nitroglycerin (nī-trō-glis′er-in) causes dilation of all the veins and arteries, including coronary arteries, without an increase in heart rate or stroke volume. When all blood vessels dilate, a greater volume of blood pools in the dilated blood vessels, causing a decrease in the venous return to the heart. The flow of blood through coronary arteries also increases. The reduced preload causes cardiac output to decline, decreasing the amount of work performed by the heart. Nitroglycerin is frequently given to patients who have coronary artery disease that restricts coronary blood flow. The decreased work performed by the heart reduces the amount of O_2 required by the cardiac muscle. Consequently, the heart does not suffer from lack of O_2, and angina pectoris does not develop.

Beta-adrenergic blocking agents reduce the rate and strength of cardiac muscle contractions, reducing the heart's demand for O_2. These blocking agents bind to receptors for norepinephrine and epinephrine and prevent these substances from having their normal effects. These blocking agents are often used to treat rapid heart rate, certain types of arrhythmia, and hypertension.

Calcium channel blockers reduce the rate at which Ca^{2+} diffuses into cardiac and smooth muscle cells. Because the action potentials that produce cardiac muscle contractions depend in part on the flow of Ca^{2+} into cardiac muscle cells, calcium channel blockers can be used to control the force of heart contractions and to reduce arrhythmia, tachycardia, and hypertension. Because the entry of Ca^{2+} into smooth muscle cells causes contraction, calcium channel blockers dilate coronary blood vessels and can be used to treat angina pectoris.

Antihypertensive (an′tē-hī-per-ten′siv) **agents** comprise several drugs used to treat hypertension. These drugs lower blood pressure and therefore reduce the work required by the heart to pump blood. In addition, reduced blood pressure decreases the risk for heart attack and stroke. Drugs used to treat hypertension include those that reduce the activity of the sympathetic nervous system, dilate arteries and veins, increase urine production (diuretics), and block the conversion of angiotensinogen to angiotensin I.

Anticoagulants (an′tē-kō-ag′ū-lantz) prevent clot formation in people who have damaged heart valves or blood vessels or in those who have had a myocardial infarction. Aspirin functions as a weak anticoagulant.

Instruments and Selected Procedures

An **artificial pacemaker** is an instrument, placed beneath the skin, equipped with an electrode that extends to the heart and provides an electrical stimulus at a set frequency. Artificial pacemakers are used in patients whose natural heart pacemakers do not produce a heart rate high enough to sustain normal physical activity. Artificial pacemakers can increase the heart rate as physical activity increases. Pacemakers can also detect cardiac arrest, extreme arrythmias, or fibrillation. In response, strong stimulation of the heart by the pacemaker may restore heart function.

Heart valve replacement or repair is a surgical procedure performed on valves that are so deformed and scarred from conditions such as endocarditis that they have become severely incompetent or stenosed. Substitute valves made of synthetic materials, such as plastic or Dacron, are effective; valves transplanted from pigs are also used.

A **heart transplant** is a surgical procedure in which the heart of a recently deceased donor is transplanted to the recipient, and the recipient's diseased heart is removed. A heart transplant is possible only if the characteristics of the donor closely match those of the recipient (see chapter 22). People who have received heart transplants must continue to take drugs that suppress their immune responses for the rest of their lives. If they do not, the immune system will reject the transplanted heart.

An **artificial heart** is a mechanical pump that replaces the heart. Although still experimental and not able to substitute permanently for the heart, artificial hearts have been used to keep patients alive until a donor heart can be found.

Cardiac assistance involves temporarily implanting a mechanical device that assists the heart in pumping blood. In some cases, the decreased workload on the heart provided by the device appears to promote recovery of failing hearts, whereupon the device has been successfully removed. In **cardiomyoplasty,** a piece of a back muscle (latissimus dorsi) is wrapped around the heart and stimulated to contract in synchrony with the heart.

Prevention of Heart Disease

Heart disease is a major cause of death. Several precautions can help prevent heart disease. Proper nutrition is important in reducing the risk for heart disease (see chapter 25).

The recommended diet is low in fats, especially saturated fats and cholesterol, and low in refined sugar. The diet should be high in fiber, whole grains, fruits, and vegetables. Total food intake should be limited to avoid obesity, and sodium chloride intake should be reduced.

Smoking and excessive alcohol consumption should be avoided. Smoking increases the risk for heart disease at least tenfold, and excessive alcohol consumption substantially increases the risk for heart disease.

Chronic stress, frequent emotional upsets, and lack of physical exercise can increase the risk for cardiovascular disease. Remedies include relaxation techniques and aerobic exercise programs involving gradual increases in the duration and difficulty of activities such as walking, swimming, jogging, and aerobic dancing.

Hypertension (hī′per-ten′shŭn), abnormally high systemic blood pressure, affects about one-fifth of the U.S. population. People are advised to have their blood pressure measured regularly because hypertension does not produce obvious symptoms. If hypertension cannot be controlled by diet and exercise, blood pressure–lowering drugs are prescribed. The cause of hypertension is unknown in most cases.

Some data suggest that taking an aspirin daily reduces the chance of having a heart attack. Aspirin inhibits the synthesis of prostaglandins in platelets, thereby helping prevent clot formation (see chapter 19).

Systems PATHOLOGY | Myocardial Infarction

Background Information

Paul, an overweight, out-of-shape executive, was a smoker and indulged in high-fat foods. Last fall, Paul felt intense pain in his chest that radiated down his left arm. Out of breath and dizzy, Paul became anxious and disoriented and eventually lost consciousness, but he did not stop breathing. Paul's coworkers noticed him and called 911. Paramedics arrived and found that Paul's blood pressure was low and he exhibited arrhythmia and tachycardia. They conducted an ECG and administered O_2 and medication to control the arrhythmia. At the hospital, Paul was given tissue plasminogen activator (t-PA) to improve blood flow to the damaged area of the heart by activating plasminogen, which dissolves blood clots. Over the next few days, enzymes, such as creatine phosphokinase, increased in Paul's blood, which confirmed that cardiac muscle had been damaged by an infarction.

In the hospital, Paul began to experience shortness of breath because of pulmonary edema, and after a few days he developed pneumonia. He was treated for the pneumonia and gradually improved over the next few weeks. An **angiogram** (an′jē-ō-gram) performed several days after Paul's infarction indicated that he had suffered damage to a significant part of the lateral wall of his left ventricle (figure 20.25). Although blood flow in some of Paul's coronary arteries was seriously restricted, his physicians did not believe that angioplasty or bypass surgery was necessary.

Paul experienced a myocardial infarction, in which a thrombosis in one of the branches of the left coronary artery reduced the blood supply to the lateral wall of the left ventricle, resulting in ischemia of the left ventricle wall. The fact that t-PA was an effective treatment supports the conclusion that the infarction was caused by a thrombosis. An ischemic area of the heart wall is not able to contract normally; therefore, Paul's heart's pumping effectiveness was dramatically reduced. The reduced pumping capacity was responsible for the low blood pressure, which decreased the blood flow to Paul's brain, resulting in confusion, disorientation, and unconsciousness.

Low blood pressure, increasing blood CO_2 levels, pain, and anxiousness increased sympathetic stimulation of the heart and adrenal glands. Increased sympathetic stimulation of the adrenal medulla caused the release of epinephrine. Increased parasympathetic stimulation of the heart resulted from pain sensations. In such cases, the heart is periodically arrhythmic due to the combined effects of parasympathetic stimulation, sympathetic stimulation, and the release of epinephrine and norepinephrine from the adrenal glands. In addition, the ischemic areas of the left ventricle produce ectopic beats.

Myocardial infarctions can lead to dysfunction in other systems of the body (figure 20.26). Pulmonary edema resulted from the increased pressure in Paul's pulmonary veins because of the left ventricle's inability to pump blood. The edema allowed bacteria to infect the lungs and cause pneumonia.

Paul's heart began to beat rhythmically in response to medication because the infarction had not damaged the conducting system of the heart, which is an indication that no permanent arrhythmias had developed. (Permanent arrhythmias indicate damage to cardiac muscle specialized to conduct action potentials in the heart.)

Analysis of the electrocardiogram, blood pressure measurements, and an angiogram (figure 20.25) indicated that the infarction was located on the left side of Paul's heart. Paul's lifestyle correlated with an increased probability of myocardial infarction in several ways: lack of physical exercise, overweight, smoking, and stress.

Paul's physician made it very clear that he was lucky to have survived a myocardial infarction and recommended a weight-loss program and a low-sodium and low-fat diet. The physician also suggested that Paul stop smoking. She explained that Paul would have to take medication for high blood pressure if his blood pressure did not decrease in response to the recommended changes. The physician recommended an aerobic exercise program for Paul after a period of recovery. She also advised Paul to seek ways to reduce the stress associated with his job and recommended that he take a small amount of aspirin regularly to reduce the probability of thrombosis. Because aspirin inhibits prostaglandin synthesis, it reduces the tendency for blood to clot. Paul followed the doctor's recommendations; after several months, his blood pressure was normal and he began to feel better than he had in years.

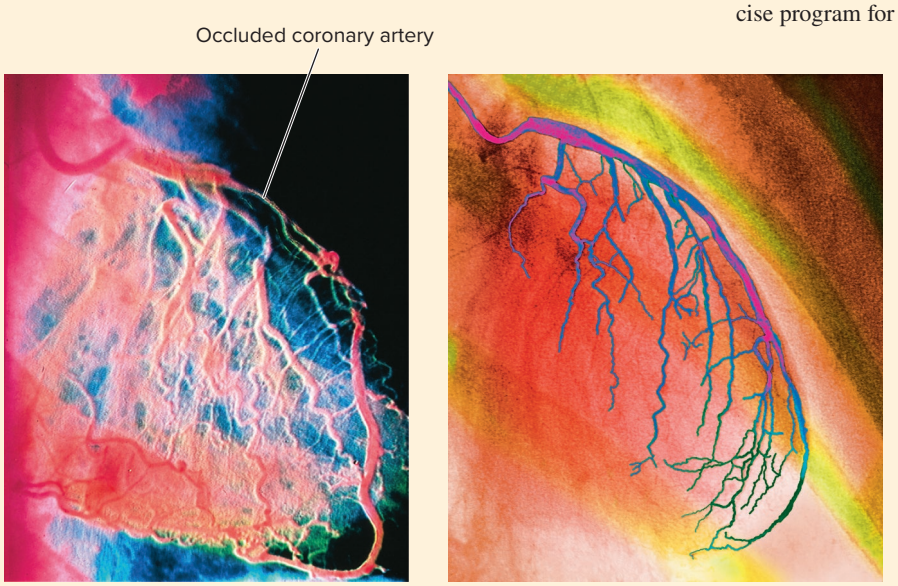


FIGURE 20.25 Angiograms
An angiogram is usually obtained by placing a catheter into a blood vessel and injecting a dye that can be detected with x-rays. Note the occluded (blocked) coronary blood vessel in this angiogram, which has been computer-enhanced to show colors. The angiogram on the right is of a normal heart.
(Left) ©CNRI/Science Source; (Right) ©SPL/Science Source

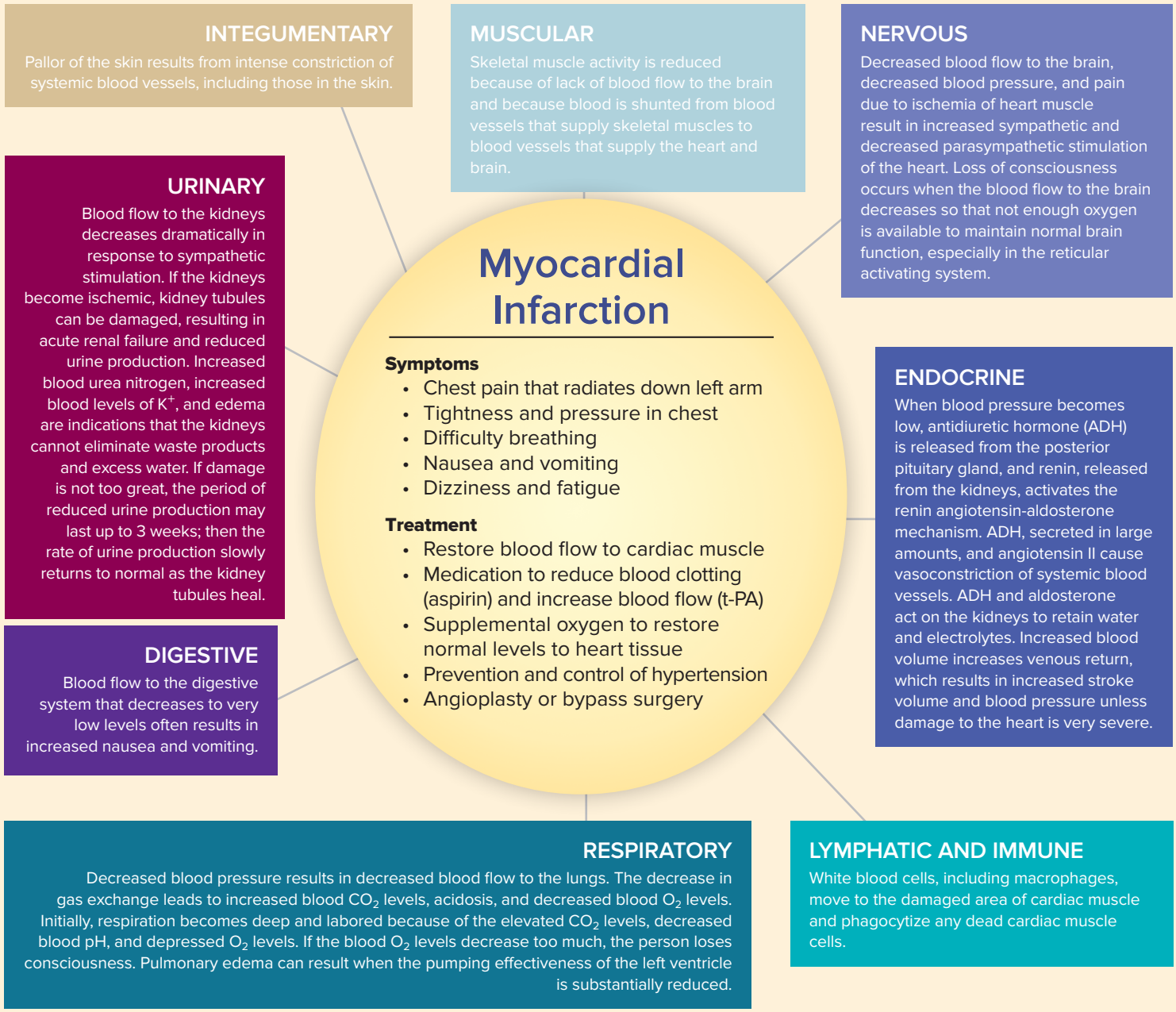


FIGURE 20.26 Systems Interactions: Myocardial Infarction
A myocardial infarction can affect many systems of the body, as this diagram illustrates.

Predict 9

Severe ischemia in the wall of a ventricle can cause the death of cardiac muscle cells. Inflammation develops around the necrotic (dead) tissue, and macrophages invade the necrotic tissue and phagocytize dead cells. At the same time, blood vessels and connective tissue grow into the area and begin to deposit connective tissue to replace the necrotic tissue. Suppose that Paul had been recovering from his myocardial infarction for about a week when suddenly his blood pressure decreased to very low levels and he died within a very short time. At autopsy, a large amount of blood was found in the pericardial sac, and the wall of the left ventricle was ruptured. Explain.

Case STUDY 20.1 Aortic Valve Stenosis

Norma is a 62-year-old woman who had rheumatic fever when she was 12 years old. She has had a heart murmur ever since. Norma went to her doctor, complaining of fatigue; dizziness, especially on rising from a sitting or lying position; and pain in her chest when she exercises. Her doctor listened to Norma's heart and determined she has a systolic murmur (see Clinical Impact 20.4). Norma's blood pressure (90/65 mm Hg) and heart rate (55 beats/min) were lower than normal. Norma's doctor referred her to a cardiologist, who did additional tests. An electrocardiogram indicated she has left ventricular hypertrophy. Imaging techniques confirmed the left ventricular hypertrophy and indicated a stenosed aortic semilunar valve. The cardiologist explained to Norma that the rheumatic fever she had as a child damaged her aortic semilunar valve and that the valve's condition had gradually become worse. The cardiologist recommended surgical replacement of Norma's aortic semilunar valve. Otherwise, she is likely to develop heart failure.

Predict 10

a. What effect does Norma's stenosed valve have on stroke volume?

b. Norma has left ventricular hypertrophy, which means the left ventricle is enlarged and has thicker walls than normal. Explain how that condition developed.

c. Explain Norma's low blood pressure.

d. Explain why Norma becomes dizzy on rising from a sitting or lying position (*Hint:* venous return).

e. Predict how Norma's heart rate changes on standing (see figure 20.23).

f. Norma experiences chest pain when she exercises, a condition called angina pectoris (see Clinical Impact 20.2). Why doesn't she feel this pain at rest?

A rise in the extracellular concentration of Ca^{2+} produces a greater force of cardiac contraction because of a higher influx of Ca^{2+} into the sarcoplasm during action potential generation. Elevated plasma Ca^{2+} levels have an indirect effect on heart rate because they reduce the frequency of action potentials in nerve fibers, thus reducing sympathetic and parasympathetic stimulation of the heart (see chapter 11). Generally, elevated blood Ca^{2+} levels lower the heart rate.

A low blood Ca^{2+} level increases the heart rate, although the effect is imperceptible until blood Ca^{2+} levels are reduced to approximately one-tenth of their normal value. The reduced extracellular Ca^{2+} levels cause Na^+ channels to open, which allows Na^+ to diffuse more readily into the cell, resulting in depolarization and action potential generation. However, reduced Ca^{2+} levels usually cause death due to tetany of skeletal muscles before they decrease enough to markedly influence the heart's function.

Effect of Body Temperature

Under resting conditions, the temperature of cardiac muscle normally does not change dramatically, although alterations in temperature influence the heart rate. Small increases in cardiac muscle temperature cause the heart rate to speed up, and decreases in temperature cause the heart rate to slow. For example, during exercise or fever, increased heart rate and force of contraction accompany temperature elevations, but the heart rate drops under conditions of hypothermia. During heart surgery, body temperature is sometimes reduced dramatically on purpose to slow the heart rate and other metabolic functions.

ASSESS YOUR PROGRESS

44. *Explain how the nervous system detects and responds to each of the following:*
   a. a decrease in blood pressure
   b. an increase in blood carbon dioxide level
   c. a decrease in blood pH
   d. a decrease in blood oxygen level

45. *Describe the baroreceptor reflex and the heart's response to an increase in venous return.*

46. *What effect does an increase or a decrease in extracellular potassium, calcium, and sodium ions have on the heart's rate and force of contraction?*

47. *What effect does temperature have on heart rate?*

20.11 Effects of Aging on the Heart

LEARNING OUTCOME

After reading this section, you should be able to

A. **List the major age-related changes that affect the heart.**

Gradual changes in heart function normally occur with aging. These age-related changes are minor under resting conditions but become more significant in response to exercise or other age-related diseases. Under resting conditions, the mechanisms that regulate the heart compensate effectively for most of the age-related changes.

Hypertrophy of the left ventricle is a common age-related change. This appears to result from a gradual increase in the pressure in the aorta, against which the left ventricle must pump blood, and a gradual increase in the stiffness of cardiac muscle tissue. The elevated aortic pressure results from a gradual reduction in arterial elasticity, leading to increased stiffness of the aorta and other large arteries. Myocardial cells accumulate lipids, and the number of collagen fibers increases in cardiac tissue. These changes make the cardiac muscle tissue stiffer and less compliant. The increased volume of the left ventricle can sometimes result in higher left atrial pressure and increased pulmonary capillary pressure.

TABLE 20.2 **Representative Diseases and Disorders of the Heart**

Condition	Description
Inflammation of Heart Tissue	
Endocarditis	Inflammation of the endocardium; affects the valves more severely than other areas of the endocardium; may lead to scarring, causing stenosed or incompetent valves
Pericarditis	Inflammation of the pericardium; see Clinical Impact 1.1
Cardiomyopathy	Disease of the myocardium of unknown cause or occurring secondarily to other disease; results in weakened cardiac muscle, causing all chambers of the heart to enlarge; may eventually lead to congestive heart failure
Rheumatic heart disease	Results from a streptococcal infection in young people; toxin produced by the bacteria can cause rheumatic fever several weeks after the infection that can result in rheumatic endocarditis
Reduced Blood Flow to Cardiac Muscle	
Coronary heart disease	Reduces the amount of blood the coronary arteries can deliver to the myocardium
Coronary thrombosis	Formation of blood clot in a coronary artery
Myocardial infarction	Damaged cardiac muscle tissue resulting from lack of blood flow to the myocardium; often referred to as a heart attack; see Clinical Impact 20.2
Congenital Heart Diseases (occur at birth)	
Septal defect	Hole in the septum between the left and right sides of the heart, allowing blood to flow from one side of the heart to the other and greatly reducing the heart's pumping effectiveness
Patent ductus arteriosus	Ductus arteriosus fails to close after birth, allowing blood to flow from the aorta to the pulmonary trunk under a higher pressure, which damages the lungs; also, the left ventricle must work harder to maintain adequate systemic pressure
Stenosis of the heart valve	Narrowed opening through one or more of the heart valves; aortic or pulmonary semilunar stenosis increases the heart's workload; bicuspid valve stenosis causes blood to back up in the left atria and lungs, resulting in edema of the lungs; tricuspid valve stenosis results in similar blood flow problems and edema in the peripheral tissues
Incompetent heart valve	Heart valves do not close correctly, and blood flows through in the reverse direction; see Clinical Impact 20.4
Cyanosis (sī-ə-nō′sis; *cyan,* blue + *osis,* condition of)	Symptom of inadequate heart function in babies with congenital heart disease; the infant's skin appears blue because of low oxygen levels in the blood in peripheral blood vessels
Heart Failure	Progressive weakening of the heart muscle, reducing the heart's pumping action; hypertension leading to heart failure due to increased afterload; advanced age, malnutrition, chronic infections, toxins, severe anemias, hyperthyroidism, and hereditary factors can lead to heart failure

This can cause pulmonary edema and a tendency for older people to feel out of breath when they exercise strenuously.

The maximum heart rate gradually declines, as can be roughly predicted by the following formula:

$$\text{Maximum heart rate} = 220 - \text{Age of individual}$$

The rate at which cardiac muscle breaks down ATP increases, and the rate of Ca^{2+} transport decreases. The maximum rate at which cardiac muscle can carry out aerobic respiration also decreases. In addition, the degree to which epinephrine and norepinephrine can increase the heart rate declines. These changes lead to longer contraction and relaxation times for cardiac muscle and a decrease in the maximum heart rate. Both the resting and maximum cardiac outputs slowly decline as people age; by 85 years of age, the cardiac output may have decreased by 30–60%.

Age-related changes also occur in the connective tissue of the heart valves. The connective tissue becomes less flexible, and Ca^{2+} deposits increase. The result is an increased tendency for the heart valves to function abnormally. The aortic semilunar valve is especially likely to become stenosed, but other heart valves, such as the bicuspid valve, may become either stenosed or incompetent.

The atrophy and replacement of cells of the left bundle branch and a decrease in the number of SA node cells alter the electrical conducting system of the heart and lead to a higher rate of cardiac arrhythmias in elderly people.

The enlarged and thickened cardiac muscle, especially in the left ventricle, requires more O_2 to pump the same amount of blood pumped by a younger heart. This change is not significant unless the coronary circulation is diminished by coronary artery disease. However, the development of coronary artery disease is age-related, as is congestive heart disease. Approximately 10% of elderly people over 80 have congestive heart failure, and a major contributing factor is coronary artery disease. Because of age-related changes in the heart, many elderly people are limited in their ability to respond to emergencies, infections, blood loss, and stress.

Exercise has many beneficial effects on the heart. Regular aerobic exercise improves the heart's functional capacity at all

ages, provided the person has no other conditions that cause the extra workload on the heart to be harmful.

ASSESS YOUR PROGRESS

48. *Explain how age-related changes affect the function of the left ventricle.*

49. *Describe age-related changes in the heart rate.*

50. *Describe how increasing age affects the function of the conducting system and the heart valves.*

51. *Discuss the effect of two age-related heart diseases on the function of the aging heart.*

Answer

Learn to Predict

We learned in this chapter that the heart valves maintain a one-way flow of blood through the heart—from the atria to the ventricles. We also learned that an incompetent valve is one that leaks, or allows some blood to flow in the opposite direction—from the ventricles to the atria. An irregular swooshing noise following the first heart sound, as noted by Stan's regular physician, is a typical sign of an incompetent valve. The first heart sound is produced when the bicuspid and tricuspid valves close. The swooshing sound is the regurgitation of blood into the atria. The cardiologist determined that the bicuspid valve was incompetent, resulting in abnormal blood flow on the left side of the heart.

Stan's difficulty breathing resulted from the abnormal blood flow caused by his incompetent valve. After reviewing the blood flow through the heart in this chapter, we are aware that blood entering the left atrium is returning from the lungs through the pulmonary veins. As a result of the incompetent valve, the pressure in the left atrium, which is normally low, increases substantially during ventricular systole. The increased left atrial pressure causes the pressure in the pulmonary veins and pulmonary capillaries to increase. As a result, fluid leaks from the pulmonary capillaries into the lungs, causing pulmonary edema, or fluid accumulation in the lungs, making it difficult for Stan to breathe.

Answers to odd-numbered Predict questions from this chapter appear in appendix E.

Summary

20.1 Functions of the Heart

The heart produces the force that causes blood to circulate.

20.2 Size, Shape, and Location of the Heart

1. The heart is approximately the size of a closed fist and is shaped like a blunt cone.
2. The heart lies obliquely in the mediastinum, with its base directed posteriorly and slightly superiorly and its apex directed anteriorly, inferiorly, and to the left.
3. The base is deep to the second intercostal space, and the apex extends to the fifth intercostal space.

20.3 Anatomy of the Heart

The heart consists of two atria and two ventricles.

Pericardium

1. The pericardium is a sac that surrounds the heart and consists of the fibrous pericardium and the serous pericardium.
2. The fibrous pericardium helps hold the heart in place.
3. The serous pericardium reduces friction as the heart beats. It consists of the following parts:
   - The parietal pericardium lines the fibrous pericardium.
   - The visceral pericardium lines the exterior surface of the heart.
   - The pericardial cavity lies between the parietal and visceral pericardia and is filled with pericardial fluid, which reduces friction as the heart beats.

Heart Wall

1. The heart wall has three layers:
   - The outer epicardium (visceral pericardium) provides protection against the friction of rubbing organs.
   - The middle myocardium is responsible for contraction.
   - The inner endocardium reduces the friction resulting from blood passing through the heart.
2. The inner surfaces of the atria are mainly smooth. The auricles have muscular ridges called pectinate muscles.
3. The ventricles have ridges called trabeculae carneae.

External Anatomy and Coronary Circulation

1. Each atrium has a flap called an auricle.
2. The coronary sulcus separates the atria from the ventricles. The interventricular grooves separate the right and left ventricles.
3. The inferior and superior venae cavae and the coronary sinus enter the right atrium. The four pulmonary veins enter the left atrium.
4. The pulmonary trunk exits the right ventricle, and the aorta exits the left ventricle.
5. Coronary arteries branch off the aorta to supply the heart. Blood returns from the heart tissues to the right atrium through the coronary sinus and cardiac veins.

Heart Chambers and Valves

1. The interatrial septum separates the atria from each other, and the interventricular septum separates the ventricles.
2. The tricuspid valve separates the right atrium and ventricle. The bicuspid valve separates the left atrium and ventricle. The chordae tendineae attach the papillary muscles to the atrioventricular valves.
3. The semilunar valves separate the aorta and pulmonary trunk from the ventricles.

20.4 Route of Blood Flow Through the Heart

1. Blood from the body flows through the right atrium into the right ventricle and then to the lungs.
2. Blood returns from the lungs to the left atrium, enters the left ventricle, and is pumped back to the body.

20.5 Histology

Heart Skeleton

The fibrous heart skeleton supports the openings of the heart, electrically insulates the atria from the ventricles, and provides a point of attachment for heart muscle.

Cardiac Muscle

1. Cardiac muscle cells are branched and have a centrally located nucleus. Actin and myosin are organized to form sarcomeres. The sarcoplasmic reticulum and T tubules are not as organized as in skeletal muscle.
2. Cardiac muscle cells are joined by intercalated disks, which allow action potentials to move from one cell to the next. Thus, cardiac muscle cells function as a unit.
3. Cardiac muscle cells have a slow onset of contraction and a prolonged contraction time caused by the length of time required for Ca^{2+} to move to and from the myofibrils.
4. Cardiac muscle is well supplied with blood vessels that support aerobic respiration.
5. Cardiac muscle aerobically uses glucose, fatty acids, and lactate to produce ATP for energy. Cardiac muscle does not develop a significant oxygen deficit.

Conducting System

1. The SA node and the AV node are in the right atrium.
2. The AV node is connected to the bundle branches in the interventricular septum by the AV bundle.
3. The bundle branches give rise to Purkinje fibers, which supply the ventricles.
4. The SA node is made up of small-diameter cardiac muscle cells that initiate action potentials, which spread across the atria and cause them to contract.
5. Action potentials are slowed in the AV node, allowing the atria to contract and blood to move into the ventricles. Then the action potentials travel through the AV bundles and bundle branches to the Purkinje fibers, causing the ventricles to contract, starting at the apex. The AV node is also made up of small-diameter cardiac muscle fibers.

20.6 Electrical Properties

Action Potentials

1. After depolarization and partial repolarization, a plateau is reached, during which the membrane potential only slowly repolarizes.
2. The movement of Na^+ through the voltage-gated Na^+ channels causes depolarization.
3. During depolarization, voltage-gated K^+ channels close, and voltage-gated Ca^{2+} channels begin to open.
4. Early repolarization results from closure of the voltage-gated Na^+ channels and the opening of some voltage-gated K^+ channels.
5. The plateau exists because voltage-gated Ca^{2+} channels remain open.
6. The rapid phase of repolarization results from closure of the voltage-gated Ca^+ channels and the opening of many voltage-gated K^+ channels.
7. The entry of Ca^{2+} into cardiac muscle cells causes Ca^{2+} to be released from the sarcoplasmic reticulum to trigger contractions.

Autorhythmicity of Cardiac Muscle

1. Cardiac pacemaker muscle cells are autorhythmic because of the spontaneous development of a pacemaker potential.
2. The pacemaker potential results from the movement of Na^+ and Ca^{2+} into the pacemaker cells.
3. Ectopic foci are areas of the heart that regulate heart rate under abnormal conditions.

Refractory Periods of Cardiac Muscle

Cardiac muscle has a prolonged depolarization and thus a prolonged refractory period, which allows time for the cardiac muscle to relax before the next action potential causes a contraction.

Electrocardiogram

1. An ECG records only the electrical activities of the heart.
   - Depolarization of the atria produces the P wave.
   - Depolarization of the ventricles produces the QRS complex. Repolarization of the atria occurs during the QRS complex.
   - Repolarization of the ventricles produces the T wave.
2. Based on the magnitude of the ECG waves and the time between waves, ECGs can be used to diagnose heart abnormalities.

20.7 Cardiac Cycle

1. The cardiac cycle involves repetitive contraction and relaxation of the heart chambers.
2. Blood moves through the circulatory system from areas of higher pressure to areas of lower pressure. Contraction of the heart produces the pressure.
3. The cardiac cycle is divided into five periods:
   - Active ventricular filling results when the atria contract and pump blood into the ventricles.
   - Although the ventricles are contracting, during the period of isovolumetric contraction, ventricular volume does not change because all the heart valves are closed.
   - During the period of ejection, the semilunar valves open, and blood is ejected from the heart.
   - Although the heart is relaxing, during the period of isovolumetric relaxation, ventricular volume does not change because all the heart valves are closed.
   - Passive ventricular filling results when blood flows from the higher pressure in the veins and atria to the lower pressure in the relaxed ventricles.

Events Occurring During the Cardiac Cycle

1. Most ventricular filling occurs when blood flows from the higher pressure in the veins and atria to the lower pressure in the relaxed ventricles.
2. Contraction of the atria completes ventricular filling.
3. Contraction of the ventricles closes the AV valves, opens the semilunar valves, and ejects blood from the heart.

4. The volume of blood in a ventricle just before it contracts is the end-diastolic volume. The volume of blood after contraction is the end-systolic volume.
5. Relaxation of the ventricles results in the closing of the semilunar valves, the opening of the AV valves, and the movement of blood into the ventricles.

Heart Sounds

1. Closure of the atrioventricular valves produces the first heart sound.
2. Closure of the semilunar valves produces the second heart sound.
3. Turbulent flow of blood into the ventricles can be heard in some people, producing a third heart sound.

Aortic Pressure Curve

1. Contraction of the ventricles forces blood into the aorta, producing the peak systolic pressure.
2. Blood pressure in the aorta falls to the diastolic level as blood flows out of the aorta.
3. Elastic recoil of the aorta maintains pressure in the aorta and produces the dicrotic notch and dicrotic wave.

20.8 Mean Arterial Blood Pressure

1. Mean arterial pressure is the average blood pressure in the aorta. Adequate blood pressure is necessary to ensure delivery of blood to the tissues.
2. Mean arterial pressure is proportional to cardiac output (amount of blood pumped by the heart per minute) times peripheral resistance (total resistance to blood flow through blood vessels).
3. Cardiac output is equal to stroke volume times heart rate.
4. Stroke volume, the amount of blood pumped by the heart per beat, is equal to end-diastolic volume minus end-systolic volume.
   - Venous return is the amount of blood returning to the heart. Increased venous return increases stroke volume by increasing end-diastolic volume.
   - Increased force of contraction increases stroke volume by decreasing end-systolic volume.
5. Cardiac reserve is the difference between resting and exercising cardiac output.

20.9 Regulation of the Heart

Intrinsic Regulation

1. Venous return is the amount of blood that returns to the heart during each cardiac cycle.
2. The Starling law of the heart describes the relationship between preload and the stroke volume of the heart. An increased preload causes the cardiac muscle cells to contract with a greater force and produce a greater stroke volume.

Extrinsic Regulation

1. The cardioregulatory center in the medulla oblongata regulates parasympathetic and sympathetic nervous control of the heart.
2. Parasympathetic stimulation is supplied by the vagus nerve.
   - Parasympathetic stimulation decreases heart rate.
   - Postganglionic neurons secrete acetylcholine, which increases membrane permeability to K^+, producing hyperpolarization of the membrane.
3. Sympathetic stimulation is supplied by the cardiac nerves.
   - Sympathetic stimulation increases heart rate and force of contraction (stroke volume).
   - Postganglionic neurons secrete norepinephrine, which increases membrane permeability to Na^+ and Ca^{2+} and produces depolarization of the membrane.
4. Epinephrine and norepinephrine are released into the blood from the adrenal medulla as a result of sympathetic stimulation.
   - The effects of epinephrine and norepinephrine on the heart are long-lasting, compared with those of neural stimulation.
   - Epinephrine and norepinephrine increase the rate and force of heart contraction.

20.10 The Heart and Homeostasis

Effect of Blood Pressure

1. Baroreceptors monitor blood pressure.
2. In response to a decrease in blood pressure, the baroreceptor reflexes increase sympathetic stimulation and decrease parasympathetic stimulation of the heart, resulting in increased heart rate and force of contraction.

Effect of pH, Carbon Dioxide, and Oxygen

1. Chemoreceptors monitor blood CO_2, pH, and O_2 levels.
2. In response to increased CO_2 and decreased pH, medullary chemoreceptor reflexes increase sympathetic stimulation and decrease parasympathetic stimulation of the heart.
3. Carotid body chemoreceptor receptors stimulated by low O_2 levels result in decreased heart rate and vasoconstriction.
4. All regulatory mechanisms functioning together in response to low blood pH, high blood CO_2, and low blood O_2 levels usually produce increased heart rate and vasoconstriction. Decreased O_2 levels stimulate an increase in heart rate indirectly by stimulating respiration, and the stretch of the lungs activates a reflex that increases sympathetic stimulation of the heart.

Effect of Extracellular Ion Concentration

1. An increase or a decrease in extracellular K^+ decreases heart rate.
2. Increased extracellular Ca^{2+} increases force of contraction of the heart and decreases heart rate. Decreased Ca^{2+} levels produce the opposite effect.

Effect of Body Temperature

Heart rate increases when body temperature increases, and it decreases when body temperature decreases.

20.11 Effects of Aging on the Heart

1. Aging results in gradual changes in heart function, which are minor under resting conditions but more significant during exercise.
2. Hypertrophy of the left ventricle is a common age-related condition.
3. The maximum heart rate declines so that, by age 85, the cardiac output may be decreased by 30–60%.
4. There is an increased tendency for valves to function abnormally and for arrhythmias to occur.
5. Because increased O_2 consumption is required to pump the same amount of blood, age-related coronary artery disease is more severe.
6. Exercise improves the functional capacity of the heart at all ages.

REVIEW AND COMPREHENSION

1. Which of these structures returns blood to the right atrium?
   a. coronary sinus
   b. inferior vena cava
   c. superior vena cava
   d. Both b and c are correct.
   e. All of these are correct.

2. The valve located between the right atrium and the right ventricle is the
   a. aortic semilunar valve.
   b. pulmonary semilunar valve.
   c. tricuspid valve.
   d. bicuspid (mitral) valve.

3. The papillary muscles
   a. are attached to chordae tendineae.
   b. are found in the atria.
   c. contract to close the foramen ovale.
   d. are attached to the semilunar valves.
   e. surround the openings of the coronary arteries.

4. Given these blood vessels:
   (1) aorta
   (2) inferior vena cava
   (3) pulmonary trunk
   (4) pulmonary vein

   Choose the arrangement that lists the vessels in the order a red blood cell would encounter them going from the systemic veins to the systemic arteries.
   a. 1,3,4,2
   b. 2,3,4,1
   c. 2,4,3,1
   d. 3,2,1,4
   e. 3,4,2,1

5. The bulk of the heart wall is
   a. epicardium.
   b. pericardium.
   c. myocardium.
   d. endocardium.
   e. exocardium.

6. Cardiac muscle has
   a. sarcomeres.
   b. a sarcoplasmic reticulum.
   c. transverse tubules.
   d. many mitochondria.
   e. All of these are correct.

7. Action potentials pass from one cardiac muscle cell to another
   a. through gap junctions.
   b. by a special cardiac nervous system.
   c. because of the large voltage of the action potentials.
   d. because of the plateau phase of the action potentials.
   e. by neurotransmitters.

8. During the transmission of action potentials through the conducting system of the heart, there is a temporary delay at the
   a. bundle branches.
   b. Purkinje fibers.
   c. AV node.
   d. SA node.
   e. AV bundle.

9. Given these structures of the conducting system of the heart:
   (1) atrioventricular bundle
   (2) AV node
   (3) bundle branches
   (4) Purkinje fibers
   (5) SA node

   Choose the arrangement that lists the structures in the order an action potential passes through them.
   a. 2,5,1,3,4
   b. 2,5,3,1,4
   c. 2,5,4,1,3
   d. 5,2,1,3,4
   e. 5,2,4,3,1

10. Purkinje fibers
    a. are specialized cardiac muscle cells.
    b. conduct impulses much more slowly than ordinary cardiac muscle.
    c. conduct action potentials through the atria.
    d. connect the SA node and the AV node.
    e. ensure that ventricular contraction starts at the base of the heart.

11. T waves on an ECG represent
    a. depolarization of the ventricles.
    b. repolarization of the ventricles.
    c. depolarization of the atria.
    d. repolarization of the atria.

12. The greatest amount of ventricular filling occurs during
    a. the first one-third of diastole.
    b. the middle one-third of diastole.
    c. the last one-third of diastole.
    d. ventricular systole.

13. While the semilunar valves are open during a normal cardiac cycle, the pressure in the left ventricle is
    a. higher than the pressure in the aorta.
    b. lower than the pressure in the aorta.
    c. the same as the pressure in the left atrium.
    d. lower than the pressure in the left atrium.

14. Blood flows neither into nor out of the ventricles during
    a. the period of isovolumetric contraction.
    b. the period of isovolumetric relaxation.
    c. diastole.
    d. systole.
    e. Both a and b are correct.

15. Stroke volume is the
    a. amount of blood pumped by the heart per minute.
    b. difference between end-diastolic and end-systolic volume.
    c. difference between the amount of blood pumped at rest and that pumped at maximum output.
    d. amount of blood pumped from the atria into the ventricles.

16. Cardiac output is defined as
    a. blood pressure times peripheral resistance.
    b. peripheral resistance times heart rate.
    c. heart rate times stroke volume.
    d. stroke volume times blood pressure.
    e. blood pressure minus peripheral resistance.

17. Pressure in the aorta is at its lowest
    a. at the time of the first heart sound.
    b. at the time of the second heart sound.
    c. just before the AV valves open.
    d. just before the semilunar valves open.

18. Just after the dicrotic notch on the aortic pressure curve
    a. the pressure in the aorta is greater than the pressure in the left ventricle.
    b. the pressure in the left ventricle is greater than the pressure in the aorta.
    c. the pressure in the left atrium is greater than the pressure in the left ventricle.
    d. the pressure in the left atrium is greater than the pressure in the aorta.
    e. blood pressure in the aorta is 0 mm Hg.

19. The "lubb" sound (first heart sound) is caused by the
    a. closing of the AV valves.
    b. closing of the semilunar valves.
    c. blood rushing out of the ventricles.
    d. filling of the ventricles.
    e. ventricular contraction.

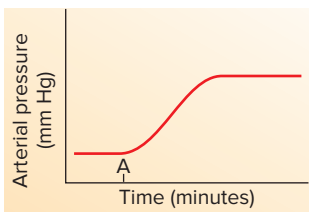
20. Increased venous return results in
    a. increased stroke volume.
    b. increased cardiac output.
    c. decreased heart rate.
    d. Both a and b are correct.

21. Parasympathetic nerve fibers are found in the _____ nerves and release _____ at the heart.
    a. cardiac, acetylcholine
    b. cardiac, norepinephrine
    c. vagus, acetylcholine
    d. vagus, norepinephrine
22. Increased parasympathetic stimulation of the heart
    a. increases the force of ventricular contraction.
    b. increases the rate of depolarization in the SA node.
    c. decreases heart rate.
    d. increases cardiac output.
23. Because of the baroreceptor reflex, when normal arterial blood pressure decreases, the
    a. heart rate decreases.
    b. stroke volume decreases.
    c. frequency of afferent action potentials from baroreceptors decreases.
    d. cardioregulatory center stimulates parasympathetic neurons.
24. A decrease in blood pH and an increase in blood CO_2 levels result in
    a. increased heart rate.
    b. increased stroke volume.
    c. increased sympathetic stimulation of the heart.
    d. increased cardiac output.
    e. All of these are correct.
25. An increase in extracellular potassium levels can cause
    a. an increase in stroke volume.
    b. an increase in force of contraction.
    c. a decrease in heart rate.
    d. Both a and b are correct.

Answers appear in appendix F.

CRITICAL THINKING

1. Explain why the walls of the ventricles are thicker than the walls of the atria.
2. In most tissues, peak blood flow occurs during systole and decreases during diastole. In heart tissue, however, the opposite is true, and peak blood flow occurs during diastole. Explain this difference.
3. Explain why it is more efficient for contraction of the ventricles to begin at the apex of the heart than at the base.
4. Predict the consequences for the heart's pumping effectiveness if numerous ectopic foci in the ventricles produce action potentials.
5. A patient has tachycardia. Would you recommend a drug that prolongs or shortens the plateau of cardiac muscle cell action potentials?
6. Many endurance-trained athletes have a decreased resting heart rate, compared with that of nonathletes. Explain why an endurance-trained athlete's resting heart rate decreases rather than increases.
7. A doctor lets you listen to a patient's heart with a stethoscope at the same time that you feel the patient's pulse. Once in a while, you hear two heartbeats very close together, but you feel only one pulse beat. Later, the doctor tells you that the patient has an ectopic focus in the right atrium. Explain why you hear two heartbeats very close together. The doctor also tells you that the patient exhibits a pulse deficit (the number of pulse beats felt is fewer than the number of heartbeats heard). Explain why a pulse deficit occurs.
8. Explain why it is sufficient to replace the ventricles, but not the atria, in artificial heart transplantation.
9. A friend tells you an ECG revealed that her son has a slight heart murmur. Should you be convinced that he has a heart murmur? Explain.
10. An experiment on a dog was performed in which the mean arterial blood pressure was monitored before and after the common carotid arteries were partially clamped (at time A). The results are graphed here:



    Explain the change in mean arterial blood pressure. (*Hint:* Baroreceptors are located in the internal carotid arteries, which are superior to the site of clamping of the common carotid arteries.)
11. During hemorrhagic shock (caused by loss of blood), blood pressure may fall dramatically, although the heart rate is elevated. Explain why blood pressure falls despite the increase in heart rate.

Answers to odd-numbered questions appear in appendix G.

Photo: Photograph of medical professional measuring a patient's blood pressure. Blood pressure is the result of the heart forcing blood through the blood vessels. ©Stockbyte/Getty Images

21

Cardiovascular System

BLOOD VESSELS AND CIRCULATION

The complex water systems that move fluid through pipes for the numerous business and homes in a city are actually a good analogy for representing the intricacy and coordinated functions of blood vessels. The heart is the pump that provides the major force causing blood to circulate, and the blood vessels are the pipes that carry blood to the body tissues and back to the heart. In addition to providing the routes for blood movement, the blood vessels participate in regulating blood pressure and determining the degree of blood flow to the body's most active tissues. Blood pressure must be high enough to ensure sufficient blood flow to meet the tissues' metabolic needs. Regulation of both the blood vessels and the heart ensure that homeostatic blood pressure is maintained.

Learn to Predict

T.J. and Tyler were building a treehouse. While searching for a board in a pile of used lumber, T.J. stepped on a rusty nail, which penetrated deeply into his foot, causing it to bleed. Neither T.J. nor Tyler wanted to tell their parents about the accident, but after 3 days, T.J. developed septic shock. His foot had become infected, and the infection had spread into his bloodstream. **After reading this chapter and recalling information about the structure and function of the heart, described in chapter 20, explain how T.J.'s blood volume, blood pressure, heart rate, and stroke volume changed due to septic shock. Also, explain how blood flow in the periphery changed and how it affected T.J.'s appearance. Finally, explain the consequences if T.J.'s blood pressure remained abnormally low for a prolonged period of time.**

21.1 Functions of the Circulatory System

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Distinguish between pulmonary and systemic vessels.**
B. **Recite the functions of the circulatory system.**

The blood vessels are part of the cardiovascular system; however, it is common to refer to the series of blood vessels in the body as the circulatory system. The circulatory system includes many blood vessels. These blood vessels are organized into two sets: (1) pulmonary vessels and (2) systemic vessels. **Pulmonary vessels** transport blood from the right ventricle, through the lungs, and back to the left atrium. **Systemic vessels** transport blood from the left ventricle, through all parts of the body, and back to the right atrium (see figure 20.1). As described in chapter 20, the heart provides the major force that causes blood to move through these vessels. The circulatory system has five unique functions:

1. *Carries blood*. Blood vessels carry blood from the heart to almost all the body tissues and back to the heart.
2. *Exchanges nutrients, waste products, and gases with tissues*. Nutrients and O_2 diffuse from blood vessels to cells in all areas of the body. Waste products and CO_2 diffuse from the cells, where they are produced, to blood vessels.
3. *Transports substances*. Hormones, components of the immune system, molecules required for coagulation, enzymes, nutrients, gases, waste products, and other substances are transported in the blood to all areas of the body.
4. *Helps regulate blood pressure*. The circulatory system and the heart work together to maintain blood pressure within a normal range of values.
5. *Directs blood flow to tissues*. The circulatory system regulates the degree of blood flow and therefore the volume of blood to tissues to maintain homeostasis.

ASSESS YOUR PROGRESS

Answers to these questions are found in the section you have just completed. Re-read the section if you need help in answering these questions.

1. *What is the difference between pulmonary and systemic vessels?*
2. *Describe the five functions of the circulatory system.*

21.2 Structural Features of Blood Vessels

LEARNING OUTCOMES

After reading this section, you should be able to

A. **List the types of arteries, capillaries, and veins.**
B. **Describe the structure and function of arteries, capillaries, and veins.**
C. **Describe the innervation of the blood vessel walls.**
D. **Discuss age-related changes to blood vessels.**

Blood vessels are hollow tubes that conduct blood through the tissues of the body. There are three main types of blood vessels: (1) arteries, (2) capillaries, and (3) veins. These vessels form a continuous passageway for blood flow from the heart, through the body tissues, and back to the heart. Blood leaving the heart first passes through arteries. Next, the blood flows through the capillaries, which are the smallest blood vessels. Finally, blood moves through veins as it once again flows into the heart.

Structure of Blood Vessels

General Features

Except for the capillaries and the smallest veins, called venules, the blood vessel walls consist of three relatively distinct tissue layers. These tissue layers are most evident in the muscular arteries and least evident in the veins. From the lumen to the outer wall of the blood vessels, the layers, or **tunics** (too′niks), are (1) the tunica intima, (2) the tunica media, and (3) the tunica adventitia (figures 21.1 and 21.2).

The **tunica intima,** also called the *tunica interna,* is the most internal layer of a blood vessel wall. This tunic consists of four layers: (1) endothelium, (2) a basement membrane, (3) a thin layer of connective tissue called the lamina propria, and (4) a fenestrated layer of elastic fibers called the **internal elastic membrane.** The internal elastic membrane separates the tunica intima from the next layer, the tunica media.

The **tunica media,** or middle layer, consists of smooth muscle cells arranged circularly around the blood vessel. The amount of blood flowing through a blood vessel can be regulated by contraction or relaxation of the smooth muscle in the tunica media. **Vasoconstriction** (vā′sō-kon-strik′shŭn, vas′ō-kon-strik′shŭn) results from smooth muscle contraction and causes a decrease in blood vessel diameter, thereby decreasing blood flow through the vessel. **Vasodilation** (vā′sō-dī-lā′shŭn, vas-ō-dī-lā′shŭn) results from smooth muscle relaxation and causes an increase in blood vessel diameter, thereby increasing blood flow through the vessel.

The tunica media also contains variable amounts of elastic and collagen fibers, depending on the size of the vessel. An **external elastic membrane** separates the tunica media from the tunica adventitia. It can be identified at the outer border of the tunica media in some arteries. In addition, a few longitudinally oriented smooth muscle cells occur in some arteries near the tunica intima.

The **tunica adventitia** (too′ni-kă ad-ven-tish′ă), also called the *tunica externa,* is composed of connective tissue, which varies from dense connective tissue near the tunica media to loose connective tissue that merges with the connective tissue surrounding the blood vessels.

The relative thickness and composition of each layer vary with the diameter of the blood vessel and its type. The transition from one vessel type to another is gradual, as are the structural changes.

Types of Arteries

Arteries carry blood away from the heart. Although the arteries form a continuum from the largest to the smallest branches, they are normally classified as (1) elastic arteries, (2) muscular arteries,

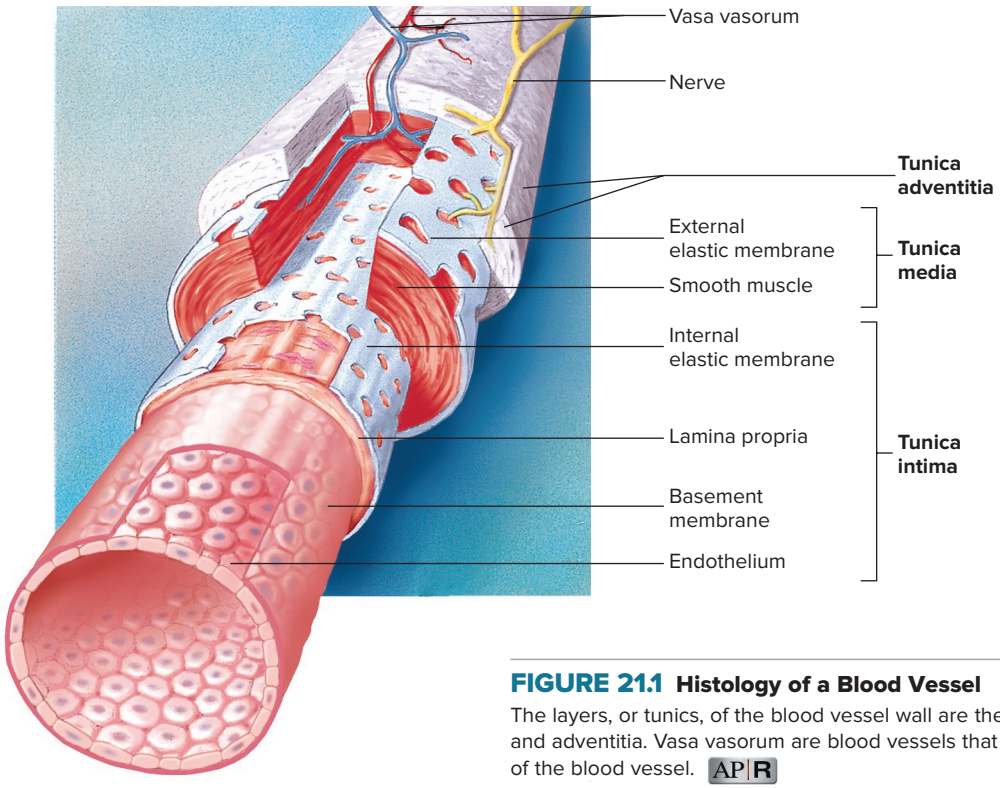


FIGURE 21.1 Histology of a Blood Vessel
The layers, or tunics, of the blood vessel wall are the tunica intima, media, and adventitia. Vasa vasorum are blood vessels that supply blood to the wall of the blood vessel. AP|R

or (3) arterioles. The ventricles pump blood from the heart into large, elastic arteries that branch repeatedly to form many progressively smaller arteries. As they become smaller, the artery walls undergo a gradual transition from having a large amount of elastic tissue and a smaller amount of smooth muscle to having less elastic tissue and more smooth muscle. From these muscular arteries, blood flows into the arterioles, the smallest of the arteries. A more detailed description of the three types of arteries is provided below.

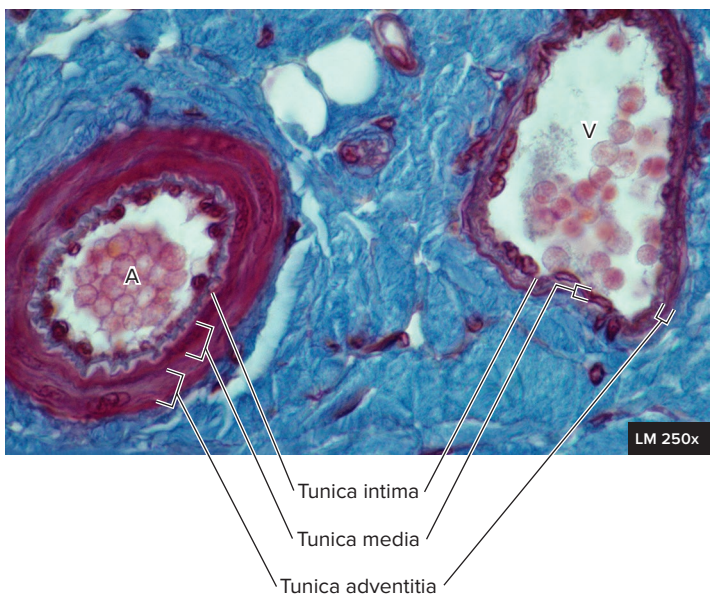


FIGURE 21.2 Comparison of an Artery and a Vein
The typical structure of a medium-sized artery (A) and a vein (V). Note that the artery has a thicker wall than the vein. The predominant layer in the wall of the artery is the tunica media, with its circular layers of smooth muscle. The predominant layer in the wall of the vein is the tunica adventitia, and the tunica media is thinner than in the artery. ©Ed Reschke/Photolibrary/Getty Images

Elastic Arteries

Elastic arteries have the largest diameters (figure 21.3*a*) and are often called *conducting arteries*. Because these vessels are the first to receive blood from the heart, blood pressure is relatively high in the elastic arteries. Also, due to the pumping action of the heart, blood pressure in the elastic arteries fluctuates between higher systolic and lower diastolic values. When stretched, the walls of elastic arteries recoil, preventing drastic decreases in blood pressure. Elastic arteries have a greater amount of elastic tissue and a smaller amount of smooth muscle in their walls, compared with other arteries. The elastic fibers are responsible for the elastic characteristics of the blood vessel wall, but collagenous connective tissue determines the degree to which the arterial wall can stretch.

The tunica intima of elastic arteries is relatively thick. The elastic fibers of the internal and external elastic membranes merge and are not recognizable as distinct layers. The tunica media consists of a meshwork of elastic fibers with interspersed, circular smooth muscle cells and some collagen fibers. The tunica adventitia is relatively thin.

Muscular Arteries

Muscular arteries include medium-sized and small arteries. The use of *muscular* in the name of these vessels refers to their thick tunica media. The walls of some muscular arteries are relatively thick, compared with their diameter, mainly because the tunica media contains 25–40 layers of smooth muscle (figure 21.3*b*). The tunica intima of the

(a) **Elastic arteries.** The tunica media is mostly elastic connective tissue. Elastic arteries recoil when stretched, which prevents blood pressure from falling rapidly.

(b) **Muscular arteries.** The tunica media is a thick layer of smooth muscle. Muscular arteries regulate blood flow to different regions of the body.

(c) **Medium and large veins.** All three layers are present. The tunica media is thin but can regulate vessel diameter because blood pressure in the venous system is low. The predominant layer is the tunica adventitia.

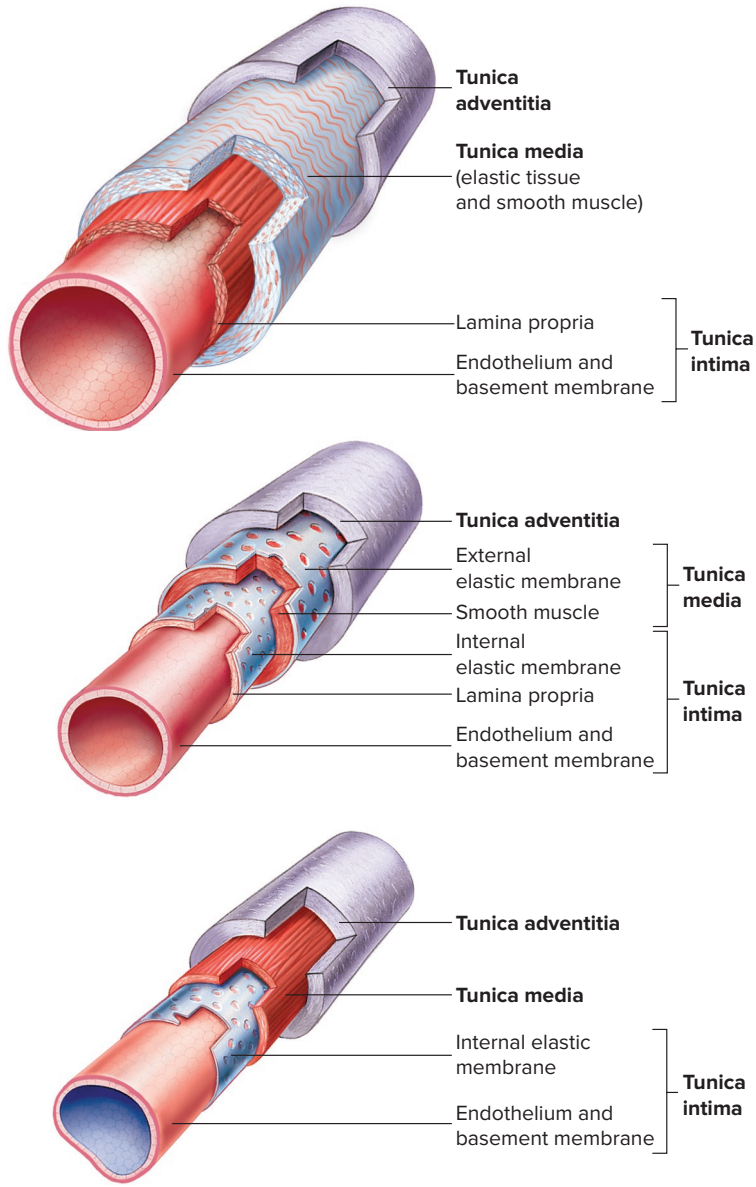


FIGURE 21.3 Structural Comparison of Blood Vessel Types
Comparison of the tissue composition of (*a*) elastic arteries, (*b*) muscular arteries, and (*c*) medium and large veins.

muscular arteries has a well-developed internal elastic membrane. The tunica adventitia is composed of a relatively thick layer of collagenous connective tissue that blends with the surrounding connective tissue. Muscular arteries are frequently called *distributing arteries* because the smooth muscle cells allow them to partially regulate blood flow to different body regions by either constricting or dilating.

Smaller muscular arteries range from 40 µm to 300 µm in diameter. Those that are 40 µm in diameter have approximately three or four layers of smooth muscle in their tunica media, whereas arteries that are 300 µm across have essentially the same structure as the larger muscular arteries. The small muscular arteries are adapted for vasodilation and vasoconstriction.

Arterioles

Arterioles (ar-tēr′ē-ōlz) are the smallest arteries in which the three layers can be identified. They transport blood from small arteries to capillaries (see figure 21.6). They range in diameter from approximately 40 µm, which is less than half the thickness of a sheet of printer paper, to as small as 9 µm. The tunica intima has no observable internal elastic membrane, and the tunica media consists of one or two layers of circular smooth muscle cells. Arterioles, like the small arteries, are capable of vasodilation and vasoconstriction.

ASSESS YOUR PROGRESS

3. *In what direction, relative to the heart, is blood carried by arteries and veins?*
4. *Name the three layers of a blood vessel wall. What kinds of tissue are in each layer?*
5. *List the types of arteries. Compare the amount of elastic fibers and smooth muscle in each type of artery.*

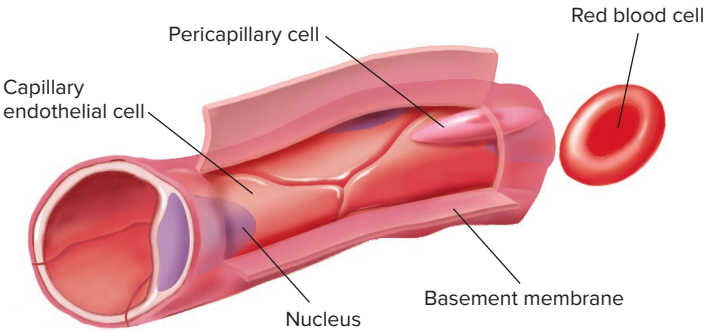


FIGURE 21.4 Capillary
Section of a capillary, showing that it is composed primarily of flattened endothelial cells.

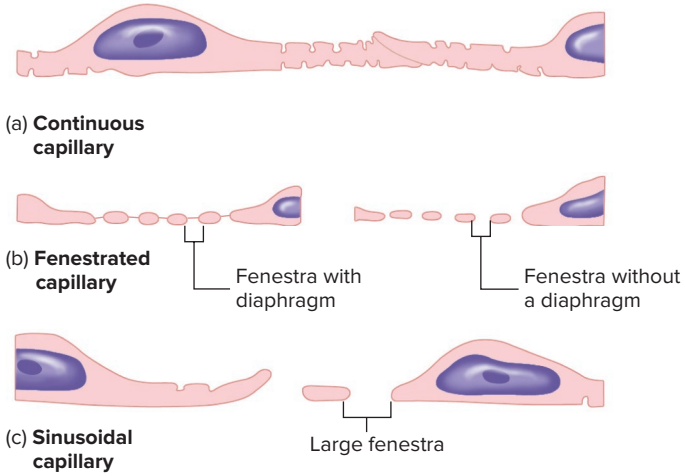


FIGURE 21.5 Structure of Capillary Walls
(*a*) Continuous capillaries have no gaps between endothelial cells and no fenestrae. They are common in muscle, nervous, and connective tissue. (*b*) Fenestrated capillaries have fenestrae 7–100 nm in diameter, covered by thin, porous diaphragms, which are not present in some capillaries. They are found in intestinal villi, ciliary processes of the eyes, choroid plexuses of the central nervous system, and glomeruli of the kidneys. (*c*) Sinusoidal capillaries have larger fenestrae without diaphragms and can have gaps between endothelial cells. They are found in endocrine glands, bone marrow, the liver, the spleen, and the lymphatic organs.

Capillaries

Blood flows from arterioles into **capillaries,** the most common type of blood vessel. Capillary walls are the thinnest of all blood vessels. Recall that one of the four layers of the tunica intima is an internal lining of simple squamous endothelial cells called the **endothelium** (en-dō-thē′lē-ŭm). In the vessels associated with the heart, this endothelial lining is continuous with the endocardium of the heart.

Most of the exchange that occurs between the blood and interstitial spaces occurs across the thin walls of capillaries. The capillary wall consists primarily of a single layer of endothelial cells (figure 21.4) that rests on a basement membrane. Outside the basement membrane is a delicate layer of loose connective tissue that merges with the connective tissue surrounding the capillary.

Scattered along the length of the capillary are **pericapillary cells** closely associated with the endothelial cells. These scattered cells lie between the basement membrane and the endothelial cells and are fibroblasts, macrophages, or undifferentiated smooth muscle cells.

Most capillaries range from 7 µm to 9 µm in diameter, and they branch without changing in diameter. Capillaries are variable in length, but in general they are approximately 1 mm long. Red blood cells flow through most capillaries single file and are frequently folded as they pass through the smaller-diameter capillaries.

Types of Capillaries

When comparing the many capillaries of the body, it becomes apparent that these vessels show variation in size and permeability, or the degree to which materials enter or leave the blood. Based on these characteristics, capillaries are classified as (1) continuous, (2) fenestrated, or (3) sinusoidal. **Continuous capillaries** are approximately 7–9 µm in diameter, and their walls exhibit no gaps between the endothelial cells (figure 21.5*a*). Continuous capillaries are less permeable to large molecules than are other capillary types; they are in muscle, nervous tissue, and many other locations.

In **fenestrated** (fen′es-trā′ted) **capillaries,** endothelial cells have numerous fenestrae (figure 21.5*b*). The **fenestrae** (fe-nes′trē; windows) are areas approximately 70–100 nm in diameter in which the cytoplasm is absent and the plasma membrane consists of a porous diaphragm that is thinner than the normal plasma membrane. In some capillaries, the diaphragm is not present. Fenestrated capillaries are in tissues where capillaries are highly permeable, such as the intestinal villi, ciliary processes of the eyes, choroid plexuses of the central nervous system, and glomeruli of the kidneys.

Sinusoidal (sī-nŭ-soy′dăl) **capillaries** are larger in diameter than either continuous or fenestrated capillaries, and their basement membrane is less prominent (figure 21.5*c*) or completely absent. Their fenestrae are larger than those in fenestrated capillaries, and gaps can exist between endothelial cells. The sinusoidal capillaries occur in places where large molecules move into the blood, such as endocrine glands.

Sinusoids are large-diameter, sinusoidal capillaries. Their basement membrane is sparse and often missing, and their structure suggests that large molecules and sometimes cells can move readily across their walls between the endothelial cells (figure 21.5*c*). Sinusoids are common in the liver and bone marrow. Macrophages are closely associated with the endothelial cells of the liver sinusoids. **Venous sinuses** are similar in structure to the sinusoidal capillaries but even larger in diameter. They are found primarily in the spleen, and there are large gaps between the endothelial cells that make up their walls.

Substances cross capillary walls by diffusing either (1) through or between the endothelial cells or (2) through fenestrae. Lipid-soluble substances, such as O_2 and CO_2, and small, water-soluble molecules readily diffuse through the endothelial cells. Larger water-soluble substances must pass through the fenestrae or gaps between the endothelial cells. In addition, transport by pinocytosis occurs, but little is known about its role in the

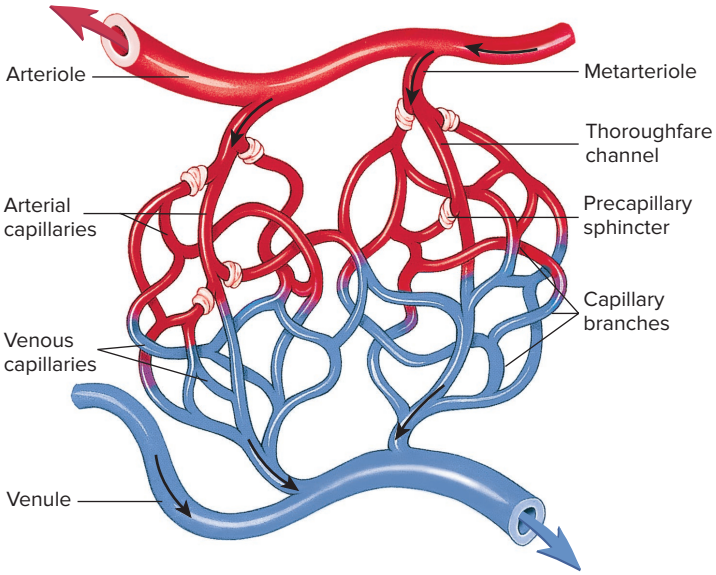


FIGURE 21.6 Capillary Network
A capillary network stems from an arteriole. Blood flows from the arteriole, through metarterioles, through the capillary network, to venules. Smooth muscle cells, called precapillary sphincters, regulate blood flow through the capillaries. Blood flow decreases when the precapillary sphincters constrict and increases when they dilate.

capillaries. The walls of the capillaries are effective permeability barriers because red blood cells and large, water-soluble molecules, such as proteins, cannot readily pass through them.

Capillary Network

Capillaries do not exist individually in tissues but form branching networks. Arterioles supply blood to each capillary network (figure 21.6). Blood flows from arterioles to capillary networks through **metarterioles** (met′ar-tēr′ē-ōlz), vessels with isolated smooth muscle cells along their walls. Blood then flows from a metarteriole into a **thoroughfare channel,** a vessel within the capillary network that extends in a relatively direct fashion from a metarteriole to a venule. Blood flow through thoroughfare channels is relatively continuous. Several capillaries branch from the thoroughfare channels, forming the capillary network. Blood flow is regulated in the capillary branches by **precapillary sphincters,** smooth muscle cells located at the origin of the branches (figure 21.6). Blood flows through the capillary network into the venules. The ends of capillaries closest to the arterioles are **arterial capillaries,** and the ends closest to venules are **venous capillaries.**

Capillary networks are more numerous and more extensive in highly metabolic tissues, such as in the lungs, liver, kidneys, skeletal muscle, and cardiac muscle. Capillaries in the skin function in thermoregulation, and heat loss results from the flow of a large volume of blood through them. Capillary networks in the dermis of skin have many more thoroughfare channels than capillary networks in cardiac or skeletal muscle. The major function of the capillaries in these muscle tissues is nutrient and waste product exchange.

Arteriovenous Anastomoses

Arteriovenous anastomoses (ă-nas′tō-mō′sēz) are specialized vascular connections that allow blood to flow directly from arterioles to small veins without passing through capillaries. A **glomus** (glō′mŭs; pl. glomera, glom′er-ă) is an arteriovenous anastomosis that consists of arterioles with abundant smooth muscle in their walls. The vessels are branched and coiled and are surrounded by connective tissue sheaths. Glomera are present in large numbers in the sole of the foot, the palm of the hand, the terminal phalanges, and the nail beds. The glomera help regulate body temperature by regulating blood flow through the hands and feet. As body temperature decreases, glomera constrict and less blood flows through them, reducing the rate of heat loss from the body. As body temperature increases, glomera dilate and more blood flows through them, increasing the rate of heat loss from the body. **Pathologic arteriovenous anastomoses** can form in areas of the body as a result of injury or tumors. These abnormal vascular connections allow for the direct flow of blood from arteries to veins. If they are sufficiently large, pathological arteriovenous anastomoses can lead to heart failure because of the tremendous increase in venous return to the heart.

ASSESS YOUR PROGRESS

6. *Describe the general structure of a capillary.*
7. *Compare the structure of the three types of capillaries. Explain the various ways that materials pass through capillary walls.*
8. *Describe a capillary network. Where is the smooth muscle that regulates blood flow into and through the capillary network located? What is the function of a thoroughfare channel?*
9. *Contrast the function of capillaries in the skin with the function of capillaries in muscle tissue.*
10. *Define* arteriovenous anastomosis *and* glomus*, and explain their functions.*

Types of Veins

From capillaries, blood flows into **veins,** vessels that carry blood toward the heart. When compared with arteries, the walls of veins are thinner. Vein walls also contain less elastic tissue and fewer smooth muscle cells (see figure 21.2). As the blood returns to the heart, it flows through veins with thicker walls and greater diameters. Veins are classified by size as (1) venules, (2) small veins, or (3) medium or large veins.

Venules and Small Veins

Venules (ven′oolz, vē′noolz) are the smallest veins. Their structure is very similar to that of capillaries in that they are tubes composed of endothelium resting on a delicate basement membrane. Venules have diameters up to 50 μm (see figure 21.4). A few isolated smooth muscle cells exist outside the endothelial cells, especially in the larger venules. As the vessels increase to 0.2–0.3 mm in diameter, the smooth muscle cells form a continuous layer; the vessels are then called **small veins.** In addition to a larger diameter compared to venules, small veins also have a tunica adventitia composed of collagenous connective tissue.

The venules collect blood from the capillaries (see figure 21.6) and transport it to small veins, which in turn transport it to medium veins. Nutrient exchange occurs across the venule walls but, as the walls of the small veins increase in thickness, the degree of nutrient exchange decreases.

Medium and Large Veins

Most of the veins observed in gross anatomical dissections are **medium veins** and **large veins.** Medium veins collect blood from small veins and deliver it to large veins. The **large veins** transport blood from the medium veins to the heart. In medium and large veins, the tunica intima is thin and consists of endothelial cells, a relatively thin layer of collagenous connective tissue, and a few scattered elastic fibers. The tunica media is also thin and is composed of a thin layer of circularly arranged smooth muscle cells containing some collagen fibers and a few sparsely distributed elastic fibers. The tunica adventitia, which is composed of collagenous connective tissue, is the predominant layer (figure 21.3*c*).

Portal Veins

In some areas of the body, a capillary network is directly connected to another capillary network by **portal** (pōr′tăl; door) **veins.** Specifically, portal veins begin in a primary capillary network, extend some distance, and end in a secondary capillary network. This connection is unique in that there is no pumping mechanism like the heart between the two capillary networks. Three portal vein systems are found in humans: (1) The hepatic portal veins carry blood from the capillaries in the gastrointestinal tract and spleen to dilated capillaries, called sinusoids, in the liver (see figure 21.27); (2) the hypothalamohypophysial portal veins carry blood from the hypothalamus of the brain to the anterior pituitary gland (see figure 18.3); and (3) the renal nephron portal systems are associated with the urine-forming structures of the kidneys (see chapter 26).

Valves

Veins that have diameters greater than 2 mm contain **valves,** which allow blood to flow toward the heart, but not in the opposite direction (figure 21.7). The valves consist of folds in the tunica intima that form two flaps shaped like the semilunar valves of the heart. The two folds overlap in the middle of the vein, so that, when blood attempts to flow in a reverse direction, the valves occlude, or block, the vessel. Medium veins contain many valves, and the number of valves is greater in veins of the lower limbs than in veins of the upper limbs.

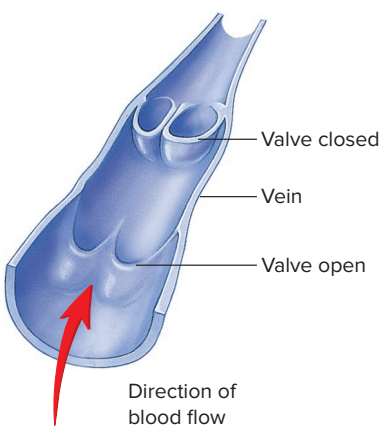
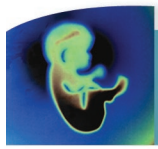


FIGURE 21.7 Valves
Folds in the tunica intima form the valves of veins, which allow blood to flow toward the heart but not in the opposite direction.



Clinical IMPACT 21.1

Varicose Veins, Phlebitis, and Gangrene

The veins of the lower limbs are subject to certain disorders. **Varicose veins** result when the veins of the lower limbs are stretched to the point that the valves become incompetent. Because of the stretching of the vein walls, the flaps of the valves no longer overlap to prevent the backflow of blood. As a consequence, the venous pressure is greater than normal in the veins of the lower limbs, resulting in edema. Blood flow in the veins can become sufficiently stagnant that the blood clots. This condition can result in **phlebitis** (fle-bī′tis), which is inflammation of the veins. If the inflammation is severe and blood flow becomes stagnant in a large area, it can lead to **gangrene** (gang′grēn), tissue death caused by a reduction in or loss of blood supply. Some people have a genetic propensity to develop varicose veins. The condition is further encouraged by activities that increase the pressure in the veins. One such condition is pregnancy, in which the venous pressure in the lower limbs increases because of compression by the expanded uterus. Also, standing in place for prolonged periods can lead to varicose veins.

Vasa Vasorum

For arteries and veins greater than 1 mm in diameter, nutrients cannot diffuse from the lumen of the vessel to all the layers of the wall. Therefore, nutrients are supplied to their walls by way of small blood vessels called **vasa vasorum** (vā′să vā′sor-ŭm), which penetrate from the exterior of the vessel to form a capillary network in the tunica adventitia and the tunica media (see figure 21.1).

ASSESS YOUR PROGRESS

11. *List the types of veins. Compare the vessel wall structure in each type of vein.*
12. *Describe portal veins. Name three examples.*
13. *In which type of blood vessels are valves found? What is their function?*
14. *What is the vasa vasorum? What is its function?*

Neural Innervation of Blood Vessels

The walls of most blood vessels are richly innervated by unmyelinated sympathetic nerve fibers (see figure 21.1). Some blood vessels, such as those in the penis and clitoris, are innervated by parasympathetic fibers. Small arteries and arterioles are innervated to a greater extent than other blood vessel types. The nerve

fibers branch to form plexuses in the tunica adventitia, and nerve terminals containing neurotransmitter vesicles project among the smooth muscle cells of the tunica media. Synapses consist of several enlargements of each of the nerve fibers among the smooth muscle cells. Sympathetic stimulation causes blood vessels to constrict; parasympathetic stimulation causes blood vessels in the penis and clitoris to dilate.

The smooth muscle cells of blood vessels act to some extent in unison. Gap junctions exist between adjacent smooth muscle cells; as a consequence, stimulation of a few smooth muscle cells in the vessel wall results in constriction of a relatively large segment of the blood vessel.

A few myelinated sensory neurons innervate some blood vessels and function as baroreceptors. They monitor stretch in the blood vessel wall and detect changes in blood pressure.

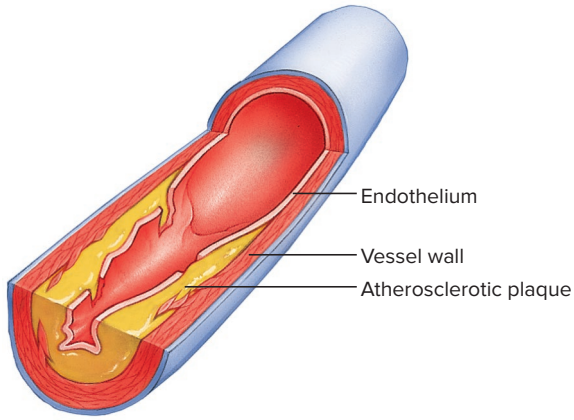


FIGURE 21.8 Atherosclerotic Plaque in an Artery
Atherosclerotic plaques develop within the tissue of the artery wall.

Aging of the Arteries

The walls of all arteries undergo changes as people age, although some arteries change more rapidly than others and some people are more susceptible to change. The most significant change occurs in the large elastic arteries, such as the aorta, in the large arteries that carry blood to the brain, and in the coronary arteries; the age-related changes described here refer to these blood vessel types. Muscular arteries exhibit age-related changes, but these are less dramatic and seldom disrupt normal vessel function.

Arteriosclerosis (ar-tēr′ē-ō-skle-rō′sis; hardening of the arteries) consists of degenerative changes in arteries that make them less elastic. These changes occur in many individuals, and they become more severe with advancing age. Arteriosclerosis greatly increases resistance to blood flow. Therefore, advanced arteriosclerosis reduces the normal circulation of blood and greatly increases the work performed by the heart.

Arteriosclerosis involves general hypertrophy of the tunica intima, including the internal elastic membrane, and hypertrophy of the tunica media. For example, when arteriosclerosis is associated with hypertension, the amount of smooth muscle and elastic tissue in the arterial walls increases. The elastic tissue can form concentric layers in the tunica intima, which becomes less elastic. Also, some of the smooth muscle cells of the tunica media can ultimately be replaced by collagen fibers. Arteriosclerosis in some older people can involve the formation of calcium deposits in the tunica media of the arteries, primarily those of the lower limbs, with little or no encroachment on their lumens. The calcium deposits reduce the vessels' elasticity.

Atherosclerosis (ath′er-ō-skle-rō′sis) is the deposition of material in the walls of arteries to form distinct plaques. It is a common type of arteriosclerosis. Like the other types, atherosclerosis is related to age and certain risk factors. Atherosclerosis affects primarily medium and larger arteries, including the coronary arteries. The plaques form when macrophages containing cholesterol accumulate in the tunica intima, and smooth muscle cells of the tunica media proliferate (figure 21.8). After the plaques enlarge, they consist of smooth muscle cells, white blood cells, lipids (including cholesterol), and, in the largest plaques, fibrous connective tissue and calcium deposits. The plaques narrow the lumens of blood vessels and make their walls less elastic. Atherosclerotic plaques can become so large that they severely restrict or block blood flow through arteries. In addition, the plaques are sites of thrombosis and embolism formation.

Some investigators propose that arteriosclerosis is not a pathological process but an aging or wearing-out process. Evidence also suggests that arteriosclerosis may be caused by inflammation, possibly a result of autoimmune disease. Atherosclerosis has been studied extensively, and many risk factors have been associated with the development of atherosclerotic plaques. These risk factors include being elderly, being a male, being a postmenopausal woman, having a family history of atherosclerosis, smoking cigarettes, having hypertension, having diabetes mellitus, having increased blood LDL and cholesterol levels, being overweight, leading a sedentary lifestyle, and having high blood triglyceride levels. Avoiding the environmental factors that influence atherosclerosis slows the development of atherosclerotic plaques. In some cases, the severity of the plaques can be reduced by behavioral modifications and/or drug therapy. For example, regulating blood glucose levels in people with diabetes mellitus and taking drugs that lower high blood cholesterol can provide some protection.

ASSESS YOUR PROGRESS

15. *Describe the innervation of blood vessel walls. Which types of vessels have the most innervation?*
16. *Describe the changes that occur in arteries due to aging. In which vessels do the most significant changes occur?*

21.3 Pulmonary Circulation

LEARNING OUTCOME

After reading this section, you should be able to

A. **Trace the path of blood flow in pulmonary circulation.**

The **pulmonary** (pŭl′mō-nār-ē; relating to the lungs) **circulation** is the system of blood vessels that carries blood from the right ventricle of the heart to the lungs and back to the left atrium of the heart. The heart pumps deoxygenated blood from the right ventricle into a short artery (about 5 cm long) called the **pulmonary trunk** (figure 21.9). The pulmonary trunk then branches into the right and left **pulmonary arteries,** transporting blood to the right lung and left lung, respectively. Within the lungs, gas exchange occurs between the air in the lungs and the blood. Two **pulmonary veins** exit each lung. All four of the pulmonary veins carry oxygenated blood to the left atrium (see figure 20.10).

ASSESS YOUR PROGRESS

17. *Name, in order, the vessels of pulmonary circulation, beginning with the right ventricle.*

21.4 Systemic Circulation: Arteries

LEARNING OUTCOME

After reading this section, you should be able to

A. **List the major arteries that supply each of the body areas.**

The **systemic circulation** is the system of vessels that carries blood from the left ventricle of the heart to the tissues of the body and back to the right atrium. Oxygenated blood entering the heart from the pulmonary veins passes through the left atrium into the left ventricle. The left ventricle pumps blood into the aorta. Blood flows from the aorta to all parts of the body (figure 21.9).

Aorta

All arteries of the systemic circulation are derived either directly or indirectly from the **aorta** (ā-ōr′tă). The aorta is usually divided into three general parts: (1) the ascending aorta, (2) the aortic arch, and (3) the descending aorta. The descending aorta is further divided into the thoracic aorta and the abdominal aorta (see figure 21.15).

At its origin from the left ventricle, the aorta is approximately 2.8 cm in diameter. Because it passes superiorly from the heart, this part is called the **ascending aorta.** It is approximately 5 cm long and has only two arteries branching from it: (1) the **right coronary artery** and (2) the **left coronary artery,** which supply blood to the cardiac muscle (see figure 20.6*a*).

The aorta then arches posteriorly and to the left as the **aortic arch.** Three major arteries branch from the aortic arch and carry blood to the head and upper limbs. These arteries are (1) the **brachiocephalic artery,** (2) the **left common carotid artery,** and (3) the **left subclavian artery.**

The next part of the aorta is the **descending aorta.** The descending aorta is the longest part of the aorta and it extends through the thorax in the left side of the mediastinum and through the abdomen to the superior margin of the pelvis. The descending aorta is described in two parts: (1) the thoracic aorta and (2) the abdominal aorta. The **thoracic aorta** is the portion of the descending aorta located in the thorax. It has several branches that supply various structures between the aortic arch and the diaphragm. The **abdominal aorta** is the part of the descending aorta that extends from the diaphragm to the point at which the aorta divides into the two **common iliac** (il′ē-ak; relating to the flank area) **arteries.** The abdominal aorta has several branches that supply the abdominal wall and organs. Its terminal branches, the common iliac arteries, supply blood to the pelvis and lower limbs.

Trauma that ruptures the aorta is almost immediately fatal. Trauma can also lead to an **aneurysm** (an′ū-rizm), a bulge caused by a weakened spot in the aortic wall. Once the aneurysm forms, it is likely to enlarge and may rupture. The weakened aortic wall may leak blood slowly into the thorax and must be corrected surgically. The majority of traumatic aortic arch ruptures occur during automobile accidents when the body is thrown with great force into the steering wheel, the dashboard, or some other object. This type of injury is effectively prevented by shoulder-type safety belts and air bags.

Coronary Arteries

The **coronary** (kōr′o-năr-ē; encircling the heart like a crown) **arteries,** which are the only branches of the ascending aorta, are described in chapter 20.

Arteries of the Head and Neck

The first vessel to branch from the aortic arch is the **brachiocephalic** (brā′kē-ō-se-fal′ik; arm and head) **artery** (figure 21.10). This short artery branches at the level of the clavicle to form the **right common carotid** (ka-rot′id) **artery** and the **right subclavian** (sŭb-klā′vē-an; below the clavicle) **artery.** The right common carotid artery transports blood to the right side of the head and neck, and the right subclavian artery transports blood to the right upper limb (see figures 21.9, 21.10, and 21.12).

The second branch of the aortic arch is the **left common carotid artery,** which transports blood to the left side of the head and neck. The third branch of the aortic arch is the **left subclavian artery,** which transports blood to the left upper limb.

The common carotid arteries extend superiorly, without branching, along each side of the neck, from their base to the inferior angle of the mandible. At this point, each common carotid artery branches into **internal** and **external carotid arteries** (figure 21.10; see figure 21.12). At the point of bifurcation on each side of the neck, the common carotid artery and the base of the internal carotid artery are dilated slightly to form the **carotid sinus,** which is important in monitoring blood pressure (baroreceptor reflex). The external carotid arteries have several branches that supply the structures of the neck and face (table 21.1; figure 21.10; see figure 21.12). The internal carotid arteries, together with the vertebral arteries, which are branches of the subclavian arteries, supply the brain (see figures 21.10, 21.11, and 21.12; table 21.1).

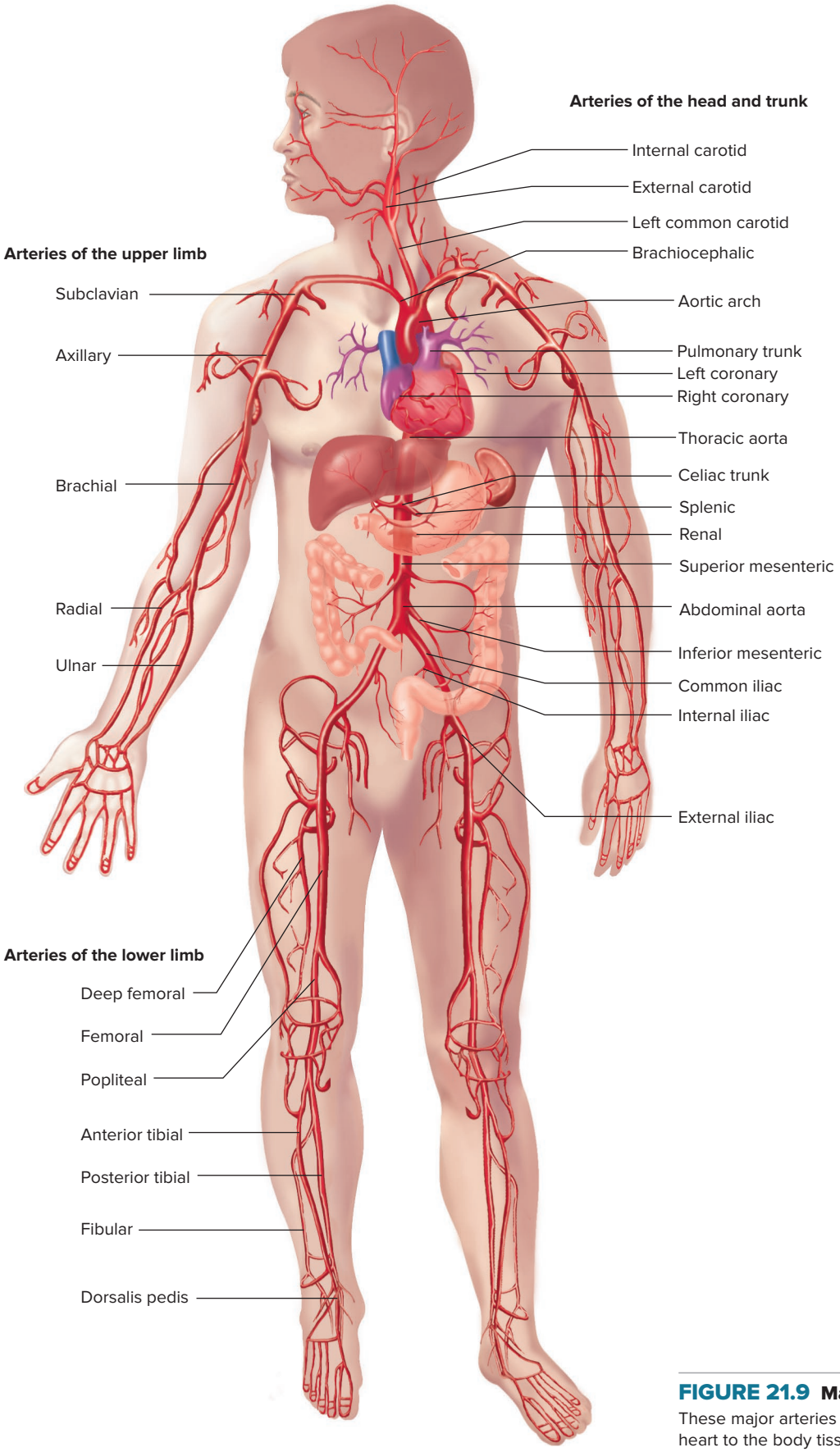


FIGURE 21.9 Major Arteries
These major arteries carry blood from the heart to the body tissues. AP|R

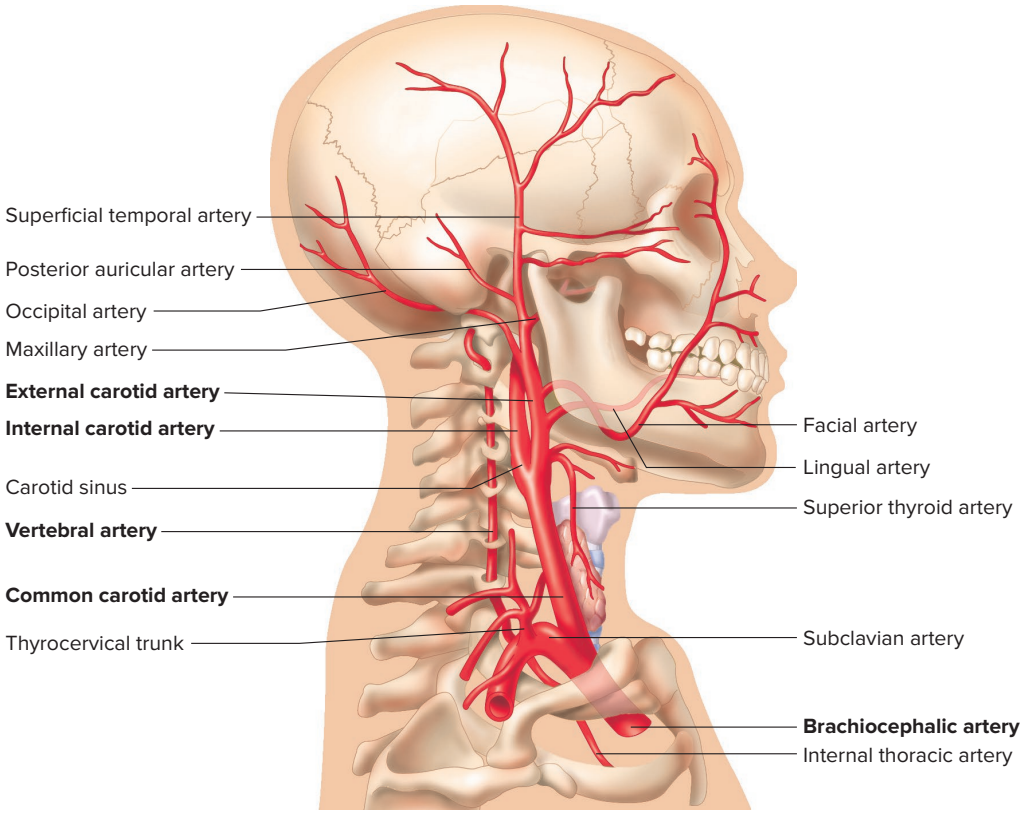


FIGURE 21.10 Arteries of the Head and Neck

The brachiocephalic artery, the right common carotid artery, and the right vertebral artery supply the head and neck. The right common carotid artery branches from the brachiocephalic artery, and the vertebral artery branches from the subclavian artery. AP|R

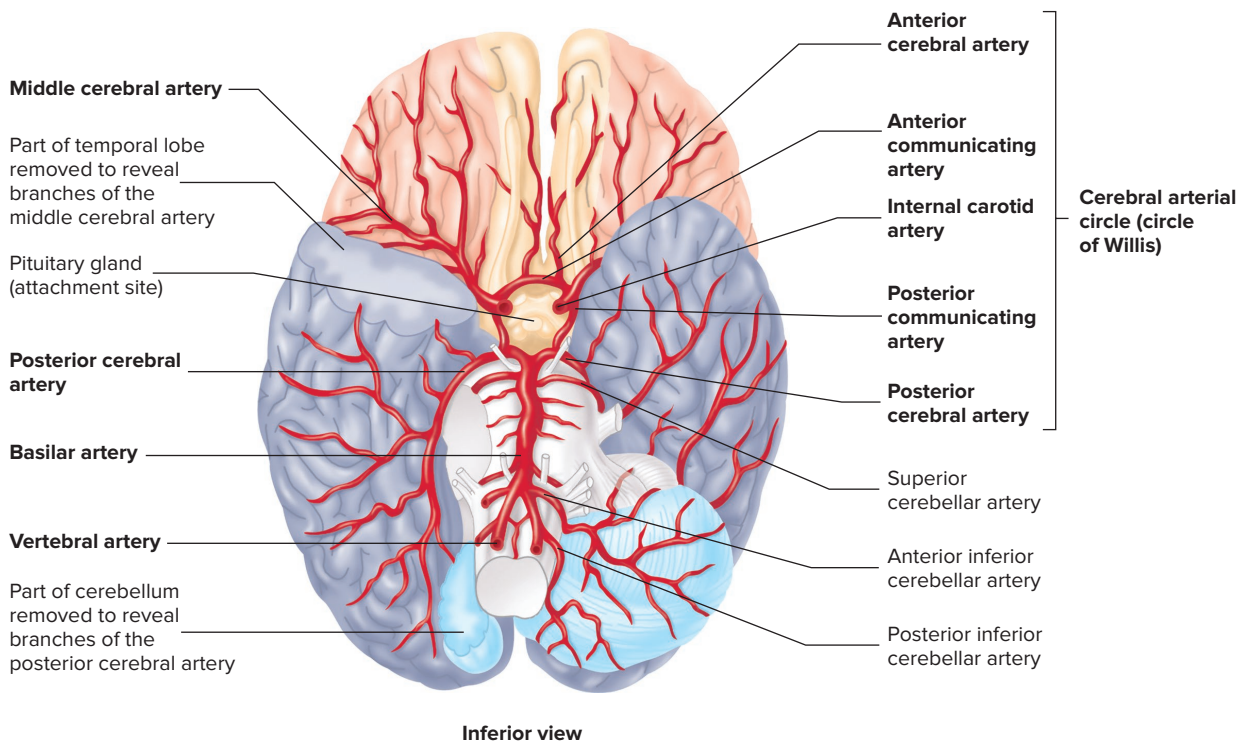


FIGURE 21.11 Cerebral Arterial Circle (Circle of Willis)

The internal carotid and vertebral arteries carry blood to the brain. The vertebral arteries join to form the basilar artery. Branches of the internal carotid arteries and the basilar artery supply blood to the brain and complete a circle of arteries around the pituitary gland and the base of the brain called the cerebral arterial circle (circle of Willis). AP|R

TABLE 21.1 Arteries of the Head and Neck (figures 21.10, 21.11, and 21.12)

Arteries	Tissues Supplied
Common Carotid Arteries	Head and neck by branches listed below
External Carotid	
Superior thyroid	Neck, larynx, and thyroid gland
Lingual	Tongue, mouth, and submandibular and sublingual glands
Facial	Mouth, pharynx, and face
Occipital	Posterior head and neck and meninges around posterior brain
Posterior auricular	Middle and inner ear, head, and neck
Ascending pharyngeal	Deep neck muscles, middle ear, pharynx, soft palate, and meninges around posterior brain
Superficial temporal	Temple, face, and anterior ear
Maxillary	Middle and inner ears, meninges, lower jaw and teeth, upper jaw and teeth, temple, external eye structures, face, palate, and nose
Internal Carotid	
Posterior communicating	Joins the posterior cerebral artery
Anterior cerebral	Anterior portions of the cerebrum; forms the anterior communicating arteries
Middle cerebral	Most of the lateral surface of the cerebrum
Vertebral Arteries (branches of the subclavian arteries)	
Anterior spinal	Anterior spinal cord
Posterior inferior cerebellar	Cerebellum and fourth ventricle
Basilar Artery (formed by junction of vertebral arteries)	
Anterior interior cerebellar	Cerebellum
Superior cerebellar	Cerebellum and midbrain
Posterior cerebral	Posterior portions of the cerebrum

Predict 1

The term *carotid* means "to put to sleep," implying that, if the carotid arteries are occluded for even a short time, the patient can lose consciousness (go to sleep). The blood supply to the brain is extremely important to brain function. Elimination of this supply for even a relatively short time can result in permanent brain damage because the brain is dependent on oxidative metabolism and quickly malfunctions in the absence of oxygen. What is the physiological significance of arteriosclerosis, which slowly reduces blood flow through the carotid arteries?

The **left** and **right vertebral arteries** originate from the left and right subclavian arteries, respectively, and pass through the transverse foramina of the cervical vertebrae. They enter the cranial cavity through the foramen magnum. Within the cranial cavity, the left and right vertebral arteries both give off arteries to the cerebellum. The left and right vertebral arteries unite to form a single, midline **basilar** (bas′i-lăr) **artery** (figures 21.11 and 21.12; table 21.1). The basilar artery gives off branches to the pons and the cerebellum. The left and right vertebral arteries branch to form the **posterior cerebral arteries,** which supply the posterior part of the cerebrum (see figure 21.11).

The internal carotid arteries enter the cranial cavity through the carotid canals and give off branches, including the **middle cerebral arteries** and the **anterior cerebral arteries.** The middle cerebral arteries supply large parts of the lateral cerebral cortex and the anterior cerebral arteries supply blood to the frontal lobes of the cerebrum (see figure 21.11). The two anterior cerebral arteries are connected to each other by an anterior communicating artery. The middle cerebral arteries connect to the posterior cerebral arteries by way of the **posterior communicating arteries.** These connections complete a circle around the pituitary gland and the base of the brain called the **cerebral arterial circle** (circle of Willis; see figures 21.11 and 21.12).

A **stroke** is a sudden neurological disorder, often caused by decreased blood supply to a part of the brain. It can occur as a result of a thrombosis, an embolism, or a hemorrhage. Any one of these conditions can reduce the brain's blood supply or cause trauma to a part of the brain. As a result, the tissue normally supplied by the arteries becomes **necrotic** (nĕ-krot′ik; dead), forming

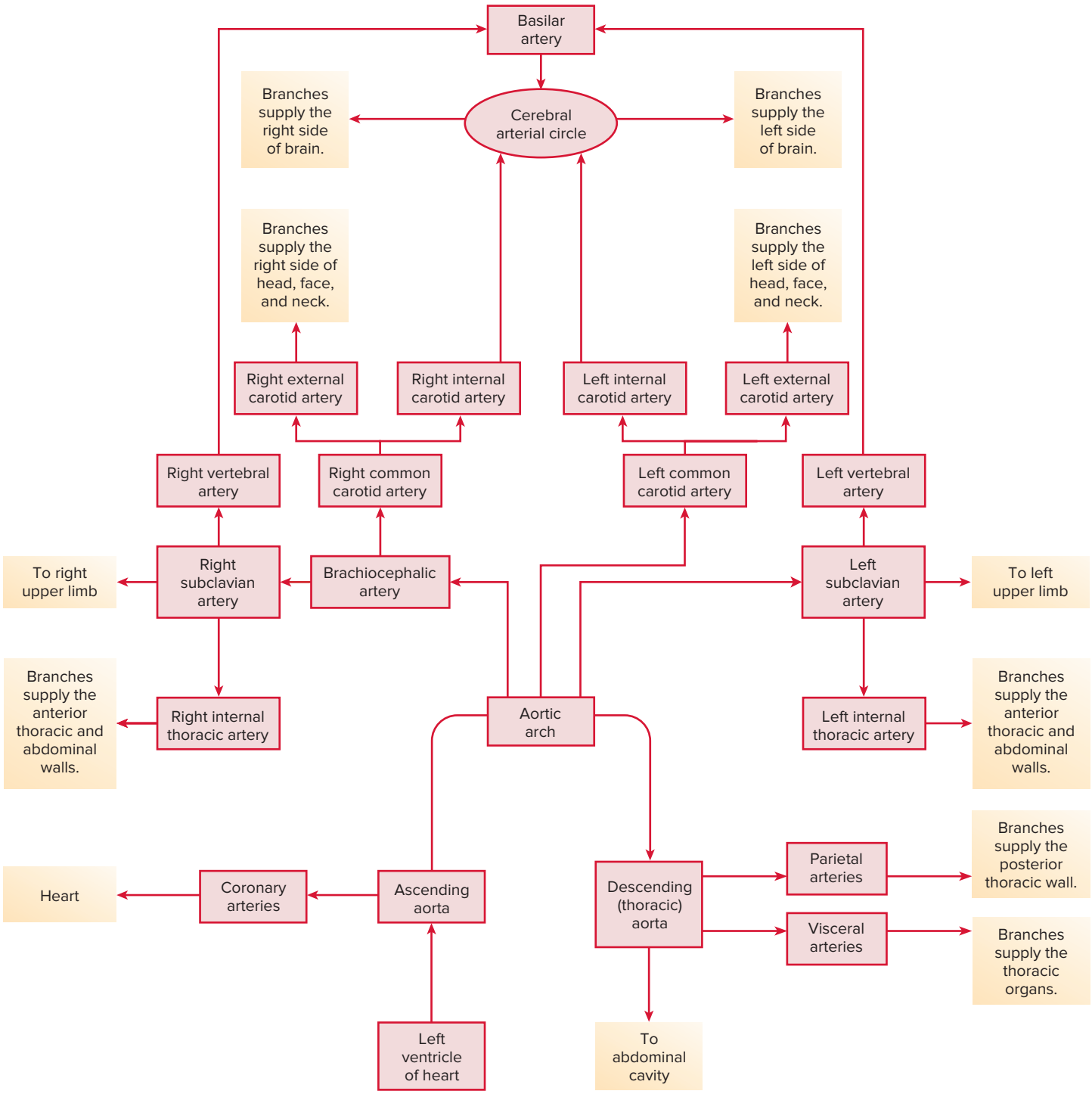


FIGURE 21.12 Major Arteries of the Head and Thorax

The relationships among the major arteries that supply blood to the structures of the head and thorax are illustrated in the diagram with red arrows indicating the direction of blood flow. Compare this diagram with the anatomical representations in figures 21.9, 21.10, and 21.11.

an infarct in the affected area(s). The neurological results of a stroke are described in chapter 14.

Arteries of the Upper Limb

The three major arteries of the upper limb are the (1) **subclavian artery,** (2) **axillary artery,** and (3) **brachial artery.** These arteries form a continuum rather than a branching system. The subclavian artery is located deep to the clavicle. The axillary artery is the continuation of the subclavian artery in the axilla. The brachial artery is the continuation of the axillary artery as it passes into the arm (figures 21.13 and 21.14; table 21.2).

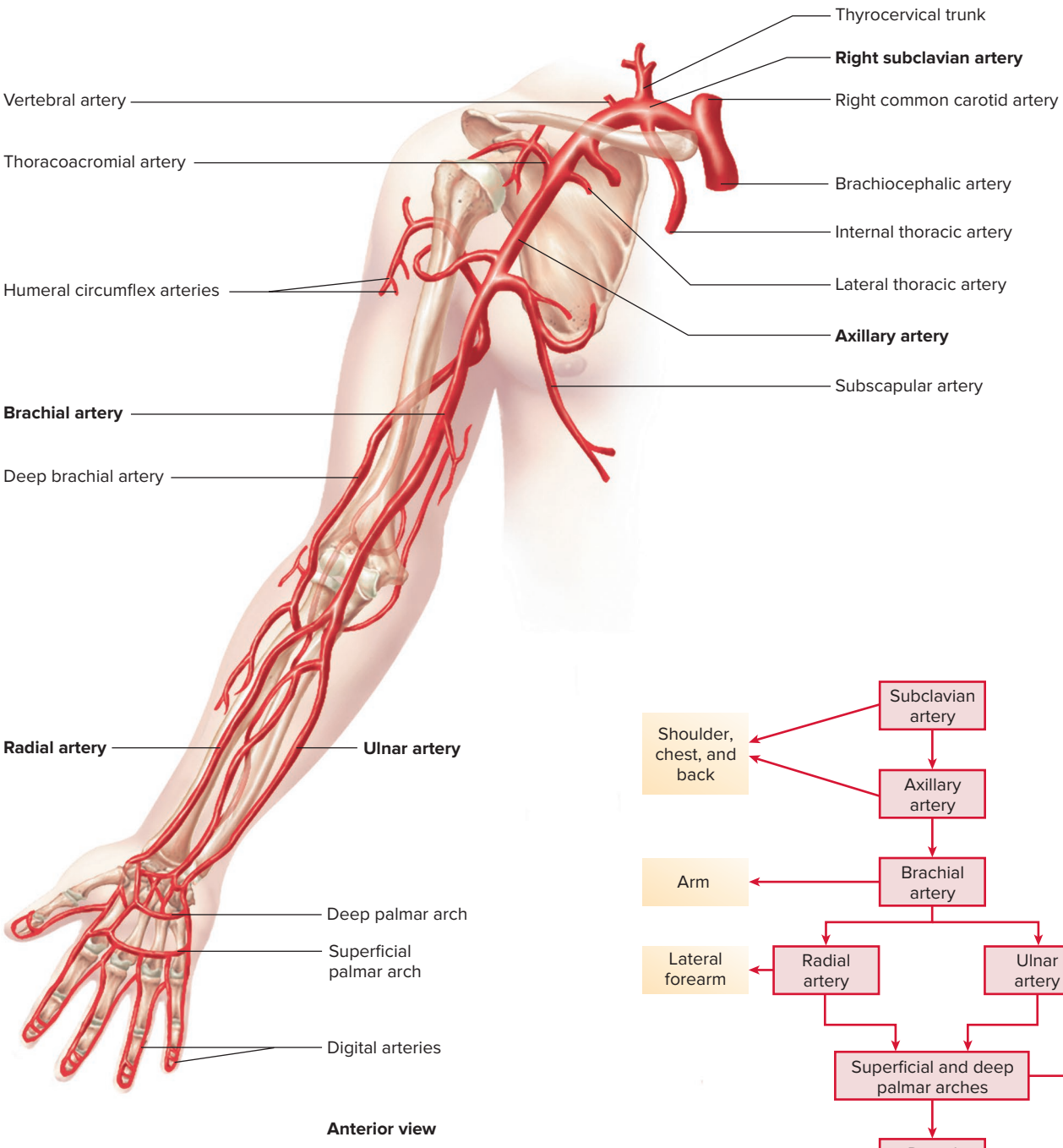


FIGURE 21.13 Arteries of the Upper Limb
The arteries of the right upper limb and their branches: the right brachiocephalic, subclavian, axillary, radial, and ulnar arteries and their branches. AP|R

FIGURE 21.14 Major Arteries of the Shoulder and Upper Limb
The relationships among the major arteries of the shoulder and upper limb are illustrated in the diagram with red arrows indicating direction of blood flow. Compare this diagram with the anatomical representation in figure 21.13.

The brachial artery divides at the elbow into **ulnar** and **radial arteries,** which form two arches within the palm of the hand: (1) The **superficial palmar arch** is formed by the ulnar artery and is completed by anastomosing with the radial artery; and (2) the **deep palmar arch** is formed by the radial artery and is completed by anastomosing with the ulnar artery. This arch is not only deep to the superficial arch but proximal as well.

Digital (dij′i-tăl; relating to the digits—the fingers and the thumb) **arteries** branch from each of the two palmar arches and unite to form single arteries on the medial and lateral sides of each digit.

TABLE 21.2 **Arteries of the Upper Limb (figures 21.13 and 21.14)**

Arteries	Tissues Supplied
Subclavian Arteries (right subclavian originates from the brachiocephalic artery, and left subclavian originates directly from the aorta)	
Vertebral	Spinal cord and cerebellum form the basilar artery (see table 21.1)
Internal thoracic	Diaphragm, mediastinum, pericardium, anterior thoracic wall, and anterior abdominal wall
Thyrocervical trunk	Inferior neck and shoulder
Axillary Arteries (continuation of subclavian)	
Thoracoacromial	Pectoral region and shoulder
Lateral thoracic	Pectoral muscles, mammary gland, and axilla
Subscapular	Scapular muscles
Brachial Arteries (continuation of axillary arteries)	
Deep brachial	Arm and humerus
Radial	Forearm
Deep palmar arch	Hand and fingers
Digital arteries	Fingers
Ulnar	Forearm
Superficial palmar arch	Hand and fingers
Digital arteries	Fingers

ASSESS YOUR PROGRESS

18. *Name the parts of the aorta.*
19. *Name the arteries that branch from the ascending aorta to supply the heart.*
20. *Name the arteries that branch from the aorta to supply the head and neck.*
21. *List the arteries that are part of, and branch from, the cerebral arterial circle.*
22. *Name the arteries that branch from the aorta to supply the upper limbs.*
23. *List, in order, the arteries that travel through the upper limb to the digits.*

Thoracic Aorta and Its Branches

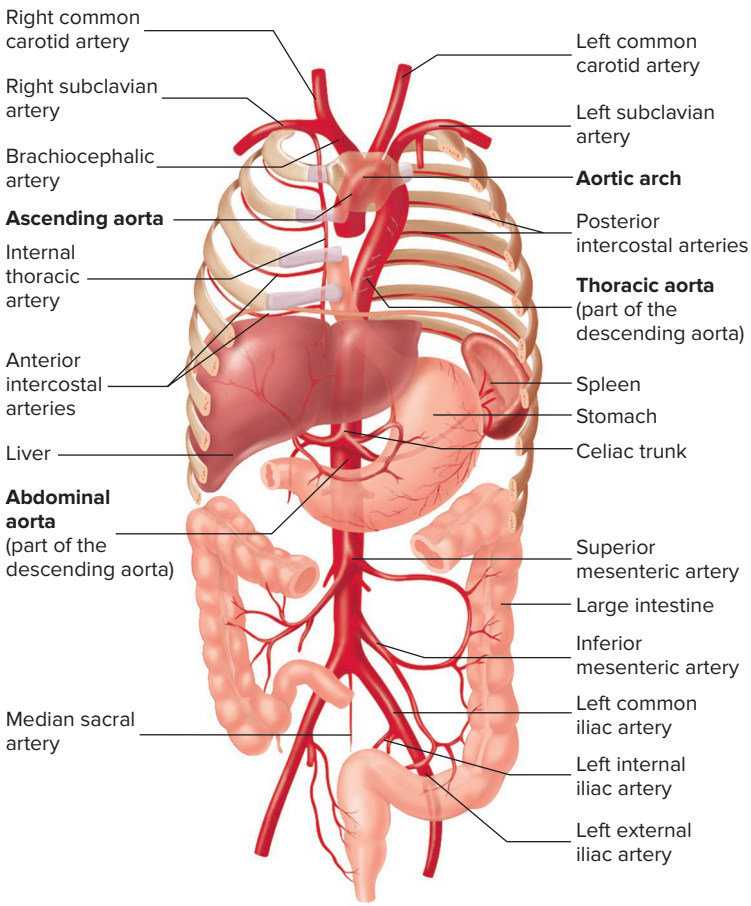
Recall that the descending aorta is divided into the thoracic aorta of the thoracic cavity and the abdominal aorta of the abdominal cavity. The branches of the thoracic aorta are divided into two groups: (1) the **visceral branches** supplying portions of the thoracic organs and (2) the **parietal branches** supplying portions of the thoracic wall (figure 21.15*a,b;* table 21.3). The visceral branches supply a portion of the lungs, including the bronchi and bronchioles (see chapter 23), as well as the esophagus, and the pericardium. Even though a large quantity of blood flows to the lungs through the pulmonary arteries, the bronchi and bronchioles require a separate oxygenated blood supply through small bronchial branches from the thoracic aorta.

The thoracic walls are supplied with blood by the **intercostal** (in-ter-kos′tăl; between the ribs) **arteries,** which consist of two sets:

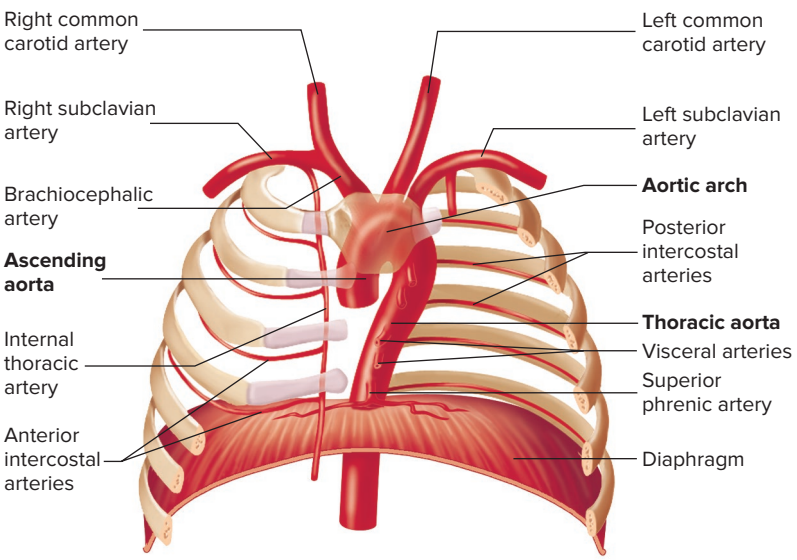
1. The **anterior intercostals** are derived from the **internal thoracic arteries,** which are branches of the subclavian arteries. They lie on the inner surface of the anterior thoracic wall (figure 21.15*a,b;* table 21.3).
2. The **posterior intercostals** are parietal arteries that are derived as bilateral branches directly from the descending aorta. The anterior and posterior intercostal arteries lie along the inferior margin of each rib and anastomose with each other approximately midway between the ends of the ribs. **Superior phrenic** (fren′ik; to the diaphragm) **arteries** supply blood to the diaphragm.

Abdominal Aorta and Its Branches

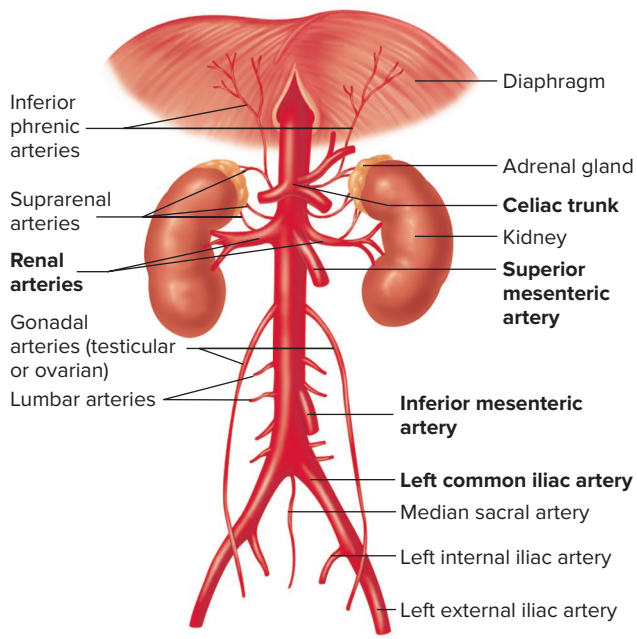
The branches of the abdominal aorta, like those of the thoracic aorta, are divided into visceral and parietal parts (figures 21.15*a,c* and 21.16; table 21.3). The visceral arteries are in turn divided into paired and unpaired branches. There are three major unpaired branches of the abdominal aorta: (1) the **celiac** (sē′lē-ak; belly) **trunk,** (2) the **superior mesenteric** (mez-en-ter′ik; relating to the mesenteries) **artery,** and (3) the **inferior mesenteric artery** (see figure 21.15*a,c*). Each has several major branches supplying the abdominal organs.



(a) **Anterior view**



(b) **Thoracic aorta, anterior view**



(c) **Abdominal aorta, anterior view**

FIGURE 21.15 Branches of the Aorta

(*a*) The aorta is considered in three portions: the ascending aorta, the aortic arch, and the descending aorta. The descending aorta consists of the thoracic aorta and the abdominal aorta. (*b*) The thoracic aorta. (*c*) The abdominal aorta.

TABLE 21.3 Thoracic and Abdominal Aorta (figures 21.15 and 21.16)

Arteries	Tissues Supplied
Thoracic Aorta	
Visceral Branches	
Bronchial	Lung tissue
Esophageal	Esophagus
Parietal Branches	
Intercostal	Thoracic wall
Superior phrenic	Superior surface of diaphragm
Abdominal Aorta	
Visceral Branches	
Unpaired	
Celiac trunk	
Left gastric	Stomach and esophagus
Common hepatic	
Gastroduodenal	Stomach and duodenum
Right gastric	Stomach
Hepatic	Liver
Splenic	Spleen and pancreas
Left gastroepiploic	Stomach
Superior mesenteric	Pancreas, small intestine, and colon
Inferior mesenteric	Descending colon and rectum
Paired	
Suprarenal	Adrenal gland
Renal	Kidney
Gonadal	
Testicular (male)	Testis and ureter
Ovarian (female)	Ovary, ureter, and uterine tube
Parietal Branches	
Inferior phrenic	Adrenal gland and inferior surface of diaphragm
Lumbar	Lumbar vertebrae and back muscles
Median sacral	Inferior vertebrae
Common iliac	
External iliac	Lower limb (see table 21.5)
Internal iliac	Lower back, hip, pelvis, urinary bladder, vagina, uterus, rectum, and external genitalia (see table 21.4)

TABLE 21.4 Arteries of the Pelvis (figures 21.16 and 21.17)

Arteries	Tissues Supplied
Internal Iliac	Pelvis through the branches listed below
Visceral Branches	
Middle rectal	Rectum
Vaginal	Vagina and uterus
Uterine	Uterus, vagina, uterine tube, and ovary
Parietal Branches	
Lateral sacral	Sacrum
Superior gluteal	Muscles of the gluteal region
Obturator	Pubic region, deep groin muscles, and hip joint
Internal pudendal	Rectum, external genitalia, and floor of pelvis
Inferior gluteal	Inferior gluteal region, coccyx, and proximal thigh

The paired visceral branches of the abdominal aorta supply the kidneys, adrenal glands, and gonads (testes and ovaries). The parietal arteries of the abdominal aorta supply the diaphragm and the abdominal wall (figure 21.16).

Arteries of the Pelvis

At the level of the fifth lumbar vertebra, the abdominal aorta divides into two **common iliac arteries.** The common iliac arteries then divide to form the **external iliac arteries,** which enter the lower limbs, and the **internal iliac arteries,** which supply the pelvic area. Visceral branches of the abdominal aorta supply the pelvic organs, such as the urinary bladder, rectum, uterus, and vagina. Parietal branches of the abdominal aorta supply blood to the walls and floor of the pelvis; the lumbar, gluteal, and proximal thigh muscles; and the external genitalia (figures 21.16 and 21.17; table 21.4).

Arteries of the Lower Limb

The arteries of the lower limb form a continuum similar to that of the arteries of the upper limb. The **external iliac artery** becomes the **femoral** (fem′ŏ-răl; relating to the thigh) **artery** in the thigh, which becomes the **popliteal** (pop-lit′ē-ăl, pop-li-tē′ăl; ham, the hamstring area posterior to the knee) **artery** in the popliteal space. The popliteal artery gives off the **anterior tibial artery** just inferior to the knee and then continues as the **posterior tibial artery.** The anterior tibial artery becomes the **dorsalis pedis artery** at the foot. The posterior tibial artery gives off the **fibular artery,** or *peroneal artery,* and then gives rise to **medial** and **lateral plantar** (plan′tăr; the sole of the foot) **arteries,** which in turn give off **digital branches** to the toes. The arteries of the lower limb are illustrated in figures 21.17 and 21.18 and are listed in table 21.5.

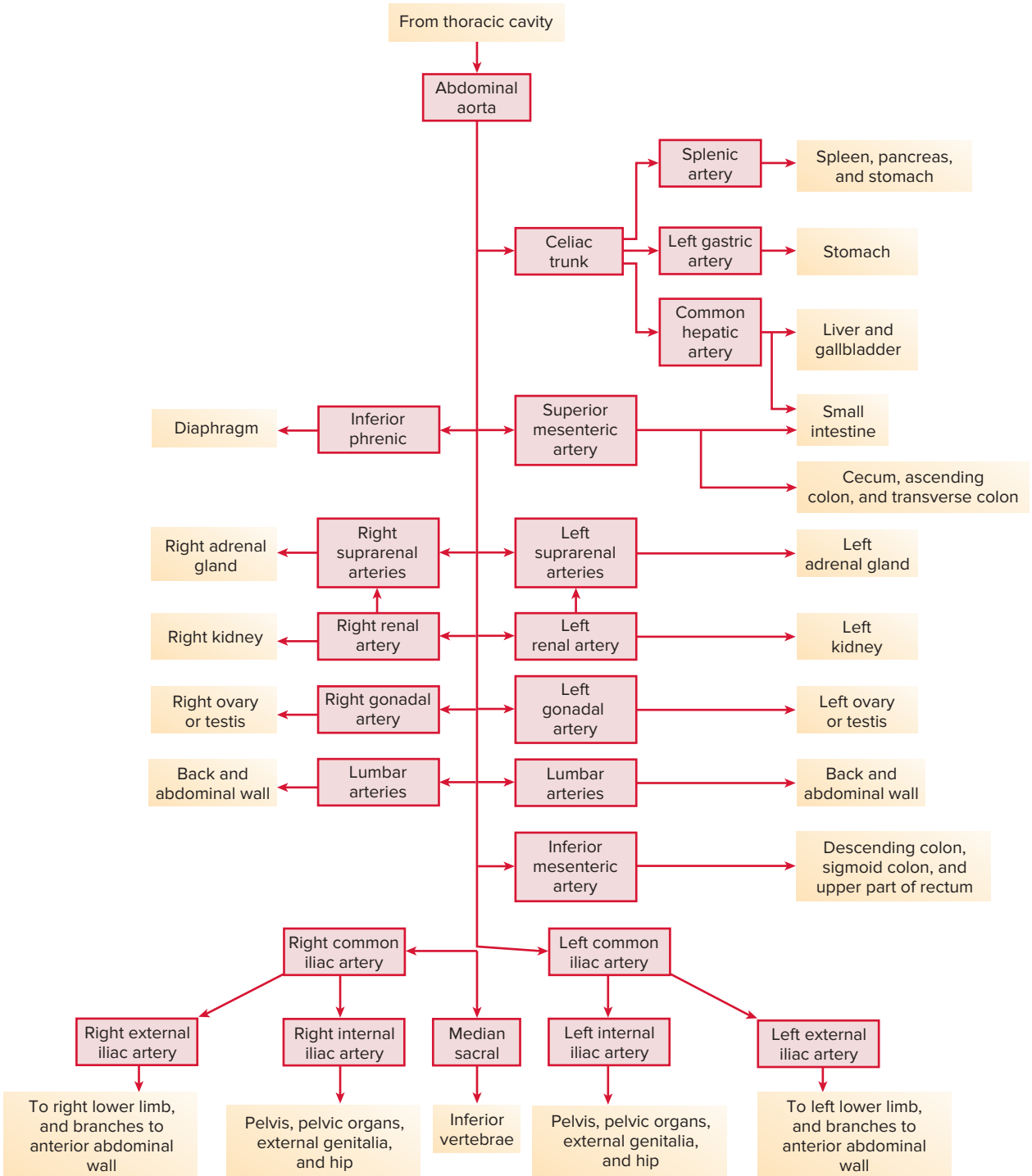


FIGURE 21.16 Major Arteries of the Abdomen and Pelvis

Visceral branches include those that are unpaired (celiac trunk, superior mesenteric, and inferior mesenteric) and those that are paired (renal, suprarenal, testicular, and ovarian). Parietal branches include inferior phrenic, lumbar, and median sacral. The relationships among the arteries of the abdomen and pelvis are illustrated in the diagram with red arrows indicating the direction of blood flow. Compare this diagram with the anatomical representation in figure 21.15.

ASSESS YOUR PROGRESS

24. *Name the two types of branches arising from the thoracic aorta. What structures are supplied from each group?*

25. *What areas of the body are supplied by the paired arteries that branch from the abdominal aorta? The unpaired arteries? Name the three major unpaired arteries.*

26. *Name the arteries that branch from the aorta to supply the pelvic area. List the organs of the pelvis that are supplied by branches of these arteries.*

27. *List, in order, the arteries that travel from the aorta to the digits of the lower limbs.*

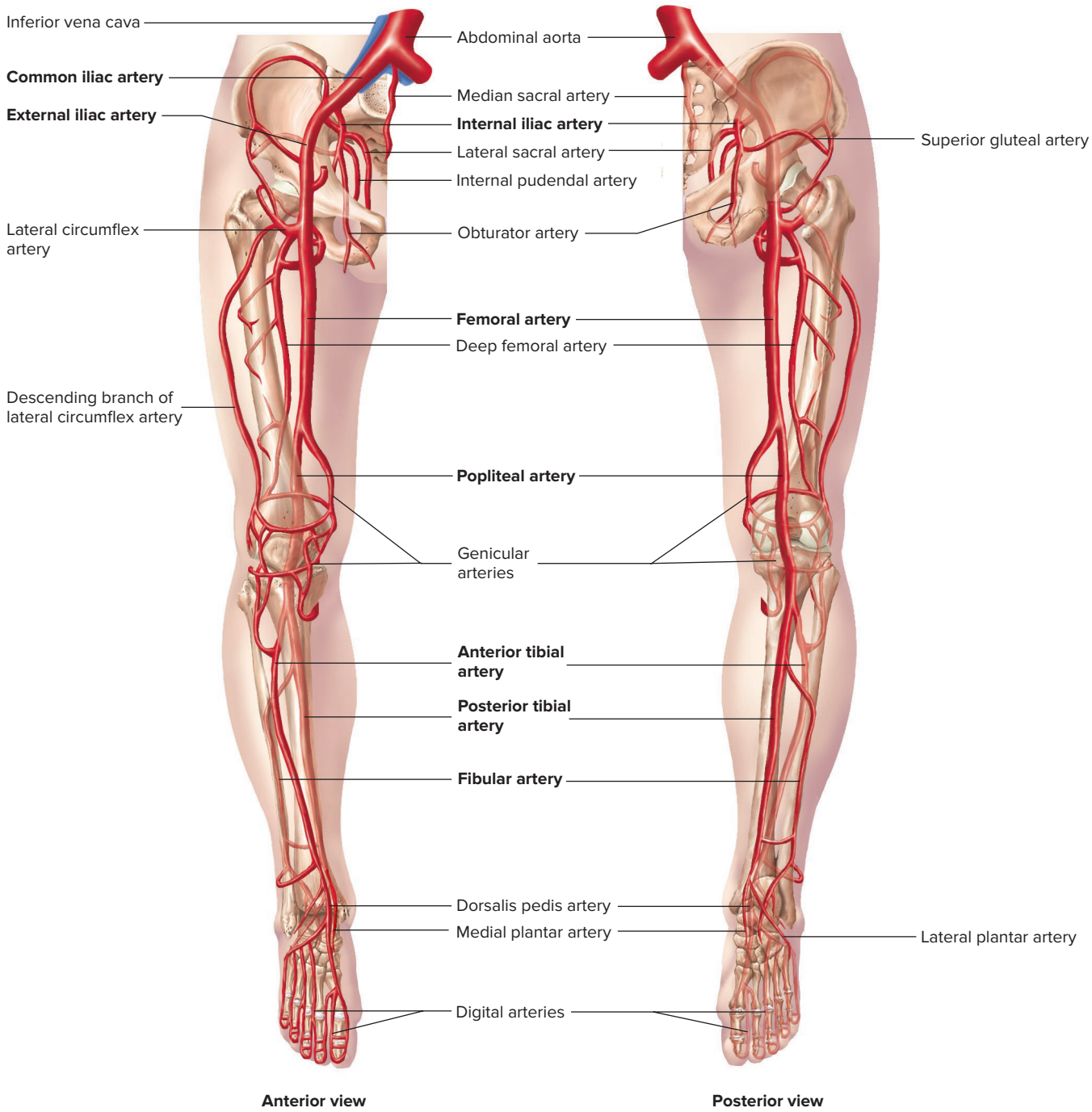


FIGURE 21.17 Arteries of the Pelvis and Lower Limb

The internal and external iliac arteries and their branches. The internal iliac artery supplies the pelvis and hip, and the external iliac artery supplies the lower limb through the femoral artery.

21.5 Systemic Circulation: Veins

LEARNING OUTCOME

After reading this section, you should be able to

A. **List the major veins that carry blood away from each of the body areas.**

Deoxygenated blood from the body is returned to the right atrium through three major veins: (1) the **coronary sinus,** returning blood from the walls of the heart (see figures 20.6*b* and 20.7); (2) the **superior vena cava** (vē′nă kā′vă, kā′vă; venous cave), returning blood from the head, neck, thorax, and upper limbs; and (3) the **inferior vena cava,** returning blood from the abdomen, pelvis, and lower limbs (figure 21.19).

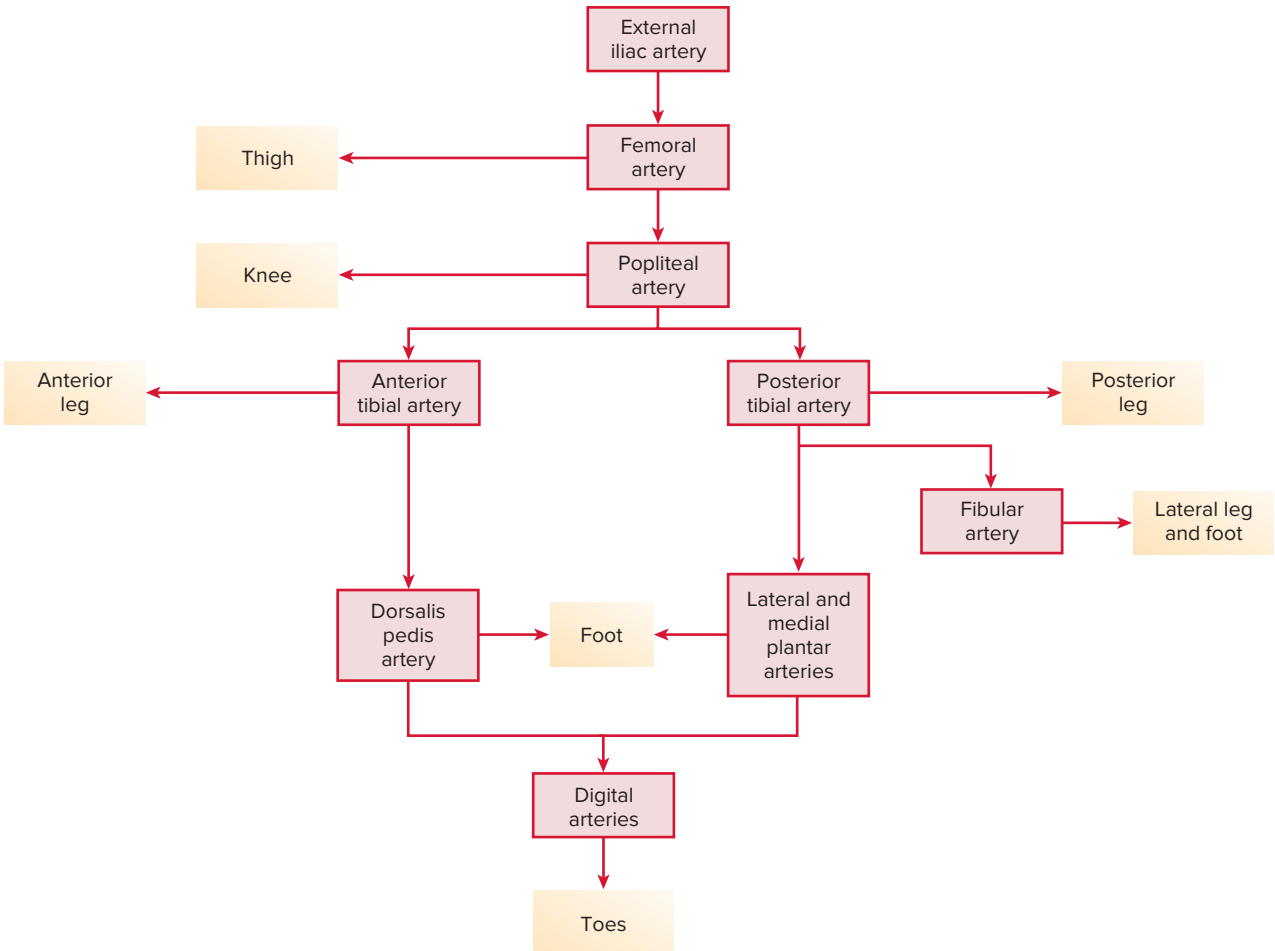


FIGURE 21.18 Major Arteries of the Lower Limb
The relationships among the major arteries of the lower limb are illustrated in the diagram with red arrows indicating the direction of blood flow. Compare this diagram with the anatomical representation in figure 21.17.

TABLE 21.5 Arteries of the Lower Limb (figures 21.17 and 21.18)

Arteries	Tissues Supplied
Femoral	Thigh, external genitalia, and anterior abdominal wall
Deep femoral	Thigh, knee, and femur
Popliteal (continuation of the femoral artery)	
Posterior tibial	Knee and leg
Fibular (peroneal)	Calf and peroneal muscles and ankle
Medial plantar	Plantar region of foot
Digital	Digits of foot
Lateral plantar	Plantar region of foot
Digital	Digits of foot
Anterior tibial	Knee and leg
Dorsalis pedis	Dorsum of foot
Digital	Digits of foot

In a very general way, the smaller veins follow the same course as the arteries, and many are given the same names. The veins, however, are more numerous and more variable. The larger veins often follow a very different course and have names different from the arteries.

Earlier in the chapter, we categorized veins based on size as venules, small veins, medium veins, and large veins. When describing the specific veins of the body, we often categorize veins based on location. In that situation, there are three major types of veins: (1) superficial veins, (2) deep veins, and (3) sinuses. In general, the superficial veins of the limbs are larger than the deep veins, whereas in the head and trunk the opposite is the case. Venous sinuses occur primarily in the cranial cavity and the heart.

Veins Draining the Heart

The **cardiac veins** transport blood from the walls of the heart and return it through the coronary sinus to the right atrium. A detailed description of the cardiac veins is found in chapter 20.

Veins of the Head and Neck

The two pairs of major veins that drain blood from the head and neck are (1) the **external jugular** (jŭg′ū-lar; neck) **veins** and

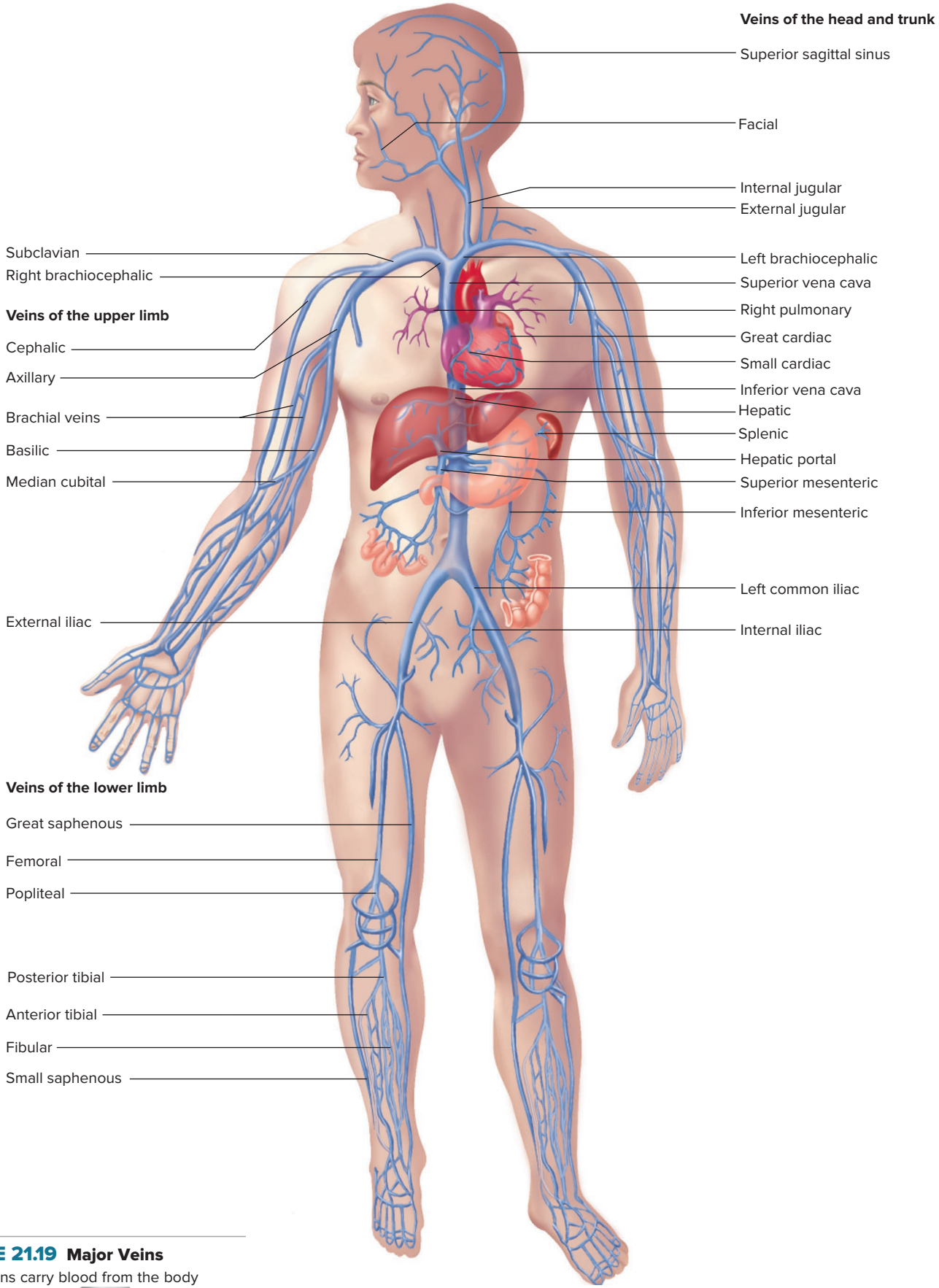


FIGURE 21.19 Major Veins
These veins carry blood from the body tissues to the heart. AP|R

(2) the **internal jugular veins.** The external jugular veins are the more superficial of the two sets, and they drain blood primarily from the posterior head and neck. The external jugular vein drains into the subclavian vein. The internal jugular veins are much larger and deeper than the external jugular veins. The internal jugular veins drain blood from the cranial cavity and the anterior head, face, and neck.

The internal jugular vein is formed primarily as the continuation of the **venous sinuses** of the cranial cavity. The venous sinuses are actually spaces within the dura mater surrounding the brain (see chapter 13). They are depicted in figure 21.20 and listed in table 21.6.

Once the internal jugular veins exit the cranial cavity, they receive several venous tributaries that drain the external head and face (figures 21.21 and 21.22; table 21.7). On each side of the body the internal jugular veins merge with the **subclavian veins** to form the **brachiocephalic veins.**

Veins of the Upper Limb

The **cephalic** (se-fal′ik; toward the head), **basilic** (ba-sil′ik), and **brachial veins** are responsible for draining most of the blood from the upper limbs (figures 21.23 and 21.24; table 21.8). Many of the tributaries of the cephalic and basilic veins in the forearm and hand can be seen through the skin. Because of the considerable variation in the tributary veins of the forearm and hand, they often are left unnamed. The basilic vein of the arm becomes the **axillary vein** as it passes through the axillary region. The cephalic vein empties into the axillary vein then becomes the **subclavian vein** at the margin of the first rib.

TABLE 21.6 Venous Sinuses of the Cranial Cavity (figure 21.20)

Veins	Tissues Drained
Internal Jugular Vein	
Sigmoid sinus	
Superior and inferior petrosal sinuses	Anterior portion of cranial cavity
Cavernous sinus	
Ophthalmic veins	Orbit
Transverse sinus	
Occipital sinus	Central floor of posterior fossa of skull
Superior sagittal sinus	Superior portion of cranial cavity and brain
Straight sinus	
Inferior sagittal sinus	Deep portion of longitudinal fissure

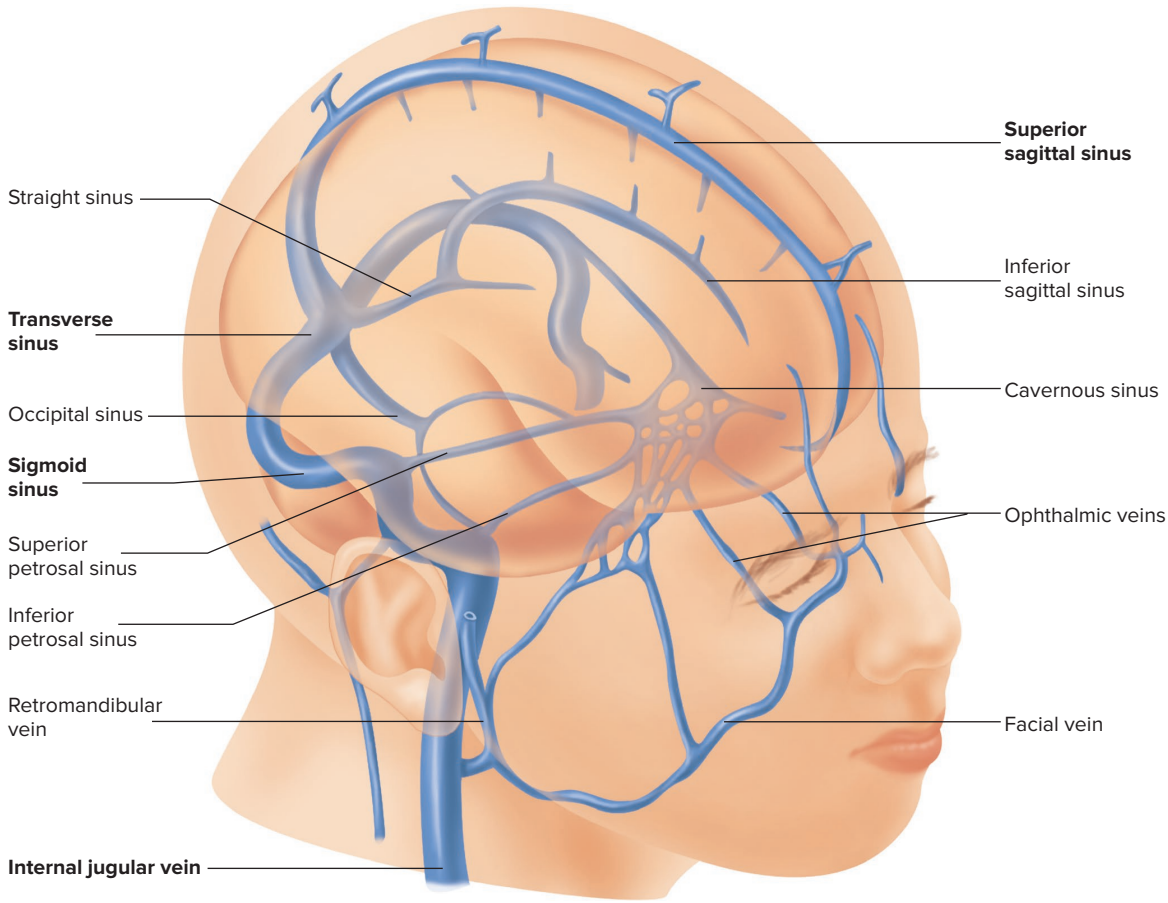


FIGURE 21.20 Venous Sinuses Associated with the Brain
The venous sinuses of the brain are drainage channels formed from the dura mater. These sinuses transport venous blood and cerebrospinal fluid away from the brain. The venous sinuses empty into the internal jugular veins.

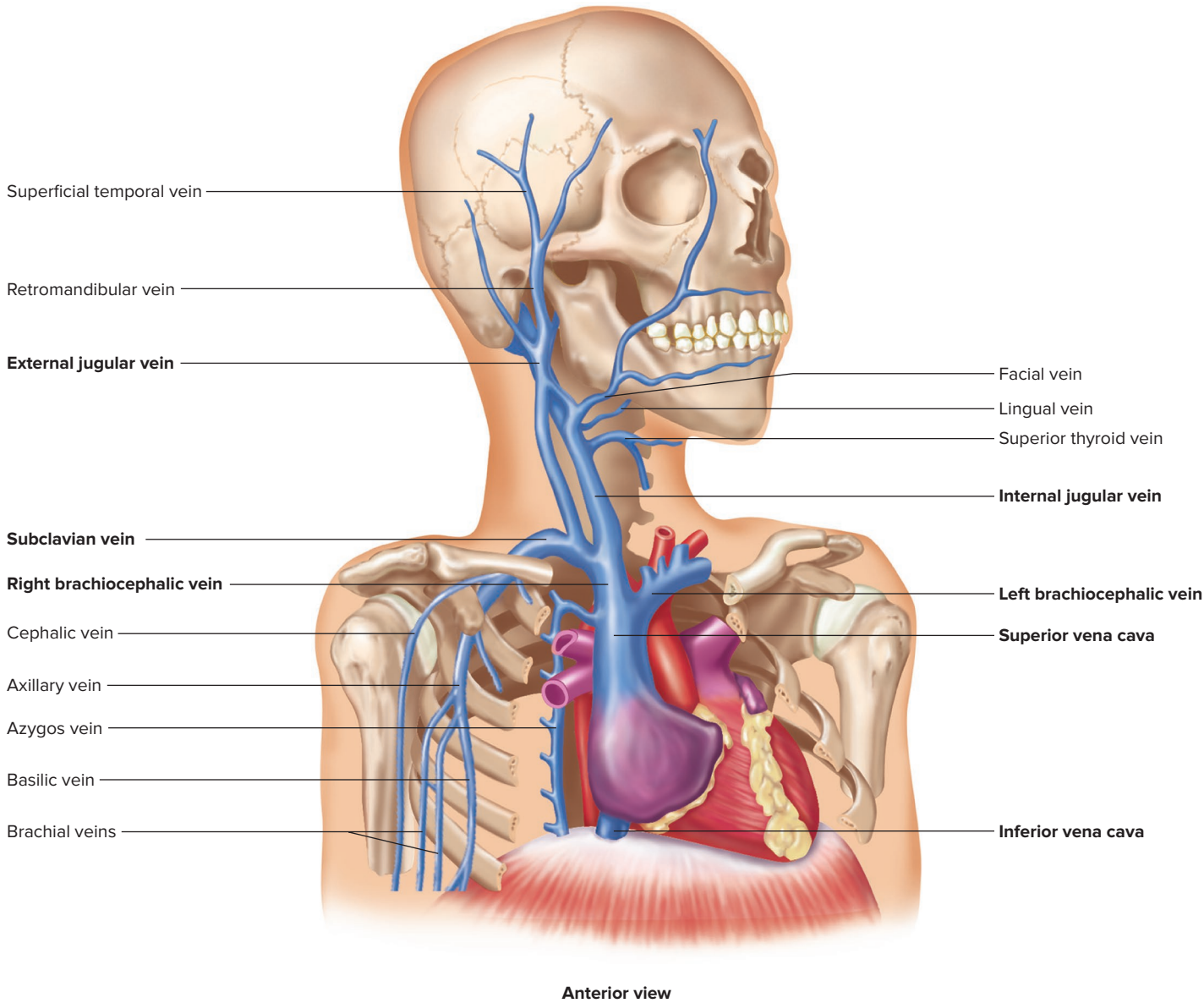


FIGURE 21.21 Veins of the Head and Neck
The right brachiocephalic vein and its tributaries. The major veins draining the head and neck are the internal and external jugular veins. AP|R

TABLE 21.7 **Veins Draining the Head and Neck (figures 21.21 and 21.22)**

Veins	Tissues Drained
Brachiocephalic	
Internal jugular	Brain
Lingual	Tongue and mouth
Superior thyroid	Thyroid and deep posterior facial structures (also empties into external jugular)
Facial	Superficial and anterior facial structures
External jugular	Superficial surface of posterior head and neck

The **median cubital** (kūʹbi-tăl; pertaining to the elbow) **vein** is a variable vein that usually connects the cephalic vein or its tributaries with the basilic vein. In many people, this vein is quite prominent on the anterior surface of the upper limb at the level of the elbow (cubital fossa); therefore, it is often used as a site for drawing blood from a patient.

The deep veins draining the upper limb follow the same course as the arteries. Thus, the **radial** and **ulnar veins** are named for the arteries they attend. They are usually paired, with one small vein lying on each side of the artery, and they have numerous connections with one another and with the superficial veins. The radial and ulnar veins empty into the **brachial veins,** which accompany the brachial artery and empty into the axillary vein (see figures 21.23 and 21.24).

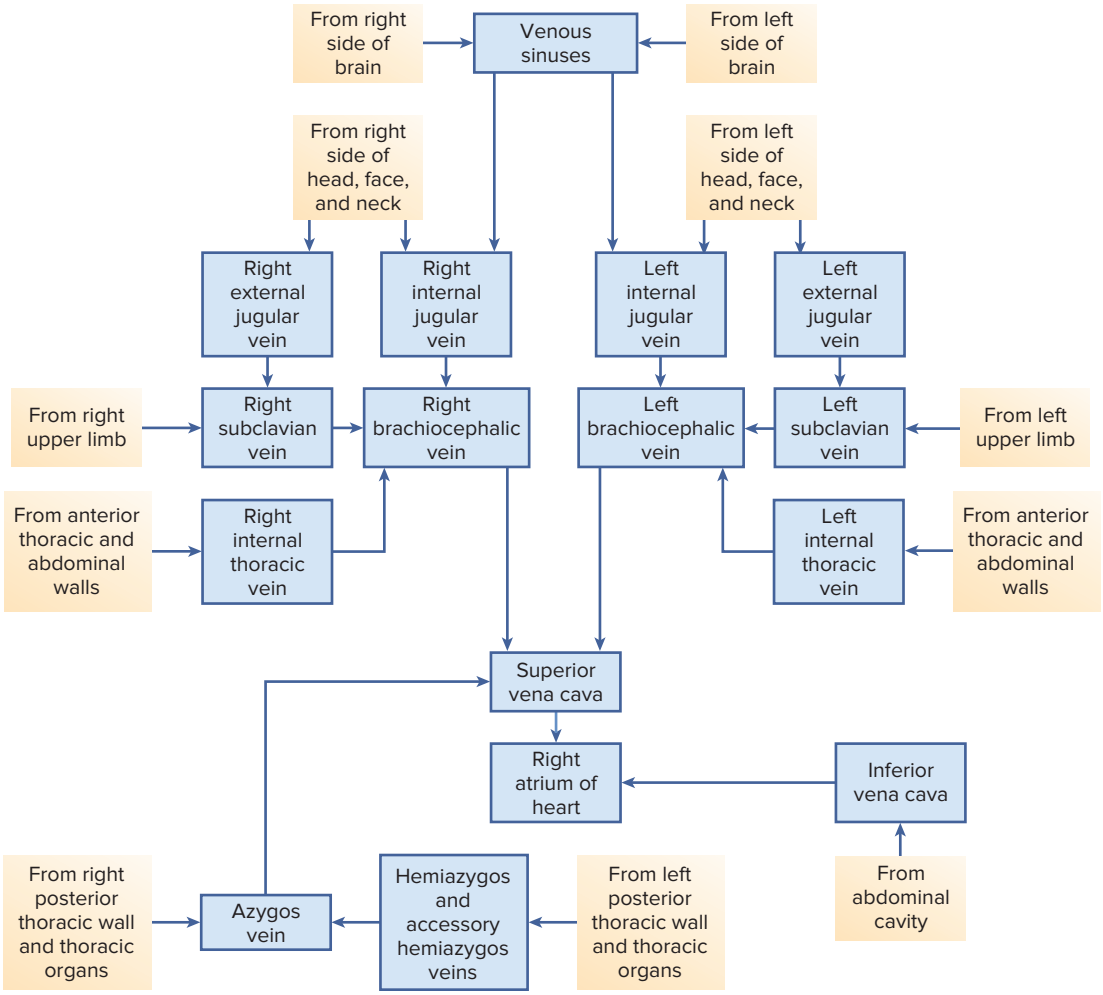


FIGURE 21.22 Major Veins of the Head and Thorax

The relationships among the major veins of the head and thorax are illustrated in the diagram with blue arrows indicating the direction of blood flow. Compare this diagram with the anatomical representation in figures 21.19, 21.20, 21.21, and 21.25.

TABLE 21.8 Veins of the Upper Limb (figures 21.23 and 21.24)

Veins	Tissues Drained
Subclavian (continuation of the axillary vein)	
Axillary (continuation of the basilic vein)	
Cephalic	Lateral arm, forearm, and hand (superficial veins of the forearm and hand are variable)
Brachial (paired, deep veins)	Deep structures of the arm
Radial	Deep forearm
Ulnar	Deep forearm
Basilic	Medial arm, forearm, and hand (superficial veins of the forearm and hand are variable)
Median cubital	Connects basilic and cephalic veins
Deep and superficial palmar venous arches	Drain into superficial and deep veins of the forearm
Digital	Fingers

Veins of the Thorax

Three major veins return blood from the thorax to the superior vena cava: (1) the right brachiocephalic vein, (2) the left brachiocephalic vein, and (3) the **azygos** (az′ī-gos; unpaired) **vein.** The thoracic drainage to the brachiocephalic veins is through the anterior thoracic wall by way of the **internal thoracic veins.** They receive blood from the **anterior intercostal veins.** Blood from the posterior thoracic wall is collected by **posterior intercostal veins** that drain into the azygos vein on the right side of the thorax and the **hemiazygos** (hem′ē-az′ī-gos) **vein** or the **accessory hemiazygos vein** on the left side of the thorax. The hemiazygos and accessory hemiazygos veins empty into the azygos vein, which drains into the superior vena cava. The thoracic veins are listed in table 21.9 and illustrated in figure 21.25 (also see figure 21.22).

ASSESS YOUR PROGRESS

28. *What are the three major veins that return blood to the right atrium?*

29. *What veins collect blood from the heart muscle?*

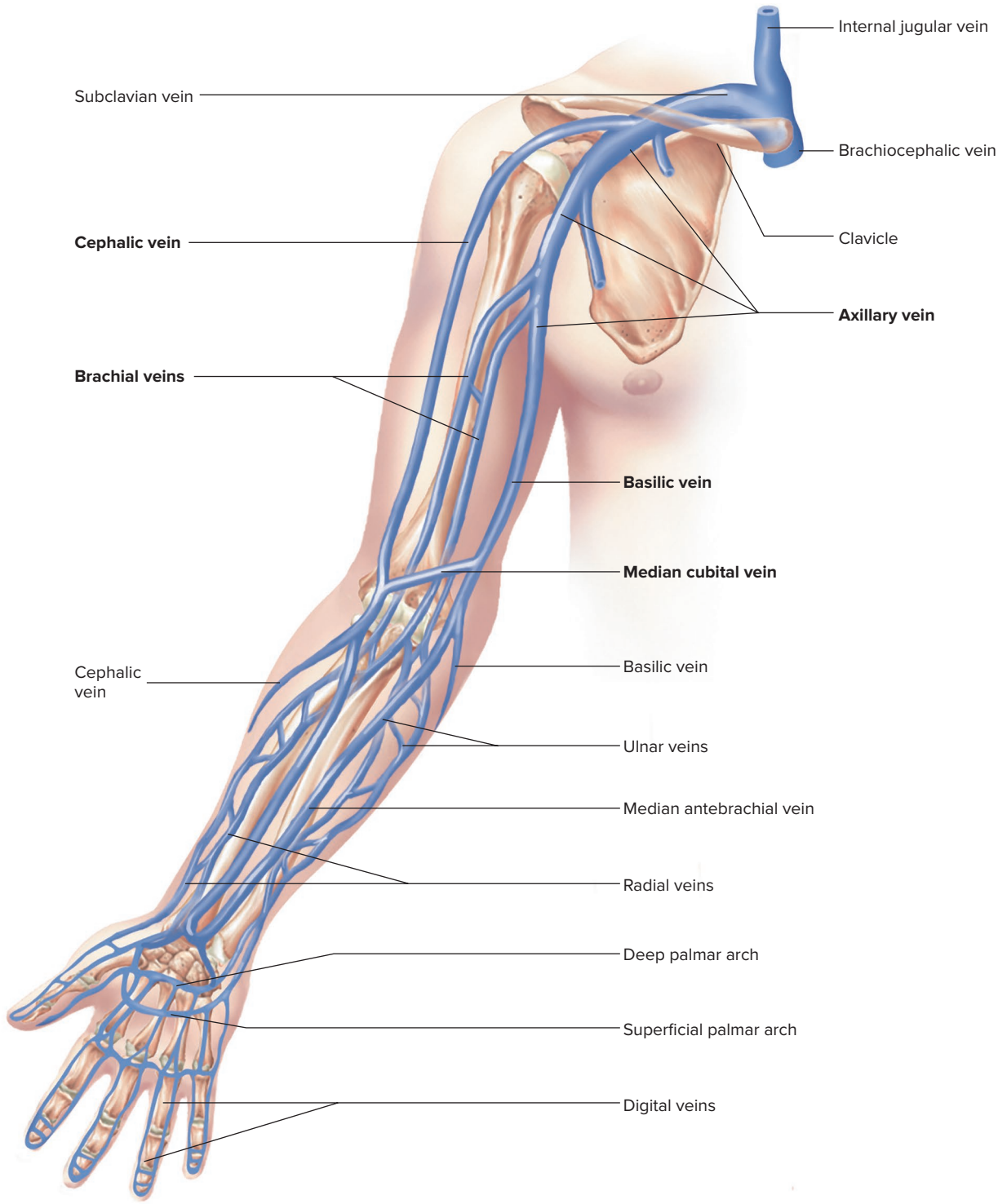


FIGURE 21.23 Veins of the Upper Limb

The subclavian vein and its tributaries. The major veins draining the superficial structures of the limb are the cephalic and basilic veins. The brachial veins drain the deep structures.

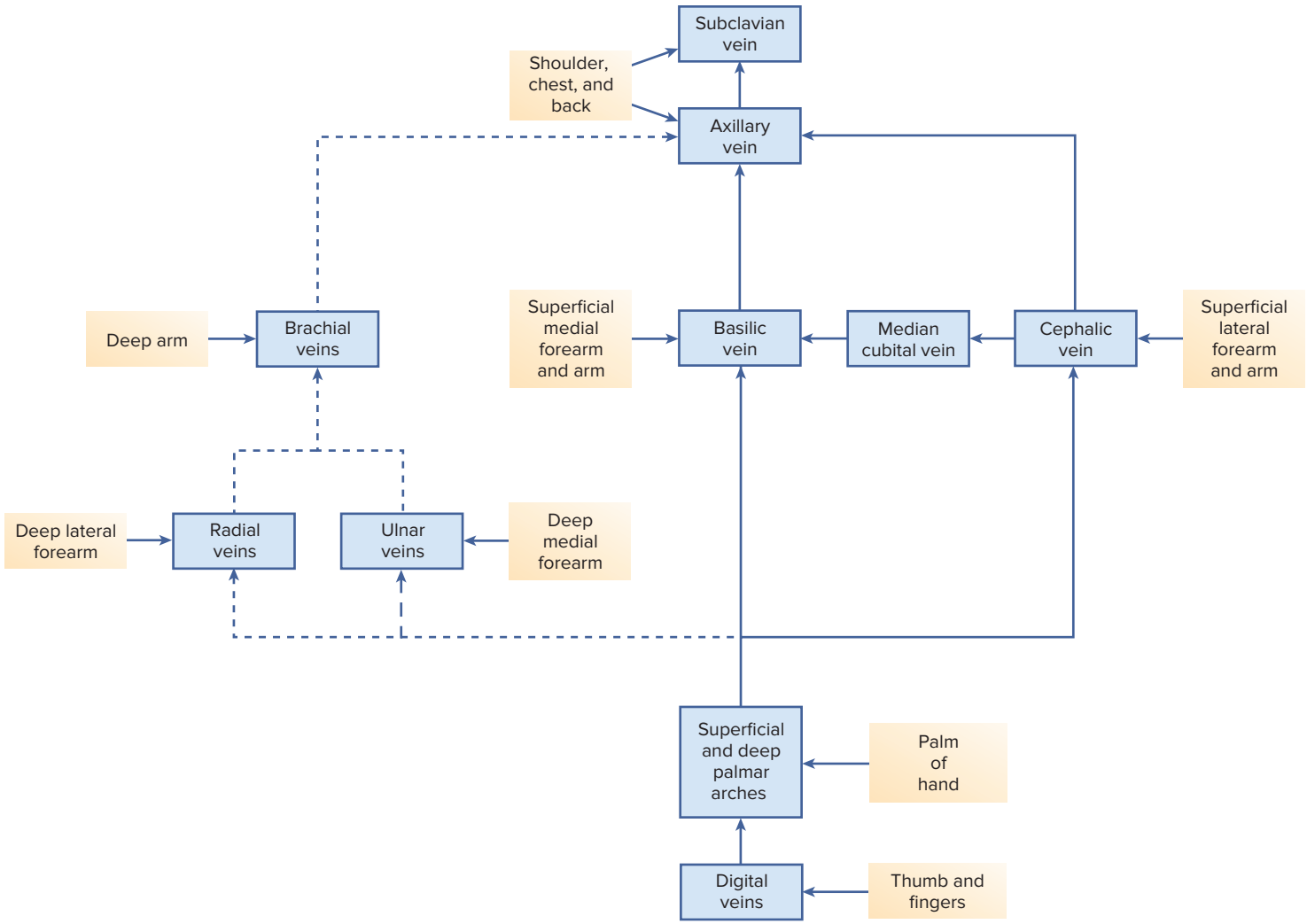


FIGURE 21.24 Major Veins of the Shoulder and Upper Limb

The relationships among the major veins of the shoulder and upper limb are illustrated in the diagram with blue arrows indicating the direction of blood flow. The deep veins, which carry far less blood than the superficial veins, are indicated by dashed lines. Compare this diagram with the anatomical representation in figure 21.23.

30. *List the two pairs of major veins that drain blood from the head and neck. Describe venous sinuses. To what large vein do the venous sinuses connect?*
31. *List the major deep and superficial veins of the upper limb.*
32. *List the three major veins that return blood from the thorax to the superior vena cava.*

Veins of the Abdomen and Pelvis

Blood from the posterior abdominal wall drains into the **ascending lumbar veins.** These veins are continuous superiorly with the hemiazygos on the left and the azygos on the right. Blood from the rest of the abdomen, pelvis, and lower limbs returns to the heart through the inferior vena cava. The gonads (testes and ovaries), kidneys, and adrenal glands are the only abdominal organs outside the pelvis that drain directly into the inferior vena cava. The **internal iliac veins** drain the pelvis and join the **external iliac veins** from the lower limbs to form the **common iliac veins.** The two common iliac veins unite to form the inferior vena cava. The major abdominal and pelvic veins are listed in table 21.10 and illustrated in figure 21.26; also see figure 21.28.

TABLE 21.9 Veins of the Thorax (figure 21.25)

Veins	Tissues Drained
Superior Vena Cava	
Brachiocephalic	
Azygos	Right side, posterior thoracic wall and posterior abdominal wall; esophagus, bronchi, pericardium, and mediastinum
Hemiazygos	Left side, inferior posterior thoracic wall and posterior abdominal wall; esophagus and mediastinum
Accessory hemiazygos	Left side, superior posterior thoracic wall

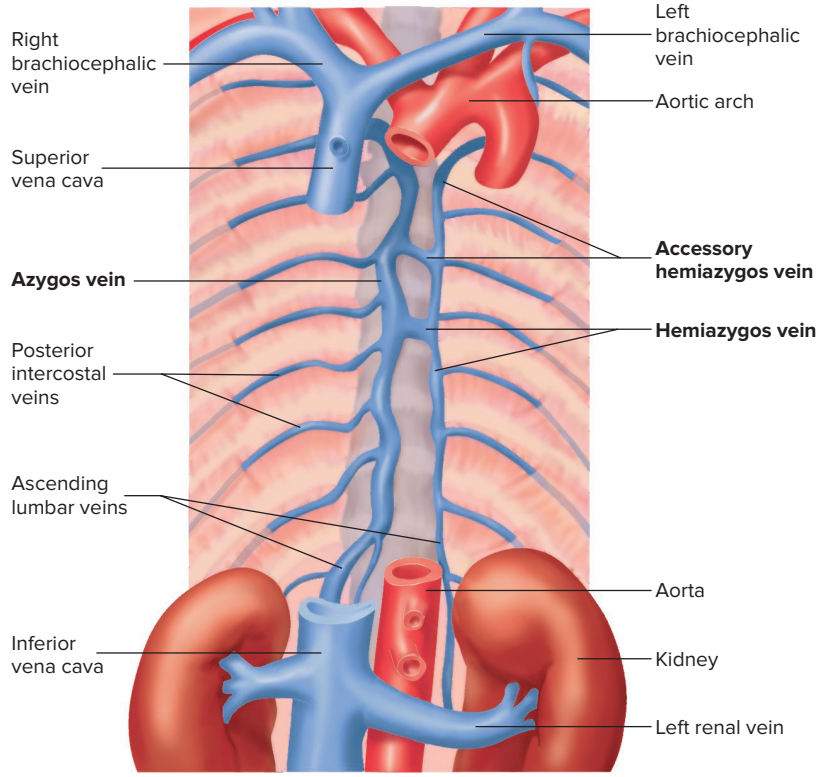


FIGURE 21.25 Veins of the Thorax

Blood from structures of the thorax return to the heart through three major veins: the right brachiocephalic vein, the left brachiocephalic vein, and the azygos vein. AP|R

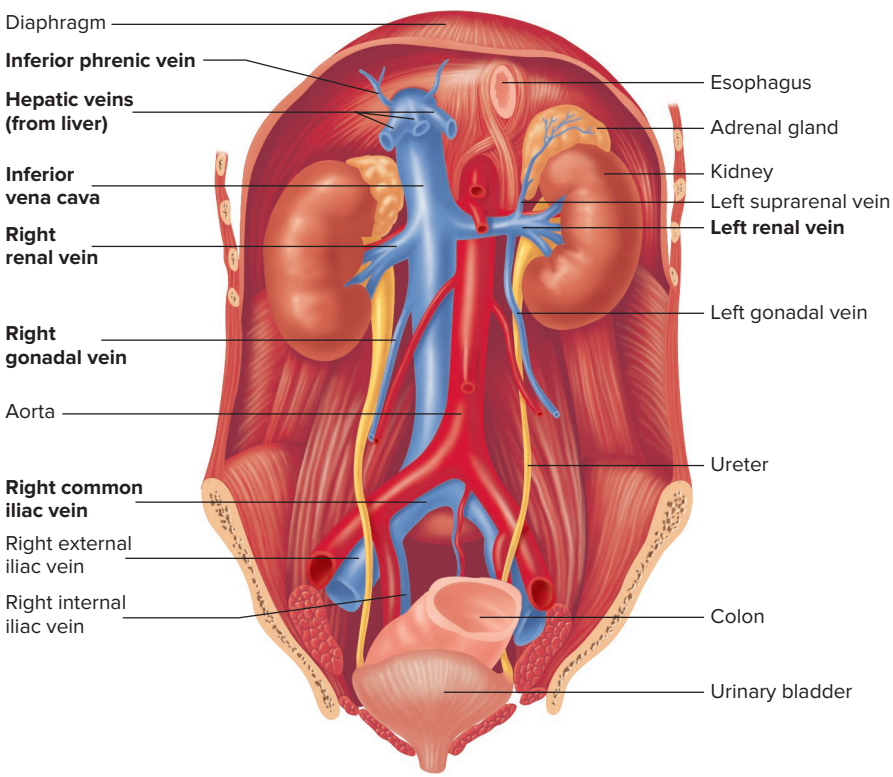


FIGURE 21.26 Inferior Vena Cava and Its Tributaries

The hepatic veins transport blood to the inferior vena cava from the hepatic portal system, which ends as a series of blood sinusoids in the liver (also see figure 21.27).

Hepatic Portal System

The **hepatic** (he-pat′ik; relating to the liver) **portal system** (figures 21.27 and 21.28; table 21.11) carries blood drained from capillaries within most of the abdominal viscera, such as the stomach, intestines, and spleen, to a series of dilated capillaries, called sinusoids, in the liver. This system delivers nutrients and other substances absorbed from the stomach or small intestine to the liver (see chapter 24).

The **hepatic portal vein,** the largest vein of the system, is formed by the union of the **superior mesenteric vein,** which drains the small intestine, and the **splenic vein,** which drains the spleen. The splenic vein receives blood from the **inferior mesenteric vein,** which drains part of the large intestine, and the **pancreatic veins,** which drain the pancreas. The hepatic portal vein also receives blood from gastric veins before entering the liver.

Blood from the liver sinusoids is collected into **central veins,** which empty into **hepatic veins.** Blood from the **cystic veins,** which drain the gallbladder, also enters the hepatic veins. The hepatic veins empty into the inferior vena cava. Blood entering

TABLE 21.10 Veins Draining the Abdomen and Pelvis (figures 21.26 and 21.28)

Veins	Tissues Drained
Inferior Vena Cava	
Hepatic	Liver (see the section "Hepatic Portal System")
Common iliac	
External iliac	Lower limb (see table 21.12)
Internal iliac	Pelvis and its viscera
Ascending lumbar	Posterior abdominal wall (empties into common iliac, azygos, and hemiazygos veins)
Renal	Kidney
Suprarenal	Adrenal gland
Gonadal	
Testicular (male)	Testis
Ovarian (female)	Ovary
Phrenic	Diaphragm

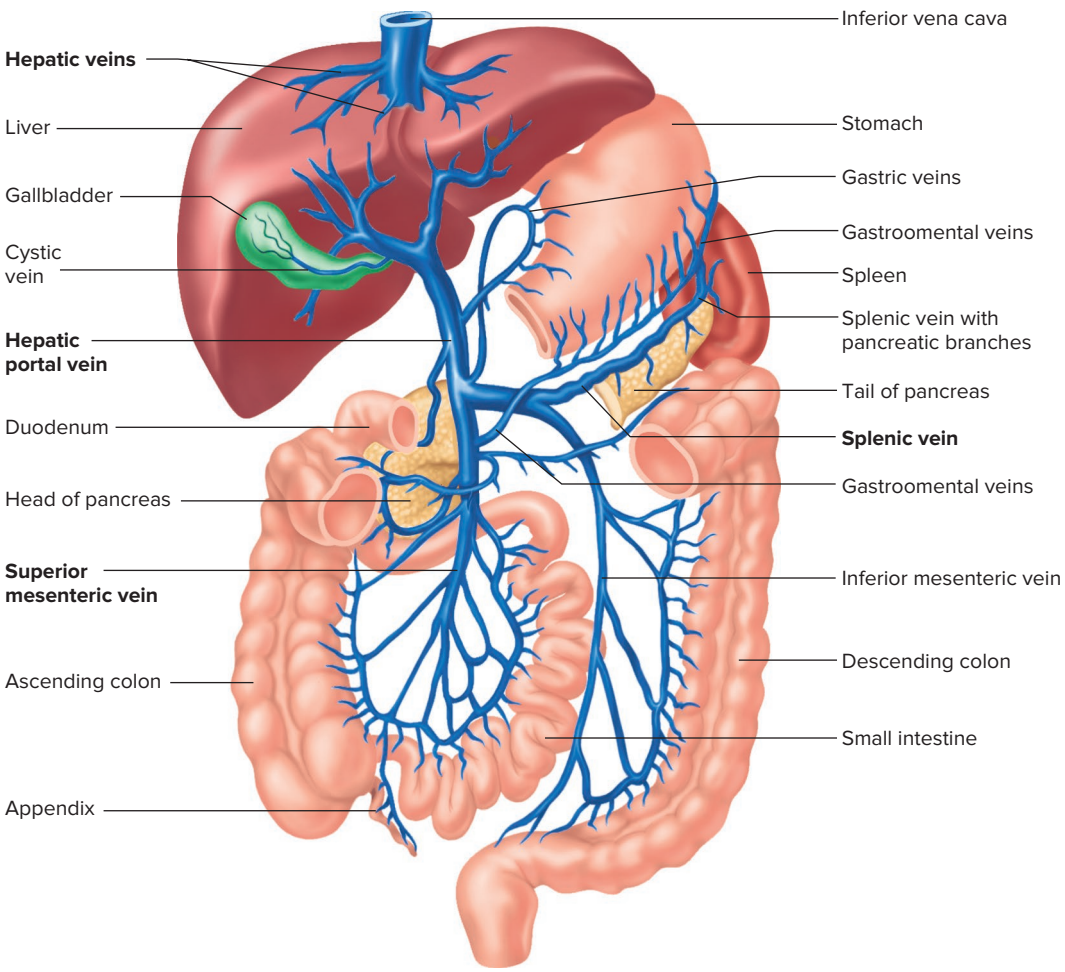


FIGURE 21.27 Veins of the Hepatic Portal System

The hepatic portal system begins as capillary beds in the stomach, pancreas, spleen, small intestine, and large intestine. The veins of the hepatic portal system converge on the hepatic portal vein, which carries blood to a series of capillaries (sinusoids) in the liver. Hepatic veins carry blood from capillaries in the liver to the inferior vena cava (also see figure 21.26).

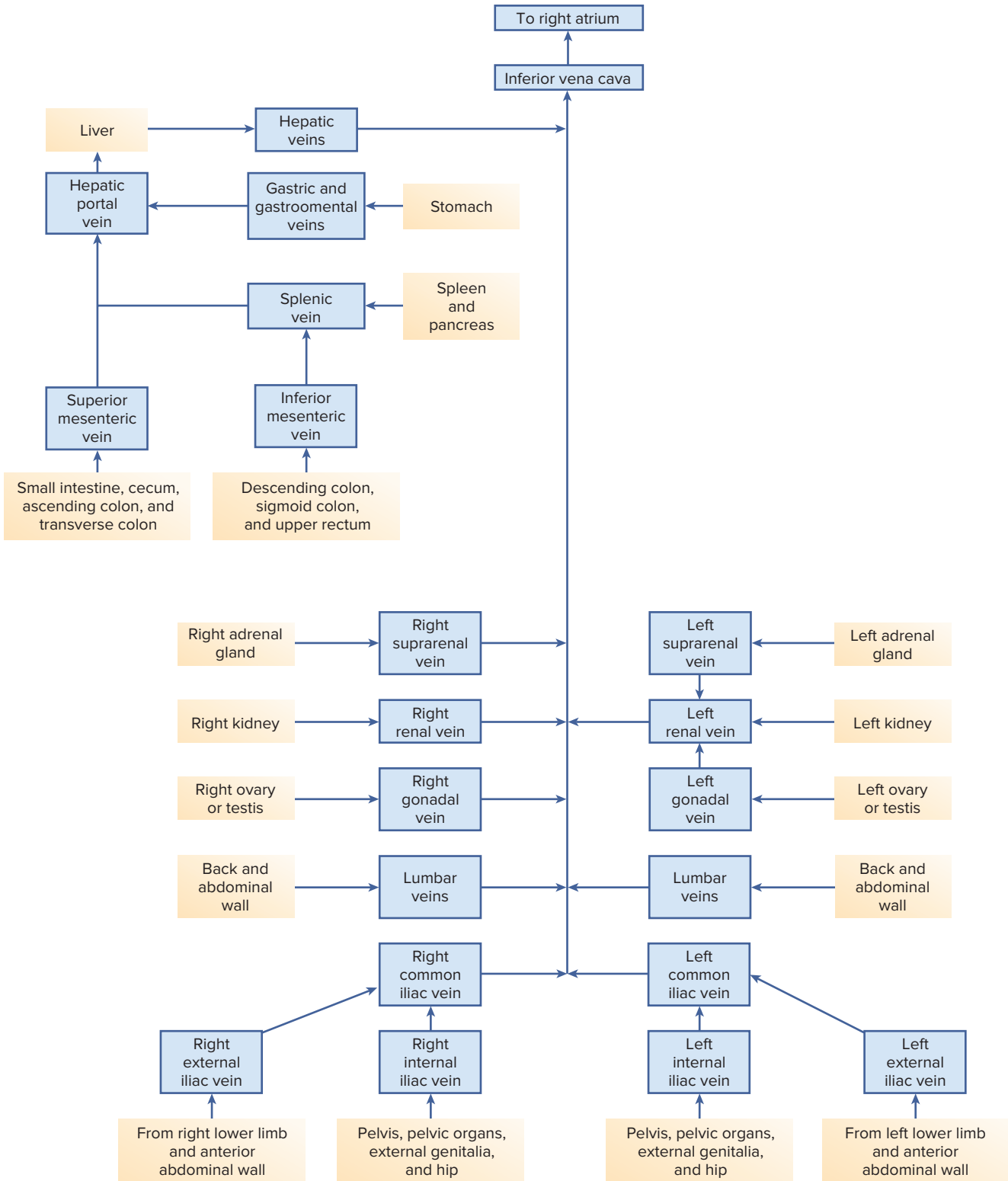


FIGURE 21.28 Major Veins of the Abdomen and Pelvis

The relationships among the major veins of the abdomen and pelvis are illustrated in the diagram with blue arrows indicating the direction of blood flow. Compare this diagram with the anatomical representations in figures 21.26 and 21.27.

TABLE 21.11 Hepatic Portal System (figures 21.27 and 21.28)

Veins	Tissues Drained
Hepatic Portal	
Superior mesenteric	Small intestine and most of the colon
Splenic	Spleen
Inferior mesenteric	Descending colon and rectum
Pancreatic	Pancreas
Gastroomental	Stomach
Gastric	Stomach
Cystic	Gallbladder

the liver through the hepatic portal vein is rich with nutrients collected from the small intestine, but it can also contain a number of toxic substances harmful to the body tissues. Within the liver, the nutrients are either taken up and stored or modified chemically so they can be used by other cells of the body (see chapter 24). The liver cells also help remove toxic substances by altering their structure or making them water-soluble, a process called **biotransformation.** The water-soluble substances can then be transported in the blood to the kidneys, which excrete them in the urine (see chapter 26).

Veins of the Lower Limb

The veins of the lower limb, like those of the upper limb, consist of superficial and deep groups. The distal deep veins of each limb are paired and follow the same path as the arteries, whereas the proximal deep veins are unpaired. The **anterior** and **posterior tibial veins** are paired and accompany the anterior and posterior tibial arteries. They unite just inferior to the knee to form the single **popliteal vein,** which ascends through the thigh and becomes the **femoral vein.** The femoral vein becomes the external iliac vein. **Fibular veins,** or *peroneal* (per-ō-nē′ăl) *veins,* are also paired in each leg and accompany the fibular arteries. They empty into the posterior tibial veins just before those veins contribute to the popliteal vein.

The superficial veins consist of the great and small saphenous veins. The **great saphenous** (să-fē′nŭs; visible) **vein** is the longest vein of the body. It originates over the dorsal and medial side of the foot and ascends along the medial side of the leg and thigh to empty into the femoral vein. The **small saphenous vein** begins over the lateral side of the foot and ascends along the posterior leg to the popliteal space, where it empties into the popliteal vein. The saphenous veins can be removed and used as a source of blood vessels for coronary bypass surgery (see chapter 20). The veins of the lower limb are illustrated in figures 21.29 and 21.30 and listed in table 21.12.

ASSESS YOUR PROGRESS

33. *Explain the three ways that blood from the abdomen returns to the heart.*

TABLE 21.12 Veins of the Lower Limb (figures 21.29 and 21.30)

Veins	Tissues Drained
External Iliac Vein (continuation of the femoral vein)	
Femoral (continuation of the popliteal vein)	Thigh
Popliteal	
Anterior tibial	Deep anterior leg
Dorsal vein of foot	Dorsum of foot
Posterior tibial	Deep posterior leg
Plantar veins	Plantar region of foot
Fibular (peroneal)	Deep lateral leg and foot
Small saphenous	Superficial posterior leg and lateral side of foot
Great saphenous	Superficial anterior and medial leg, thigh, and dorsum of foot
Dorsal vein of foot	Dorsum of foot
Dorsal venous arch	Foot
Digital veins	Toes

34. *List the vessels that carry blood from the abdominal organs to the hepatic portal vein. What happens to the blood of the hepatic portal system as it filters through the liver?*

35. *List the major deep and superficial veins of the lower limbs.*

21.6 Dynamics of Blood Circulation

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Compare laminar and turbulent blood flow.**
B. **Define *blood pressure.* Describe how it is measured.**
C. **Summarize Poiseuille's law.**
D. **Describe the relationship of viscosity to blood flow.**
E. **Relate Laplace's law to critical closing pressure.**
F. **Explain how vessel diameter and vascular compliance affect blood pressure.**
G. **List the percent distribution of blood in each of the systemic vessel types.**

The dynamics of blood circulating through blood vessels are the same as those of water flowing through pipes. Blood movement through the vessels is determined by (1) flow, (2) resistance, and (3) pressure. As we will find in the next section, these factors

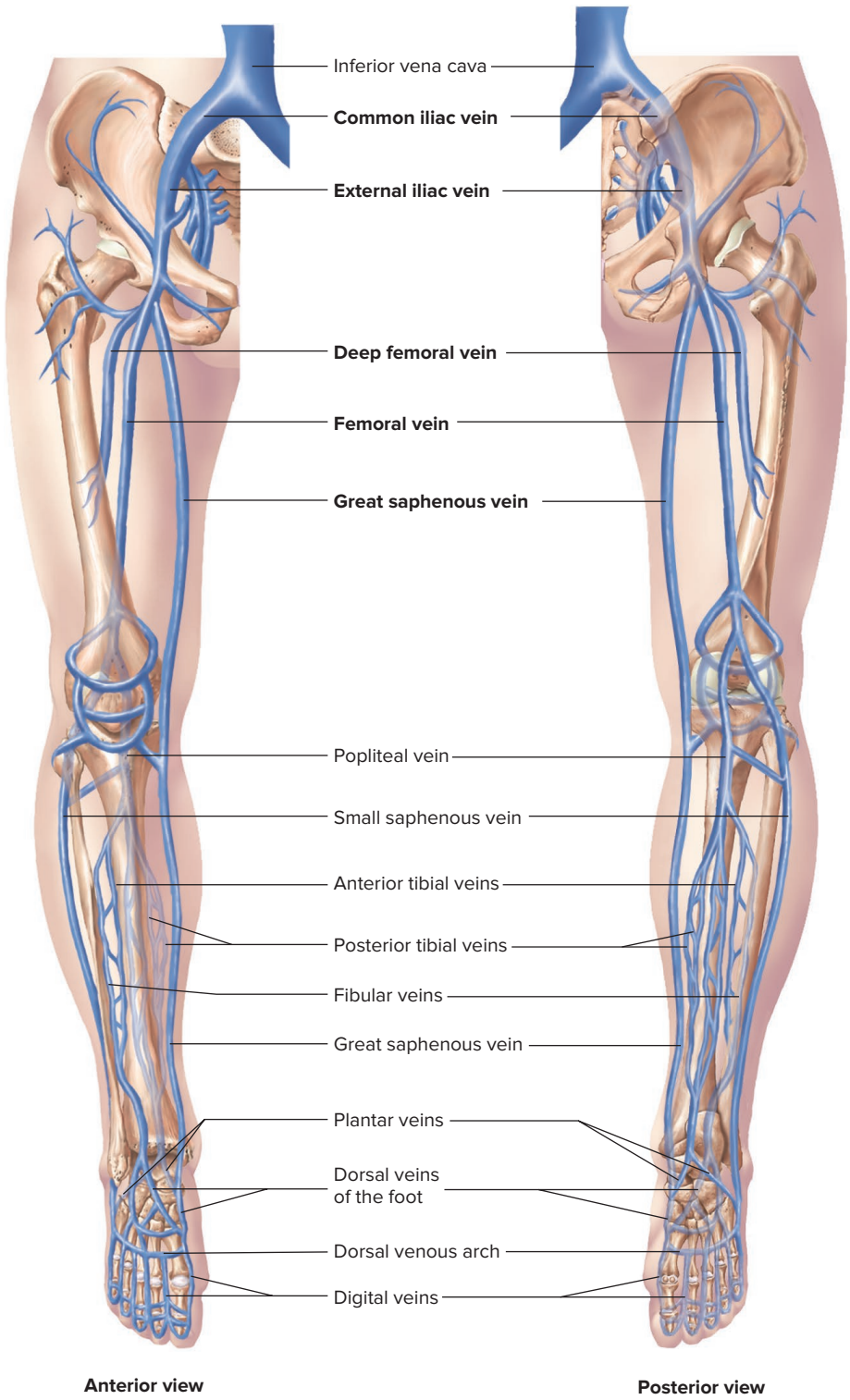


FIGURE 21.29 Veins of the Pelvis and Lower Limb
The right common iliac vein and its tributaries. AP|R

are closely interrelated, and many of these interrelationships are clinically significant. Control mechanisms that regulate blood pressure and blood flow through the tissues are critical to the functions of the circulatory system and the homeostasis of the whole body.

Laminar and Turbulent Flow in Vessels

Fluid, including blood, tends to flow through long, smooth-walled tubes in a streamlined fashion called **laminar flow** (figure 21.31*a*). Fluid behaves as if it were composed of a large number of concentric layers. The movement of these layers is not the same because

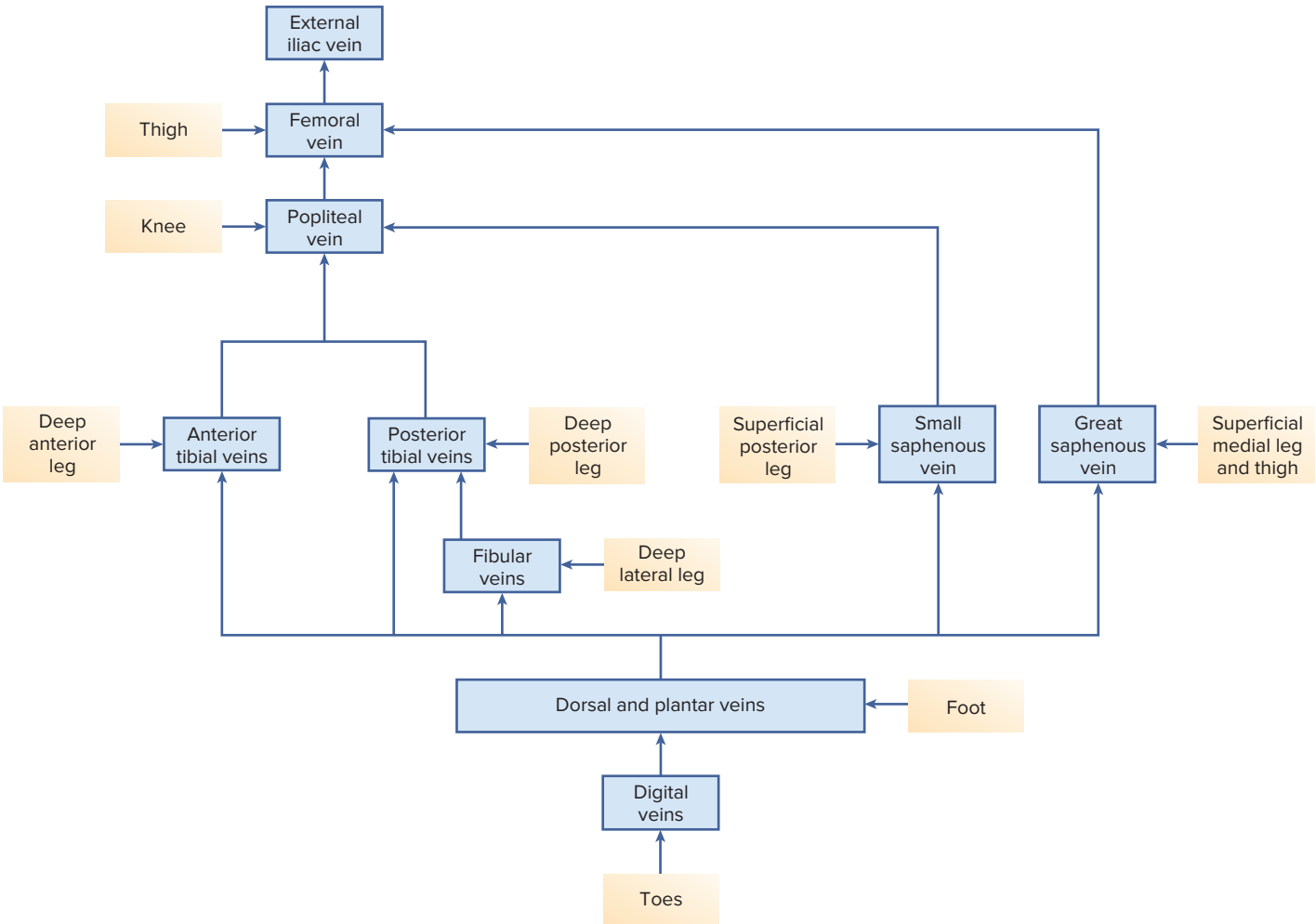


FIGURE 21.30 Major Veins of the Lower Limb

The relationships among the major veins of the lower limb are illustrated in the diagram with blue arrows indicating the direction of blood flow. Compare this diagram with the anatomical representation in figure 21.29.

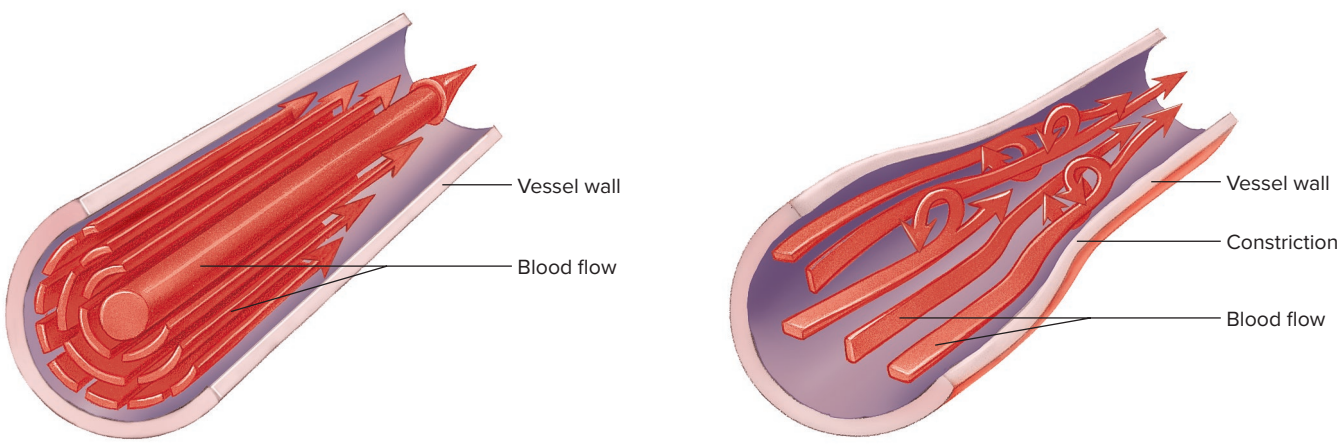


FIGURE 21.31 Laminar and Turbulent Flow

(*a*) In laminar flow, fluid flows in long, smooth-walled tubes as if it were composed of a large number of concentric layers. (*b*) Turbulent flow is caused by numerous small currents flowing crosswise or obliquely to the long axis of the vessel, resulting in flowing whorls and eddy currents.

of the effect of resistance. The layer nearest the wall of the tube experiences the greatest resistance to flow because it moves against the stationary wall. The innermost layers slip over the surface of the outermost layers and experience less resistance to movement. Thus, flow in a vessel consists of movement of concentric layers, with the outer layer moving most slowly and the layer at the center moving most rapidly. This is similar to water flow in a river, where the movement of water is fastest toward the more central area of the river and slower near the shoreline.

Laminar flow is interrupted and becomes **turbulent flow** when the rate of flow exceeds a critical velocity or when the fluid passes a constriction, a sharp turn, or a rough surface. Turbulent flow is caused by numerous small currents flowing at an angle to the long axis of the vessels. These small currents result in flowing whorls or eddy currents in the blood vessel (figure 21.31*b*). Vibrations of the liquid and blood vessel walls during turbulent flow cause the sounds heard when blood pressure is measured using a blood pressure cuff. Turbulent flow is also common as blood flows past the valves in the heart and is partially responsible for the heart sounds (see chapter 20).

Turbulent flow of blood through vessels occurs primarily in the heart and to a lesser extent where arteries branch. Sounds caused by turbulent blood flow in arteries are not normal and usually indicate that the artery is abnormally constricted. Turbulent flow in abnormally constricted arteries may indicate an increased probability that thromboses will develop.

Blood Pressure

Blood pressure is a measure of the force blood exerts against blood vessel walls. An instrument called a **mercury (Hg) manometer** measures blood pressure in millimeters of mercury (mm Hg). A blood pressure of 100 mm Hg is great enough to lift a column of mercury 100 mm.

Blood pressure can be measured directly by inserting a **cannula** (tube) into a blood vessel and connecting a manometer or an electronic pressure transducer to it. Electronic transducers are very sensitive and can precisely detect rapid fluctuations in pressure.

Placing a catheter into a blood vessel or into a chamber of the heart to monitor pressure changes is possible but not appropriate for routine clinical examinations. Health professionals most often use the **auscultatory** (aws-kŭl′tă-tō′rē) **method** to measure blood pressure. They wrap a blood pressure cuff connected to a **sphygmomanometer** (sfig′mō-mă-nom′ĕ-ter) around a patient's arm just above the elbow and place a stethoscope over the brachial artery (figure 21.32). Some sphygmomanometers have mercury manometers, and others have digital manometers, but they all measure pressure in terms of millimeters of mercury. The blood pressure cuff is inflated until the brachial artery is completely collapsed. Because blood flow through the constricted area is blocked at this point, no sounds can be heard through the stethoscope. Then the pressure in the cuff is gradually lowered. As soon as it declines below the systolic pressure, blood flows through the constricted area during systole (contraction of the ventricles). The blood flow is turbulent and produces vibrations in the blood and surrounding tissues that can be heard through the stethoscope. These sounds are called **Korotkoff** (kō-rot′kof) **sounds,** and the pressure at which a Korotkoff sound is first heard represents the **systolic pressure.**

As the pressure in the blood pressure cuff is lowered still more, the Korotkoff sounds change tone and loudness. When the pressure has dropped until continuous laminar blood flow is reestablished, the sound disappears completely. The pressure at which continuous laminar flow is reestablished is the **diastolic pressure.** This method for determining systolic and diastolic pressures is not entirely accurate, but its results are within 10% of methods that are more direct.

ASSESS YOUR PROGRESS

36. *Describe laminar flow and turbulent flow through a tube. What conditions cause turbulent flow of blood?*

37. *What creates blood pressure? Describe the auscultatory method of measuring blood pressure.*

38. *What are Korotkoff sounds?*

Blood Flow and Poiseuille's Law

The **rate** at which a liquid, such as blood, flows through a tube can be expressed as the volume that passes a specific point per unit of time. Blood flow is usually reported in either milliliters (mL) or liters (L) per minute. For example, when a person is resting, the **cardiac output** of the heart is approximately 5 L/min; thus, the rate of blood flow through the aorta is approximately 5 L/min. The rate of blood flow is influenced by pressure differences within the vessel and resistance to flow. Mathematically, the rate of blood flow in a vessel can be described by equation (21.1):

$$\text{Flow} = \frac{P_1 - P_2}{R} \qquad (21.1)$$

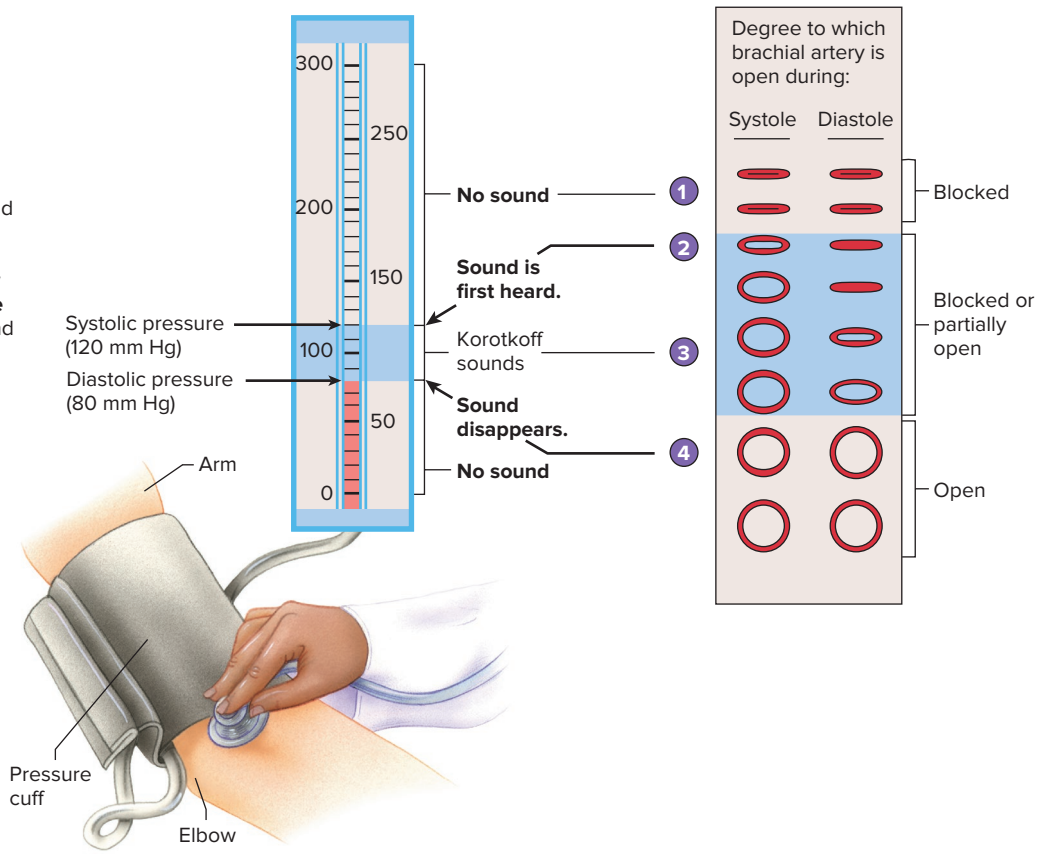
where P_1 and P_2 are the pressures in the vessel at points one and two, respectively, and R is the resistance to flow. Blood always flows from an area of higher pressure to an area of lower pressure; the greater the pressure difference, the greater the rate of flow. For example, the average blood pressure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

The flow of blood, resulting from a pressure difference between the two ends of a blood vessel, is opposed by a resistance to flow. As such, the degree of blood flow is inversely related to the amount of resistance. Another way to state this is that as resistance increases, blood flow decreases; conversely, as the resistance decreases, blood flow increases. Resistance is affected by several factors including blood viscosity, vessel length, and vessel diameter. Considering these three factors, resistance can be represented mathematically by equation (21.2):

$$\text{Resistance} = \frac{128vl}{\pi D^4} \qquad (21.2)$$

where v is the viscosity of blood, l is the length of the vessel, and D is the diameter of the vessel. Both 128 and π are constants and

1. When the cuff pressure is high enough to keep the brachial artery closed, no blood flows through it, and no sound is heard.
2. When cuff pressure decreases and is no longer able to keep the brachial artery closed, blood is pushed through the partially opened brachial artery, producing turbulent blood flow and a sound. **Systolic pressure** is the pressure at which a sound is first heard.
3. As cuff pressure continues to decrease, the brachial artery opens even more during systole. At first, the artery is closed during diastole, but as cuff pressure continues to decrease, the brachial artery partially opens during diastole. Turbulent blood flow during systole produces Korotkoff sounds, although the pitch of the sounds changes as the artery becomes more open.
4. Eventually, cuff pressure decreases below the pressure in the brachial artery, and it remains open during systole and diastole. Nonturbulent flow is reestablished, and no sounds are heard. **Diastolic pressure** is the pressure at which the sound disappears.



PROCESS FIGURE 21.32 Blood Pressure Measurement

The auscultatory method, illustrated in this figure, allows medical professionals to measure arterial blood pressure.

When the pressure cuff is inflated to close the brachial artery, which arteries in the upper limb will not receive blood flow?

for practical purposes the length of the blood vessel is constant. Thus, the diameter of the blood vessel and the viscosity of the blood determine resistance. The viscosity of blood changes slowly.

When equation (21.1) (flow) is combined with equation (21.2) (resistance), the following relationship, called **Poiseuille's** (pwah-zuh′yes) **law,** results:

$$\text{Flow} = \frac{P_1 - P_2}{R} = \frac{\pi(P_1 - P_2)\,D^4}{128vl} \qquad (21.3)$$

In Poiseuille's law (equation [21.3]), the value for diameter (D) is raised to the fourth power, so we know that it has a great impact on the overall calculation of flow. Specifically, a small change in the diameter of a vessel dramatically changes the resistance to flow, and therefore the amount of blood that flows through it. For example, decreasing the diameter of a vessel by half increases the resistance to flow 16-fold and decreases flow 16-fold. Imagine water flowing from a large tube into a smaller tube. As the water enters the smaller tube, flow will decrease dramatically.Vasoconstriction decreases the diameter of a vessel, which increases resistance to flow, and overall, decreases blood flow through the vessel. Vasodilation increases the diameter of a vessel, which decreases resistance to flow, and increases blood flow through the vessel.

Major changes in blood flow through blood vessels are produced by changes in blood pressure and blood vessel diameter. During exercise, heart rate and stroke volume increase, causing blood pressure in the aorta to increase. In addition, blood vessels in skeletal muscles vasodilate, and resistance to flow decreases. As a consequence, a dramatic increase in blood flow through blood vessels in exercising skeletal muscles occurs.

Viscosity (vis-kos′i-tē) is a measure of a liquid's resistance to flow. As the viscosity of a liquid increases, the pressure required to force it to flow also increases. The viscosity of liquids is commonly determined by considering the viscosity of distilled water as 1 and then comparing the viscosity of other liquids with that. Using this procedure, whole blood has a viscosity of 3.0–4.5, which means that about three times as much pressure is required

to force whole blood through a given tube at the same rate as forcing water through the same tube.

The viscosity of blood is influenced largely by **hematocrit** (hē′mă-tō-krit, hem′ă-tō-krit), which is the percentage of the total blood volume composed of red blood cells (see chapter 19). As the hematocrit increases, the viscosity of blood increases logarithmically. Blood with a hematocrit of 45% has a viscosity about three times that of water, whereas blood with a very high hematocrit of 65% has a viscosity about seven to eight times that of water. The plasma proteins have only a minor effect on the viscosity of blood, but dehydration or uncontrolled production of red blood cells can increase the hematocrit and the viscosity of blood substantially. Viscosity above the normal range increases the workload on the heart. If this workload is great enough, heart failure can result.

Predict 2

Predict the effect of each of the following conditions on blood flow: (a) vasoconstriction of blood vessels in the skin in response to cold exposure, (b) vasodilation of blood vessels in the skin in response to elevated body temperature, and (c) erythrocytosis, which results in a greatly increased hematocrit.

Critical Closing Pressure and Laplace's Law

The **critical closing pressure** of a blood vessel is the lowest pressure at which the vessel remains open, pressures below critical closing pressure allows the vessel to collapse and blood flow through the vessel stops. Critical closing pressure is of concern in cases such as shock. When a person is in shock, blood pressure can decrease below the critical closing pressure in vessels (see Clinical Impact 21.6). As a consequence, the blood vessels collapse, and flow ceases. The tissues supplied by those vessels can become necrotic because of the lack of blood supply. Critical closing pressure is essentially the minimum force necessary to hold open a vessel. This force is dependent on two factors: (1) the diameter of the vessel and (2) blood pressure. **Laplace's** (la-plas′ez) **law** states that the force that stretches the vessel wall is proportional to the diameter of the vessel times the blood pressure.

Laplace's law is expressed by the following equation:

$$F = D \times P \qquad (21.4)$$

where F is force, D is vessel diameter, and P is pressure. As the pressure in a vessel decreases, the force that stretches the vessel wall also decreases. Conversely, as the pressure in a vessel increases, the force that stretches the vessel wall also increases.

Laplace's law also explains how vessel diameter affects the force applied to the vessel wall. From equation (21.4), we see that as the diameter of a vessel increases, the force applied to the vessel wall increases, even if the pressure remains constant. Sometimes a part of an arterial wall becomes weakened and a bulge, called an **aneurysm,** forms in it. The vessel diameter increases at the sight of the aneursym; therefore, the force applied to the weakened part is greater than at other points along the blood vessel. The greater force causes the weakened vessel wall to bulge even more, further increasing the pressure on it. This positive feedback can proceed until the vessel finally ruptures. Ruptured aneurysms in the blood vessels of the brain or in the aorta are often fatal.

Predict 3

Richard does not know it, but he has an aneurysm at the base of his left middle cerebral artery. One of Richard's favorite activities is to take a hot sauna bath and then jump into cold water. Richard does not realize that this causes rapid vasoconstriction of his cutaneous blood vessels. How will this activity affect Richard's aneurysm?

Vascular Compliance

Compliance (kom-plī′ans) is the tendency for blood vessel volume to increase as blood pressure increases. The more easily the vessel wall stretches, the greater is its compliance. The less easily the vessel wall stretches, the smaller is its compliance.

An analogy to clarify this relationship is comparing the volume of water a plastic cup can hold with the volume of water a water balloon can hold. The water balloon has the capacity to stretch, or has a greater compliance, compared to a plastic cup.

Compliance is expressed by the following equation:

$$\text{Compliance} = \frac{\text{Increase in volume (mL)}}{\text{Increase in pressure (mm Hg)}} \qquad (21.5)$$

Vessels with a large compliance exhibit a large increase in volume when the pressure increases a small amount. Vessels with a small compliance do not show a large increase in volume when the pressure increases.

Recall that veins have thinner walls than arteries. This difference also affects the compliance of the vessel. Venous compliance is approximately 24 times greater than arterial compliance. As venous pressure increases, the volume of the veins increases greatly. Consequently, veins act as storage areas, or reservoirs, for blood because their large compliance allows them to hold much more blood than other areas of the circulatory system (table 21.13).

To illustrate this, let's consider the distribution of blood volume in the body. Approximately 84% of the total blood volume is contained in the systemic blood vessels. Because of their larger compliance compared to other vessels, veins can hold a larger volume of blood. So it is not surprising that most of that blood is in the veins (64%). Smaller volumes of blood are in the arteries (15%) and the capillaries (5%; table 21.13).

ASSESS YOUR PROGRESS

39. *Describe the relationship among blood flow, blood pressure, and resistance.*

40. *According to Poiseuille's law, what effects do viscosity, blood vessel diameter, and blood vessel length have on resistance? On blood flow?*

41. *Define* viscosity, *and state the effect of hematocrit on viscosity.*

42. *State Laplace's law. How does it relate to critical closing pressure and aneurysm?*

43. *What is vascular compliance? Do veins or arteries have greater compliance? Explain why.*

TABLE 21.13 Distribution of Blood Volume in Blood Vessels

Vessels		Total Blood Volume (%)
Systemic		
Veins		64
Large veins	(39%)	
Small veins	(25%)	
Arteries		15
Large arteries	(8%)	
Small arteries	(5%)	
Arterioles	(2%)	
Capillaries		5
TOTAL IN SYSTEMIC VESSELS		84
Pulmonary vessels		9
Heart		7
TOTAL BLOOD VOLUME		100

21.7 Physiology of the Systemic Circulation

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Explain the relationship between cross-sectional area of blood vessels and the rate of blood flow.**
B. **Explain how blood pressure and resistance to flow change as blood flows through the blood vessels.**
C. **Define *pulse pressure* and list locations on the body surface where the pulse can be detected.**
D. **Describe the exchange of materials across a capillary wall.**
E. **Explain how preload, venous tone, and gravity affect cardiac output.**

The primary function of the circulatory system is distribution, ensuring that O_2, CO_2, nutrients, hormones, and other substances are efficiently moved from one area of the body to other areas. This distribution relies on the constant flow of blood through the circulatory system. Recall from equation (21.3) that flow is determined by several factors, including pressure. In this section we will discuss the factors that affect blood flow and blood pressure as well as how blood flow and blood pressure regulate exchange of substances between the blood and other tissues.

Cross-Sectional Area of Blood Vessels

Blood flows through the vessels of the body at different velocities. The velocity of blood flow changes relative to the cross-sectional area of each blood vessel type. We can determine the cross-sectional area for each individual blood vessel; however, a more useful number is to determine the the total cross-sectional area for all blood vessels of a given type. This can be done by calculating the cross-sectional area of a particular blood vessel type and multipling each by the number of that type of blood vessel in the body (figure 21.33*a*). For example, only one aorta exists, and it has a cross-sectional area of 5 square centimeters (cm^2). An individual capillary has a very small cross-sectional area. However, the total cross-sectional area considers the combined area of all capillaries, which number approximately 10 billion in the body. So the total cross-sectional area of all capillaries is 2500 cm^2, which is much greater than the cross-sectional area of the aorta.

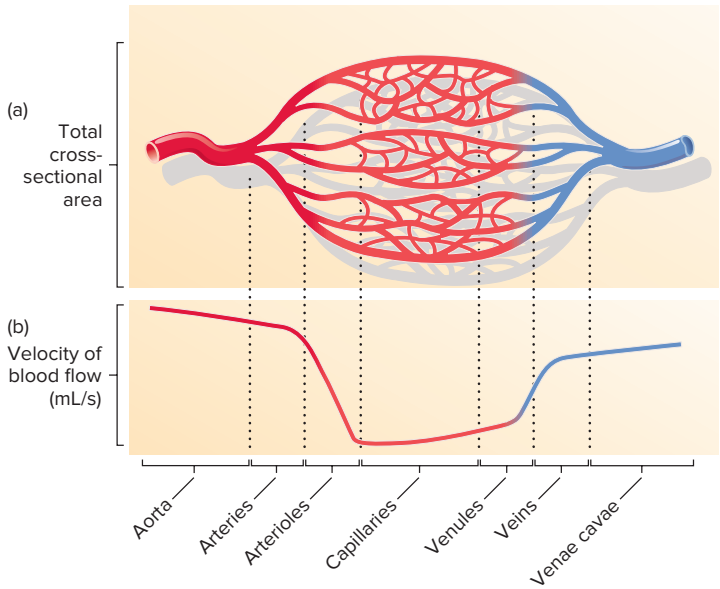


FIGURE 21.33 Blood Vessel Area and Velocity of Blood Flow
(*a*) A schematic representing the total cross-sectional area for each of the major blood vessel types. The total cross-sectional area of all the capillaries is much greater (2500 cm^2) than that of the aorta (5 cm^2), although the cross-sectional area of each capillary is much smaller than that of the aorta. (*b*) Blood velocity decreases dramatically in arterioles, capillaries, and venules and is greater in the aorta and the large veins. As the total cross-sectional area increases, the velocity of blood flow decreases.

The velocity of blood flow in a particular blood vessel type is inversely proportional to its total cross-sectional area (figure 21.33*b*). The velocity of blood flow is greatest in the aorta, but the total cross-sectional area is small. In contrast, the total cross-sectional area of the capillaries is large, but the velocity of blood flow is low. As the veins become larger in diameter, their total cross-sectional area decreases, and the velocity of blood flow increases. The relationship between total cross-sectional area and velocity of blood flow is much like a stream that flows rapidly through a narrow gorge but more slowly through a broad plane.

Pressure and Resistance

Blood pressure changes as blood moves from one blood vessel type to another. The left ventricle forcefully ejects blood from the heart into the aorta. Because the heart's pumping action is pulsatile, the aortic pressure fluctuates between a systolic pressure of 120 mm Hg and a diastolic pressure of 80 mm Hg (table 21.14; figure 21.34). As blood flows through the circulation, from arteries through the capillaries and the veins, the pressure falls progressively to a minimum of approximately 0 mm Hg or even slightly lower by the time it returns to the right atrium.

TABLE 21.14 Blood Pressure Classification in Adults

	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)
Normal blood pressure	<120	<80
Elevated blood pressure	120–129	<80
Stage 1 hypertension	130–139	80–89
Stage 2 hypertension	⩾140	⩾90

Source: Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017; Nov 13.

The decrease in blood pressure in each part of the systemic circulation is directly proportional to the resistance to blood flow. In other words, the greater the resistance in a blood vessel, the more rapidly the pressure decreases as blood flows through it. This resistance to flow is associated with the diameter of the vessel. As vessel diameter decreases, resistance to flow increases. Vessels with larger diameters have lower levels of resistance; whereas, vessels with smaller diameters have higher levels of resistance.

Resistance to flow also affects the speed at which pressure changes in the different vessels of the body. For example, resistance is small in the aorta, so the average pressure at the end of the aorta is nearly the same as at the beginning of the aorta, about 100 mm Hg. The resistance in medium arteries, which are as small as 3 mm in diameter, is also small, so their average pressure is only decreased to 95 mm Hg. In the smaller arteries, however, the resistance to blood flow is greater; by the time blood reaches the arterioles, the average pressure is approximately 85 mm Hg. The resistance to flow is greater in the arterioles than in any other part of the systemic circulation; at their ends, the average pressure is only approximately 30 mm Hg. The resistance is also fairly high in the capillaries. The blood pressure at the arterial end of the capillaries is approximately 30 mm Hg, and it decreases to approximately 10 mm Hg at the venous end. Resistance to blood flow in the veins is small because of their relatively large diameter; by the time the blood reaches the right atrium in the venous system, the average pressure has decreased from 10 mm Hg to approximately 0 mm Hg.

The muscular arteries and arterioles are capable of constricting or dilating in response to autonomic and hormonal stimulation, altering resistance and blood flow. If vessels constrict, resistance to blood flow increases, less blood flows through the constricted blood vessels, and blood is shunted to other, nonconstricted areas of the body. Muscular arteries help control the amount of blood flowing to each body region, and arterioles regulate blood flow through specific tissues. Constriction of an arteriole decreases blood flow through the local area it supplies, and vasodilation increases blood flow.

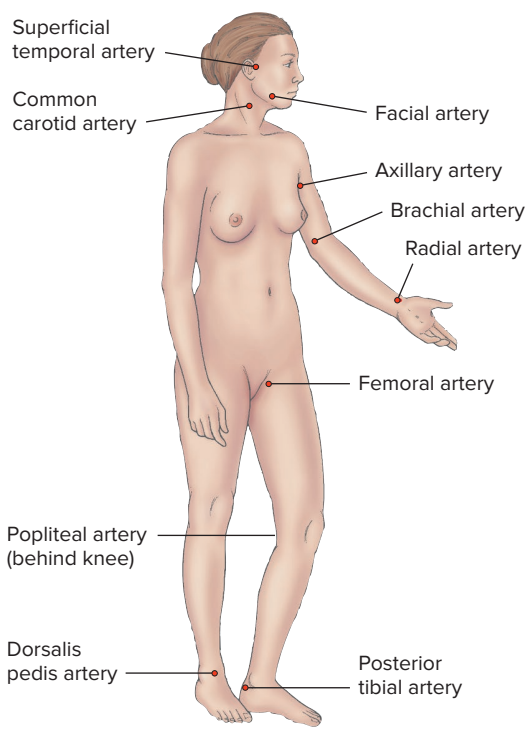


FIGURE 21.34 Major Points at Which the Pulse Can Be Monitored
Each pulse point is named after the artery on which it occurs.

ASSESS YOUR PROGRESS

44. *List the percent distribution of blood in the large arteries, small arteries, arterioles, capillaries, small veins, and large veins.*

45. *Describe the total cross-sectional areas of the aorta, arteries, arterioles, capillaries, venules, veins, and venae cavae.*

46. *Describe how the rate changes as blood flows through the aorta to the venae cavae.*

47. *Describe the changes in resistance and blood pressure as blood flows through the aorta to the venae cavae.*

48. *Explain how constriction and dilation of muscular arteries shunt blood from one area of the body to another and how constriction and dilation of arterioles change blood flow through local areas.*

Pulse and Pulse Pressure

As blood is ejected from the left ventricle into the aorta, it produces a pressure wave, or **pulse,** that travels rapidly along the arteries. Its rate of transmission is approximately 15 times greater in the aorta (7–10 m/s) and 100 times greater in the distal arteries (15–35 m/s) than the velocity of blood flow.

You are most likely familiar with the practice of "taking a person's pulse" in a clinical situation. The pulse is important clinically because health professionals can determine heart rate, rhythmicity, and other characteristics by feeling it. The pulse can be felt at 10 major locations on each side of the body where large arteries are close to the surface (figure 21.34).

On the head and neck, a pulse can be felt in three arteries: (1) the common carotid artery in the neck, (2) the superficial temporal artery immediately anterior to the ear, and (3) the facial artery at the point where it crosses the inferior border of the mandible approximately midway between the angle and the genu.

On the upper limb, a pulse can also be felt in three arteries: (1) the axillary artery in the axilla, (2) the brachial artery on the medial side of the arm slightly proximal to the elbow, and (3) the radial artery on the lateral side of the anterior forearm just proximal to the wrist. The **radial pulse,** taken at the radial artery, is traditionally used because it is the most easily accessible artery in the body.

In the lower part of the body, a pulse can be felt in four locations: (1) the femoral artery in the groin, (2) the popliteal artery just proximal to the knee, (3) the dorsalis pedis artery at the ankle, and (4) the posterior tibial artery at the ankle.

The pressure wave that we recognize as a pulse is generated by pulse pressure. **Pulse pressure** is the difference between systolic and diastolic pressures (figure 21.35). For example, in a healthy, young adult at rest, systolic pressure is approximately 120 mm Hg, and diastolic pressure is approximately 80 mm Hg; thus, the pulse pressure is approximately 40 mm Hg (= 120 mm Hg–80 mm Hg). Two major factors influence pulse pressure: (1) stroke volume of the heart and (2) vascular compliance. Pulse pressure is directly related to stroke volume. When stroke volume decreases, pulse pressure also decreases; when stroke volume increases, pulse pressure increases. For example, during exercise, such as running, the stroke volume increases; as a consequence, the pulse pressure also increases. After running, the pulse pressure gradually returns to its resting value as the stroke volume of the heart decreases.

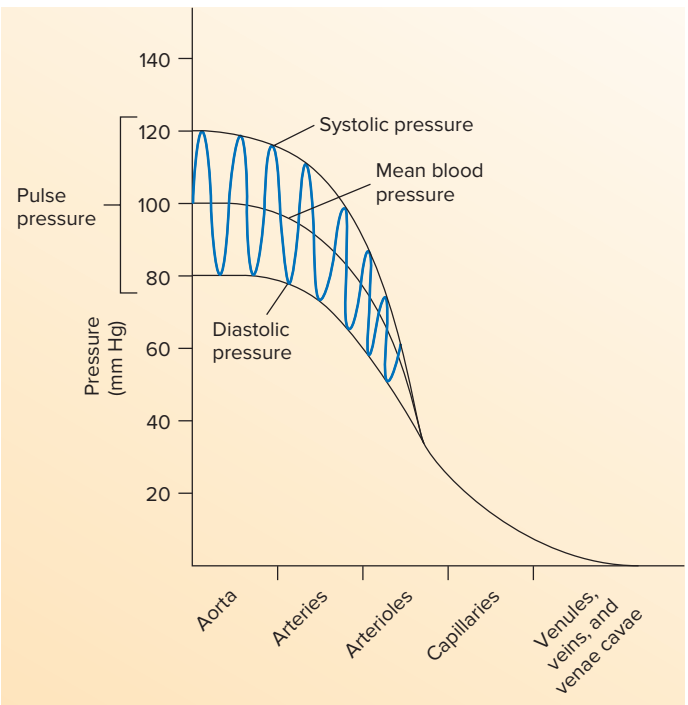


FIGURE 21.35 Blood Pressure in the Major Blood Vessel Types
In small arteries and arterioles, blood pressure fluctuations between systole and diastole are reduced. No fluctuations in blood pressure occur in capillaries and veins.

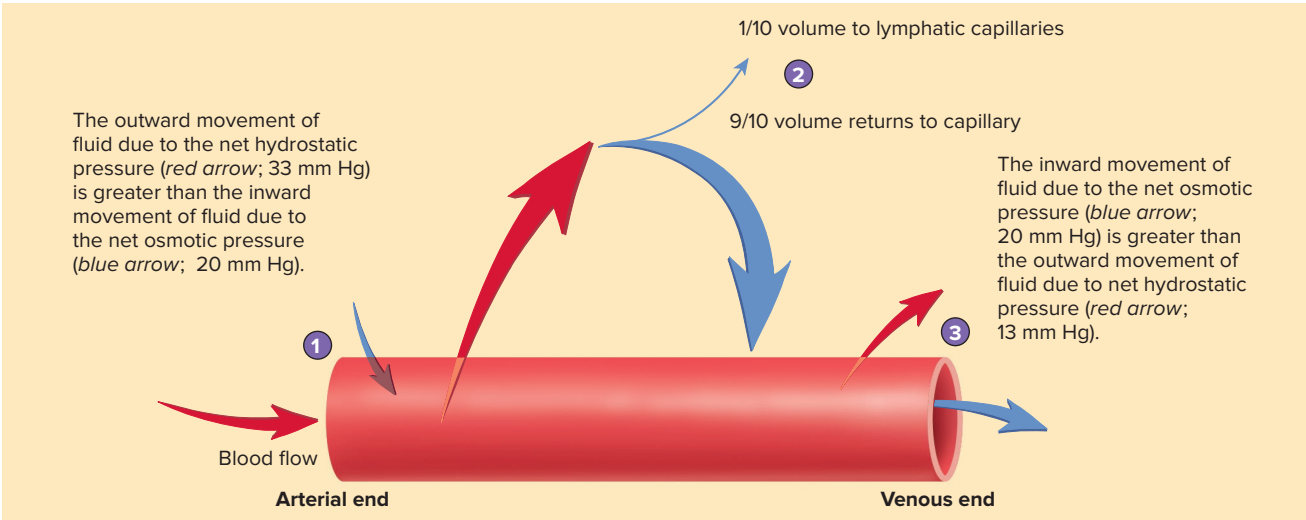
Pulse pressure is inversely related to vascular compliance. As vascular compliance increases, pulse pressure decreases. Conversely, as vascular compliance decreases, pulse pressure increases. The vascular compliance decreases as a person ages. Arteries in older people become less elastic, or arteriosclerotic, causing the pressure in the aorta to rise more rapidly and to a greater degree during systole and to fall more rapidly to its diastolic value. Thus, for a given stroke volume, systolic pressure and pulse pressure are higher as vascular compliance decreases.

As the pulse passes through the smallest arteries and arterioles, it is gradually damped, so that the fluctuation between the systolic and diastolic pressures becomes smaller until the difference is almost absent at the end of the arterioles (see figure 21.35). At the beginning of the capillary, there is a steady pressure of close to 30 mm Hg, which is adequate to force blood through the capillaries if the precapillary sphincters dilate.

Capillary Exchange and Regulation of Interstitial Fluid Volume

Approximately 10 billion capillaries exist in the body. The heart and blood vessels maintain blood flow through those capillaries and support **capillary exchange,** which is the movement of substances into and out of capillaries. Capillary exchange is the process by which cells receive everything they need to survive and to eliminate metabolic waste products. If blood flow through capillaries is not maintained, cells cannot survive.

By far, the most important means by which capillary exchange occurs is **diffusion.** Oxygen, hormones, and nutrients, such as glucose and amino acids, diffuse from a higher concentration in capillaries to a lower concentration in the interstitial fluid. Waste products, including CO_2, diffuse from a higher concentration in the interstitial fluid to a lower concentration in the capillaries. Similar to the diffusion into and out of cells (see figure 3.11), how a substance moves into and out of the capillaries depends on its solubility characteristics. Lipid-soluble molecules, such as O_2, CO_2, steroid-hormones, and fatty acids, diffuse through the plasma membranes of the endothelial cells of the capillaries. Water-soluble substances, such as glucose and amino acids, diffuse through intercellular spaces or through fenestrations of capillaries. In a few areas of the body, such as the spleen and liver, the spaces between the endothelial cells are large enough to allow proteins to pass through them. In other areas, the connections between endothelial cells are extensive, and few molecules pass between the endothelial cells; such is the case in the capillaries of the brain that form the blood-brain barrier. In these capillaries, mediated transport moves water-soluble substances across the capillary walls (see chapter 13 for a description of the blood-brain barrier). The endothelial cells of capillaries appear to take up small pinocytotic vesicles and transport them across the capillary wall. However, the pinocytotic vesicles do not appear to be a major means by which molecules move across the capillary wall.



PROCESS FIGURE 21.36 Fluid Exchange Across the Walls of Capillaries

Pressure differences exist between the inside and the outside of capillaries at their arterial and venous ends.

? *Which pressure would be affected by an obstruction in the capillary? Would this increase or decrease the net filtration pressure?*

Blood enters capillaries at their arterial ends and exits the capillaries at their venous ends. A small amount of fluid moves out of capillaries at their arterial ends and enters other tissues. Most of that fluid reenters the capillaries at their venous ends (figure 21.36). The remaining fluid enters lymphatic vessels, which eventually return it to the venous circulation (see chapter 22). Alterations in the forces affecting fluid movement across capillary walls are responsible for edema (see Clinical Impact 21.2).

Net filtration pressure (NFP) is the force responsible for moving fluid across capillary walls. It is the difference between net hydrostatic pressure and net osmotic pressure:

$$\text{NFP} = \text{Net hydrostatic pressure} - \text{Net osmotic pressure} \qquad (21.6)$$

Hydrostatic pressure is the pressure exerted by fluid, such as blood or interstitial fluid. Osmostic pressure, as defined in chapter 3, is the force required to prevent water from moving by osmosis across a selectively permeable membrane.

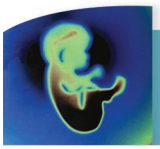
Net hydrostatic pressure is determined by two hydrostatic pressures: (1) **capillary hydrostatic pressure (CHP),** which is the blood pressure within the capillaries; and (2) **interstitial fluid hydrostatic pressure (IHP),** which is the hydrostatic pressure exerted by the interstitial fluid of the tissue surrounding the capillaries. CHP at the arterial end of a capillary is about 30 mm Hg. This pressure results mainly from the force of contraction of the heart, but it can be modified by the effect of gravity on fluids within the body (see "Blood Pressure and the Effect of Gravity," later in this section).

At the arterial end of capillaries, the net hydrostatic pressure that moves fluid across the capillary walls into the tissue spaces is the difference between CHP and IHP:

$$\begin{aligned}\text{Net hydrostatic pressure} &= \text{CHP} - \text{IHP} \\ &= 30 - (-3) \\ &= 33 \text{ mm Hg}\end{aligned} \qquad (21.7)$$

In equation (21.7), IHP is a negative number because of the suction effect produced by the lymphatic vessels as they absorb excess fluid from the tissue spaces. The lymphatic system is described in chapter 22. Here, it is only necessary to understand that excess interstitial fluid enters lymphatic capillaries and is eventually returned to the blood.

Net osmotic pressure is the difference in osmotic pressure between the blood and the interstitial fluid. Solutes, such as proteins in the blood and interstitial fluids, will greatly affect the osmotic pressure. **Blood colloid osmotic pressure (BCOP)** is caused by plasma proteins in the blood. **Interstitial colloid osmotic pressure (ICOP)** is caused by proteins in the interstitial fluid. Large proteins do not pass freely through the capillary walls, and the difference in protein concentrations between the blood and the interstitial fluid is responsible for osmosis across the capillary wall. Ions and small molecules do not make a significant contribution to osmosis across the capillary wall because they pass freely through it and their concentrations are approximately the same in the blood as in the interstitial fluid.



Clinical IMPACT 21.2

Edema

Increases in the permeability of capillaries allow plasma proteins to move from capillaries into the interstitial fluid. This causes an increase in the interstitial colloid osmotic pressure, which causes a net increase in the amount of fluid moving from capillaries into interstitial spaces. The result is edema, swelling due to excessive fluid accumulation in tissues.

Edema can result from many different conditions. Chemical mediators of inflammation increase the permeability of the capillary walls and can cause edema. Decreases in plasma protein concentration reduce the blood colloid osmotic pressure, so more fluid moves out of the capillary at its arterial end and less fluid moves into the capillary at its venous end. The result once again is edema. Severe liver infections that reduce plasma protein synthesis, loss of protein molecules in urine through the kidneys, and protein starvation all lead to edema. Blockage of veins, as in venous thrombosis, increases blood pressure in capillaries and can cause edema. Either blockage or removal of lymphatic vessels, as occurs when lymph nodes are suspected of being cancerous, allows fluid to accumulate in the interstitial spaces and results in edema.

The BCOP (28 mm Hg) is several times larger than the ICOP (8 mm Hg) because of the presence of albumin and other proteins in the plasma (see chapter 19). For demonstration purposes, we can calculate the net osmotic pressure using equation (21.8):

$$\begin{aligned}\text{Net osmotic pressure} &= \text{BCOP} - \text{ICOP}\\ &= 28 - 8\\ &= 20 \text{ mm Hg}\end{aligned} \qquad (21.8)$$

The greater the osmotic pressure of a fluid, the greater the tendency for water to move into that fluid (see chapter 3). The net osmotic pressure results in the osmosis of water into the capillary because water has a greater tendency to move into the blood than into the interstitial fluid.

Figure 21.36 illustrates the interactions between the various pressures that move fluid into and out of the blood. Using equation (21.6), the net filtration pressure at the arterial end of the capillary is calculated (figure 21.36, *step 1*). The net hydrostatic pressure, which moves fluid out of the capillary, is greater than the net osmotic pressure, which moves fluid into the capillary. As a result of these differences, there is a net movement of fluid out of the capillary at the arterial end of the capillary.

Note that in the discussion so far, we have referred to the NFP at the arterial end of the capillary. This is because NFP changes as blood flows through the capillary, primarily due to changes in the net hydrostatic pressure. The CHP decreases as blood moves through the capillary. The decrease is from about 30 mm Hg at the arterial end of the capillary to 10 mm Hg at the venous end of the capillary. This causes a reduction in the net hydrostatic pressure moving fluid out of the venous end of the capillary. Again, we can demonstrate this using equation (21.7):

$$\begin{aligned}\text{Net hydrostatic pressure} &= \text{CHP} - \text{IHP}\\ &= 10 - (-3)\\ &= 13 \text{ mm Hg}\end{aligned}$$

The concentration of proteins within capillaries and the concentration of proteins within interstitial fluid do not change significantly because only a small amount of fluid passes from the capillaries into the tissue spaces. Therefore, the net osmotic pressure moving fluid into capillaries by osmosis is still approximately 20 mm Hg. The NFP at the venous end is a negative number, which indicates the tendency for fluid to reenter the capillary (figure 21.36, *step 3*).

Exchange of fluid across the capillary wall and movement of fluid into lymphatic capillaries keep the volume of the interstitial fluid within a narrow range of values. Disruptions in the movement of fluid across the wall of the capillary can result in edema, or swelling, as a result of increased interstitial fluid volume.

Predict 4

Edema often results from a disruption in the normal inwardly and outwardly directed pressures across the capillary wall. On the basis of what you know about fluid movement across the wall of the capillary and the regulation of capillary blood pressure, explain why large fluctuations in arterial blood pressure do not cause significant edema, whereas small increases in venous pressure can lead to edema.

ASSESS YOUR PROGRESS

49. *What is a pulse? List the locations on the body where the pulse can easily be detected.*

50. *What is pulse pressure? How do stroke volume and vascular compliance affect pulse pressure?*

51. *What is the most important means by which capillary exchange occurs?*

52. *Describe the factors that influence the movement of fluid from capillaries into the tissues.*

53. *What is the main force for the return of fluids at the venous end of capillaries?*

54. *What happens to the fluid in the tissues? What is edema?*

Functional Characteristics of Veins

In chapter 20, factors that affect cardiac output were described. One important factor that is influenced by veins is the preload, which is determined by the volume of blood that enters the heart from the veins (see chapter 20). Therefore, the factors that affect flow in the veins are of great importance to the overall function of the cardiovascular system. If the volume of blood is increased because of a rapid transfusion, the amount of blood flow to the heart through the veins increases. This increases the preload, which causes the cardiac output to increase because of the Starling law of the heart. On the other hand, rapid loss of a large volume of blood decreases venous return to the heart, which decreases the preload and cardiac output.

Case STUDY 21.1 Venous Thrombosis

Harry is a 55-year-old college professor who teaches a night class in a small town about 50 miles from his home. One night, as he walked to his car after class, Harry noticed that his right leg was uncomfortable. When he arrived home, about 90 minutes later, Harry realized that the calf of his right leg had become very swollen. When he extended his knee and plantar flexed his foot, the pain in his right leg increased. Harry thought this might be a serious condition, so he drove to the hospital.

In the emergency room, technicians performed a Doppler test, which monitors the flow of blood through blood vessels. The test confirmed that a thrombus had formed in one of the deep veins of Harry's right leg. His pain and edema were consistent with the presence of a venous thrombosis.

Harry was admitted to the hospital, and his physician prescribed intravenous (IV) heparin. About 4 a.m., Harry experienced an increase in his respiratory rate, his breathing became labored, he felt pain in his chest and back, and his arterial oxygen levels decreased. In response to these changes, Harry's physician increased the amount of heparin. The chest pain subsided, and Harry's respiratory movements improved over the next 24 hours. The next day, a CT scan revealed pulmonary emboli, but no infarctions of the lung. The edema in Harry's leg also slowly improved.

Harry remained in the hospital for several days, during which heparin was continued and then oral coumadin was prescribed. Frequent blood samples were taken to determine Harry's prothrombin time (see chapter 19). After about a week, Harry was released from the hospital. His physician, however, prescribed oral coumadin for at least several months. In addition, Harry was required to have his prothrombin time checked periodically.

Predict 5

a. Explain why edema and pain developed in response to a thrombus in a deep vein of Harry's right leg.

b. If a thrombus in the posterior tibial vein gave rise to an embolus, name in order the parts of the circulatory system the embolus would pass through before lodging in a blood vessel in the lungs. Explain why the lungs are the most likely places the embolus will lodge.

c. Predict the effect of pulmonary emboli on the right ventricle's ability to pump blood.

d. Predict the effect of pulmonary emboli on blood oxygen levels, on the left ventricle's ability to pump blood, and on systemic blood pressure. What responses would be activated by this change in blood pressure? (*Hint:* See figure 21.40.)

e. Explain why Harry's physician prescribed heparin and coumadin and why coumadin was continued long after the venous thrombosis and lung emboli had dissolved.

Venous tone is a continual state of partial contraction of the veins as a result of sympathetic stimulation (see chapter 16). Increased sympathetic stimulation increases venous tone by causing the veins to constrict more, which forces the large venous volume to flow toward the heart. Consequently, venous return and preload increase, causing an increase in cardiac output. Conversely, decreased sympathetic stimulation decreases venous tone, allowing veins to relax and dilate. As the veins fill with blood, venous return to the heart, preload, and cardiac output decrease.

The periodic compression of veins by contracting skeletal muscles forces blood to flow more rapidly through them toward the heart. The valves in the veins prevent flow away from the heart, so that, when veins are compressed, blood is forced toward the heart. During exercise, the combination of arterial dilation and compression of the veins by skeletal muscles causes blood to return to the heart more rapidly than under conditions of rest.

Blood Pressure and the Effect of Gravity

Blood pressure is approximately 0 mm Hg in the right atrium and approximately 100 mm Hg in the aorta. However, the pressure in the vessels above and below the heart is affected by gravity. While a person is standing, the pressure in the venules of the feet can be as much as 90 mm Hg, instead of the usual 10 mm Hg. Arterial pressure is influenced by gravity to the same degree; thus, the arterial ends of the capillaries can have a pressure of 110 mm Hg rather than 30 mm Hg. The normal pressure difference between the arterial and the venous ends of capillaries remains the same, so that blood continues to flow through the capillaries. The major effect of the high pressure in the feet and legs when a person stands for a prolonged time without moving is edema. Without skeletal muscle movement, the pressure at the venous end of the capillaries increases. Up to 15–20% of the total blood volume can pass through the walls of the capillaries into the interstitial spaces of the lower limbs during 15 minutes of standing still.

When a person changes position from lying down to standing, the blood pressure in the veins of the lower limbs increases. Because of the structure of their walls, the compliance of veins is approximately 24 times greater than the compliance of arteries. The increased blood pressure causes the distensible (compliant) veins to expand but has little effect on the arteries. As the veins expand and fill with blood, venous return decreases because less blood is returning to the heart. As venous return decreases, cardiac output and blood pressure decrease (see chapter 20). If negative-feedback mechanisms do not compensate and cause blood pressure to increase, the delivery of blood to the brain is not adequate to maintain homeostasis, and the person may feel dizzy or even faint.

ASSESS YOUR PROGRESS

55. *How do blood volume and venous tone affect cardiac output?*
56. *What effect does standing still for a prolonged time have on the blood pressure in the feet and in the head? Explain why this effect occurs.*
57. *Why does a person feel dizzy if he or she stands up too quickly from sitting or lying down?*

21.8 Control of Blood Flow in Tissues

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Explain how local mechanisms regulate blood flow.**
B. **Explain how nervous and hormonal mechanisms control blood flow.**

Blood flow provided to the tissues by the circulatory system is highly controlled and matched closely to the metabolic needs of tissues. Mechanisms that control blood flow through tissues are classified as (1) local control or (2) nervous and hormonal control (table 21.15).

Local Control of Blood Flow in Tissues

Blood flow is not equal in all tissues of the body. Some organs require a greater blood flow than others. For example, blood flow through the brain, kidneys, and liver is relatively high. By contrast, blood flow through resting skeletal muscles is not high, but it is greater than that through other tissue types because skeletal muscle constitutes 35–40% of the total body mass. However, blood flow through exercising skeletal muscles can increase up to 20-fold, and the flow through the viscera, including the kidneys and liver, either remains the same or decreases. Local control of blood flow is achieved by the periodic relaxation and contraction of precapillary sphincters regulating blood flow through capillary networks of the tissues. In most tissues, blood flow is proportional

TABLE 21.15 **Homeostasis: Control of Blood Flow**

Stimulus	Response
Local Control	
Regulation by Metabolic Need of Tissues	
Increased vasodilator substances (e.g., CO_2, lactate, adenosine, adenosine monophosphate, adenosine diphosphate, endothelium-derived relaxation factor, K^+, decreased pH) or decreased O_2 and nutrients (e.g., glucose, amino acids, fatty acids, and other nutrients) as a result of increased metabolism	Relaxation of precapillary sphincters and subsequent increase in blood flow through capillaries
Decreased vasodilator substances and a reduced need for O_2 and nutrients	Contraction of precapillary sphincters and subsequent decrease in blood flow through capillaries
Autoregulation	
Increased blood pressure	Contraction of precapillary sphincters to maintain constant capillary blood flow
Decreased blood pressure	Relaxation of precapillary sphincters to maintain constant capillary blood flow
Long-Term Local Blood Flow	
Increased metabolic activity of tissues over a long period	Increased diameter and number of capillaries
Decreased metabolic activity of tissues over a long period	Decreased diameter and number of capillaries
Nervous Control	
Increased physical activity or increased sympathetic activity	Constriction of blood vessels in skin and viscera
Increased body temperature detected by neurons of the hypothalamus	Dilation of blood vessels in skin (see chapter 5)
Decreased body temperature detected by neurons of the hypothalamus	Constriction of blood vessels in skin (see chapter 5)
Decreased skin temperature below a critical value	Dilation of blood vessels in skin (protects skin from extreme cold)
Anger or embarrassment	Dilation of blood vessels in skin of face and upper thorax
Hormonal Control (reinforces increased activity of the sympathetic nervous system)	
Increased physical activity and increased sympathetic activity, causing release of epinephrine and small amounts of norepinephrine from adrenal medulla	Constriction of blood vessels in skin and viscera; dilation of blood vessels in skeletal and cardiac muscle

to the metabolic needs of the tissue; therefore, as metabolic needs increase, as is the case when the activity of skeletal muscle increases, blood flow increases to supply the greater need for O_2 and other nutrients. Blood flow also increases in response to a buildup of metabolic end products.

In some tissues, blood flow serves purposes other than delivering nutrients and removing waste products. In the skin, blood flow dissipates heat from the body. In the kidneys, it eliminates metabolic waste products, regulates water balance, and controls the pH of body fluids. Among other functions, blood flow delivers nutrients that enter the blood from the small intestine to the liver for processing.

Functional Characteristics of the Capillary Bed

The innervation of the metarterioles and the precapillary sphincters in capillary networks is sparse. Local factors primarily regulate these structures. As the rate of metabolism increases in a tissue, blood flow through its capillaries increases. The precapillary sphincters relax, allowing blood to flow into the local capillary network. Blood flow can increase sevenfold to eightfold as a result of vasodilation of the metarterioles and the relaxation of precapillary sphincters in response to an increased rate of metabolism.

As the rate of metabolism increases in a tissue, **vasodilator substances** are produced in the extracellular fluid. These substances include CO_2, lactate, adenosine, adenosine monophosphate, adenosine diphosphate, endothelium-derived relaxation factor (EDRF), K^+, and H^+. Once produced, the vasodilator substances diffuse from the tissues supplied by the capillary to the area of the precapillary sphincter, the metarterioles, and the arterioles to cause vasodilation and relaxation of the precapillary sphincters (figure 21.37).

Lack of O_2 and nutrients can also be important in regulating blood flow in tissues. For example, O_2 and nutrients are required to maintain vascular smooth muscle contraction. An increased rate of metabolism decreases the amount of O_2 and nutrients in the tissues. Smooth muscle cells of the precapillary sphincter relax in response to lower levels of O_2 and nutrients, resulting in vasodilation (figure 21.37).

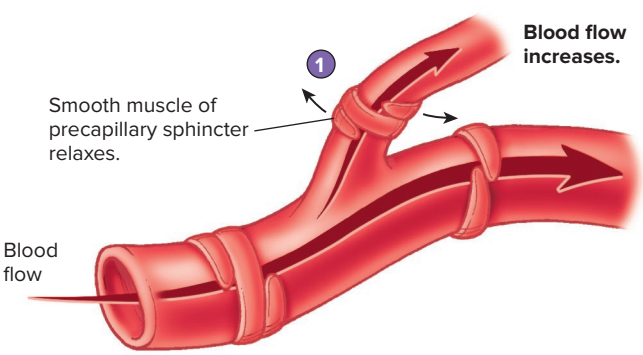
The rate of blood flow through capillaries is not constant, but fluctuates. The cyclic fluctuation is the result of **vasomotion** (vā-sō-mō′shŭn, vas-ō-mō′shŭn), the periodic contraction and relaxation of the precapillary sphincters. Blood flows through the capillaries until the by-products of metabolism are reduced in concentration and until nutrient supplies to precapillary smooth muscles are replenished. Then the precapillary sphincters constrict and remain constricted until the by-products of metabolism increase and nutrients decrease (figure 21.37).

Autoregulation of Blood Flow

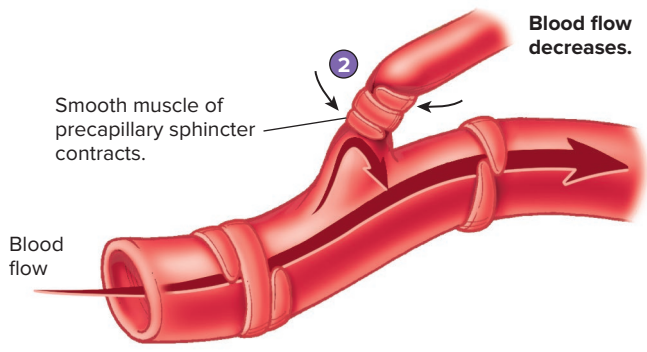
Arterial pressure can change over a wide range, whereas blood flow through tissues remains relatively constant. The maintenance of blood flow by tissues is called **autoregulation** (aw′tō-reg-ū-lā′shŭn). Between arterial pressures of approximately 75 mm Hg and 175 mm Hg, blood flow through tissues remains within 10–15% of its normal value. The mechanisms responsible for autoregulation are the same as those for vasomotion. The need for O_2 and nutrients and the buildup of metabolic by-products cause precapillary sphincters to dilate, and blood flow through tissues increases if a minimum blood pressure exists. On the other hand, once the supply of O_2 and nutrients to tissues is adequate, the precapillary sphincters constrict, and blood flow through the tissues decreases, even if blood pressure is very high.

Long-Term Local Blood Flow

The long-term regulation of blood flow through tissues is matched closely to the tissues' metabolic requirements. Because of this



1 Vasodilation of precapillary sphincters
Precapillary sphincters relax as the tissue concentration of O_2 and nutrients, such as glucose, amino acids, and fatty acids, decreases. The sphincters also relax as the concentration of vasodilator substances, such as CO_2, lactate, adenosine, adenosine monophosphate, adenosine diphosphate, nitric oxide, and K^+, increase, and as the pH decreases.

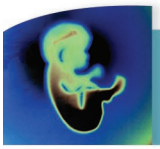


2 Constriction of precapillary sphincters
Precapillary sphincters contract as the tissue concentration of O_2 and nutrients, such as glucose, amino acids, and fatty acids, increases. The sphincters also contract as the tissue concentration of metabolic by-products, such as CO_2, lactate, adenosine, adenosine monophosphate, adenosine diphosphate, nitric oxide, and K^+, decrease, and as the pH increases.

PROCESS FIGURE 21.37 Local Control of Blood Flow Through Capillary Beds AP|R

Precapillary sphincters relax and contract to regulate blood flow to tissues to match the tissues' needs.

? *Which condition (1 or 2) would most likely exist in your skeletal muscle tissue when you are sleeping? Explain your answer.*



Clinical IMPACT 21.3 Hypertension

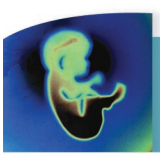
Hypertension, or high blood pressure, affects nearly 30% of the population at sometime in their lives. Generally, a person is considered hypertensive if the systolic blood pressure is greater than 130 mm Hg and the diastolic pressure is greater than 80 mm Hg. However, current methods of evaluation take into consideration diastolic and systolic pressures in determining whether a person is suffering from hypertension (see table 21.14).

Chronic hypertension has an adverse effect on the function of both the heart and the blood vessels. Hypertension requires the heart to work harder than normal. This extra work leads to hypertrophy of the cardiac muscle, especially in the left ventricle, and can result in heart failure. Hypertension also increases the rate at which arteriosclerosis develops. Arteriosclerosis, in turn, increases the probability that blood clots, or thromboemboli (throm′bō-em′bō-lī), will form and that blood vessels will rupture. Common medical problems associated with hypertension are cerebral hemorrhage, coronary infarction, hemorrhage of renal blood vessels, and poor vision caused by burst blood vessels in the retina.

Some conditions leading to hypertension include a decrease in functional kidney mass, excess aldosterone or angiotensin production, and increased resistance to blood flow in the renal arteries. All of these conditions lead to an increase in total blood volume, which causes cardiac output to increase. Increased cardiac output forces blood to flow through capillaries, causing the precapillary sphincters to constrict. Thus, increased blood volume increases cardiac output and peripheral resistance, both of which result in greater blood pressure.

Although many known conditions result in hypertension, roughly 90% of the diagnosed cases are called **idiopathic hypertension,** or *essential hypertension,* which means that the cause of the condition is unknown. Drugs that dilate blood vessels (called vasodilators), drugs that increase the rate of urine production (called diuretics), and drugs that decrease cardiac output are normally used to treat idiopathic hypertension. The vasodilator drugs increase the rate of blood flow through the kidneys and thus increase urine production; the diuretics increase urine production as well. Increased urine production reduces blood volume, which reduces blood pressure. Substances that decrease cardiac output, such as β-adrenergic blocking agents, decrease the heart rate and force of contraction. In addition to these treatments, low-salt diets are normally recommended to reduce the amount of sodium chloride (NaCl) and water absorbed from the intestine into the bloodstream.

close association between regulation and metabolic requirements, a tissue's capillary density can change over time. If the metabolic activity of a tissue increases and remains elevated for an extended period, the diameter and the number of capillaries in the tissue increase, and local blood flow increases. An example is the increased density of capillaries in the well-trained skeletal muscles of athletes, compared with that in poorly trained skeletal muscles.



Clinical IMPACT 21.4

Occlusion of Blood Vessels and Collateral Circulation

Occlusion, or blockage, of a blood vessel leads to an increase in the diameter of smaller blood vessels that bypass the occluded vessel. In many cases, the development of these collateral vessels is marked. For example, if the femoral artery is occluded, the small vessels that bypass the occluded vessel become greatly enlarged, and an adequate blood supply to the lower limb is often reestablished over a period of weeks. If the occlusion is sudden and so complete that tissues supplied by a blood vessel suffer from ischemia (lack of blood flow), cell necrosis (death) can occur. In this instance, collateral circulation does not have a chance to develop before necrosis sets in.

The availability of O_2 to a tissue can be a major factor in determining the adjustment of the tissue's vascularity to its long-term metabolic needs. If O_2 is scarce, capillaries increase in diameter and in number but, if O_2 levels remain elevated in a tissue, the vascularity decreases.

Nervous and Hormonal Control of Blood Flow in Tissues

Nervous control of arterial blood pressure is important in the minute-to-minute regulation of blood flow in tissues. The blood pressure must be adequate to cause blood to flow through capillaries while at rest, during exercise, or in response to circulatory shock, during which blood pressure becomes very low. For example, during exercise, increased arterial blood pressure is needed to sustain increased blood flow through the capillaries of skeletal muscles, in which precapillary sphincters have dilated. The increased blood flow supplies increased levels of O_2 and nutrients to the exercising skeletal muscles.

Nervous regulation also provides a means to regulate blood flow by altering the volume of blood flowing to different regions of the body. For example, in response to blood loss, blood flow to the viscera and the skin is reduced dramatically. This helps maintain the arterial blood pressure within a range sufficient to allow adequate blood flow through the capillaries of the brain and cardiac muscle.

Nervous regulation by the autonomic nervous system, particularly the sympathetic division, can function rapidly (within 1–30 seconds). Sympathetic vasomotor fibers are neurons that regulate the level of smooth muscle contraction in vessel walls. Because of their control of vasoconstriction, these fibers are referred to as vasoconstrictor fibers. These fibers innervate all the blood vessels

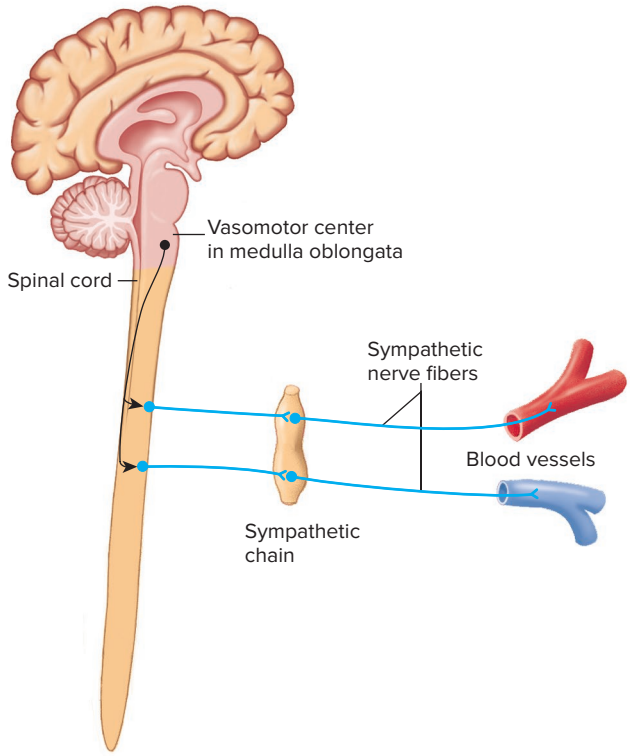


FIGURE 21.38 Nervous Regulation of Blood Vessels
Most blood vessels are innervated by sympathetic nerve fibers. The vasomotor center within the medulla oblongata plays a major role in regulating the frequency of action potentials in nerve fibers that innervate blood vessels.

of the body except the capillaries, the precapillary sphincters, and most metarterioles (figure 21.38). The innervation of the small arteries and arterioles allows the sympathetic nervous system to increase or decrease resistance to blood flow. Though sympathetic fibers extend to most parts of the circulatory system, sympathetic innervation of blood vessels is not the same in all tissues of the body. Sympathetic vasoconstrictor fibers are less prominent in skeletal muscle, cardiac muscle, and the brain and more prominent in the kidneys, the digestive tract, the spleen, and the skin.

The degree to which blood vessels are constricted is regulated by centers in the brain. An area of the lower pons and upper medulla oblongata, called the **vasomotor** (vā-sō-mō′ter, vas-ō-mō′ter) **center** (figure 21.38), is tonically active. A low frequency of action potentials is transmitted continually through the sympathetic vasoconstrictor fibers. As a consequence, the peripheral blood vessels are partially constricted, a condition called **vasomotor tone.**

Predict 6

A strong athlete just finished a 1-mile run and sat down to have a drink with her friends. During the run, her blood pressure was not dramatically elevated, but her cardiac output increased greatly. After the run, her cardiac output decreased dramatically, but her blood pressure decreased only to its resting level. Predict how the sympathetic stimulation of her large veins, the arteries in her digestive system, and the arteries in her skeletal muscles changes while she is relaxing. Explain why this is consistent with the decrease in her cardiac output.

Part of the vasomotor center inhibits vasomotor tone. Thus, the vasomotor center consists of an excitatory part, which is tonically active, and an inhibitory part, which can induce vasodilation. Vasoconstriction results from an increase in vasomotor tone, whereas vasodilation results from a decrease in vasomotor tone.

Areas throughout the brain can either stimulate or inhibit the vasomotor center. For example, the hypothalamus can exert either strong excitatory or strong inhibitory effects on the vasomotor center. Increased body temperature detected by temperature receptors in the hypothalamus causes vasodilation of blood vessels in the skin (see chapter 5). The cerebral cortex can also either excite or inhibit the vasomotor center. For example, action potentials that originate in the cerebral cortex during periods of emotional excitement activate hypothalamic centers, which in turn increase vasomotor tone (table 21.15).

The neurotransmitter for the vasoconstrictor fibers is norepinephrine, which binds to α-adrenergic receptors on vascular smooth muscle cells to cause vasoconstriction. Sympathetic action potentials also cause the release of epinephrine and norepinephrine into the blood from the adrenal medulla. These neurohormones are transported in the blood to all parts of the body. In most vessels, they cause vasoconstriction, but in some vessels, especially those in skeletal muscle, epinephrine binds to β-adrenergic receptors, which are present in larger numbers, and can cause the blood vessels in skeletal muscle to dilate.

ASSESS YOUR PROGRESS

58. *How is local control of blood flow in tissues achieved?*
59. *Explain how vasodilator substances, O_2, and nutrients are involved with local control of blood flow.*
60. *What is vasomotion? What is autoregulation of local blood flow?*
61. *How is long-term regulation of blood flow through tissues accomplished?*
62. *Describe nervous and hormonal control of blood flow. Under what conditions is nervous control of blood flow important? What is vasomotor tone?*

21.9 Regulation of Mean Arterial Pressure

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Recall the definitions of *mean arterial pressure*, *cardiac output*, and *peripheral resistance*.**
B. **Relate the factors that determine mean arterial pressure.**
C. **Describe the short-term and the long-term mechanisms that regulate arterial blood pressure.**

Blood flow to all areas of the body depends on the maintenance of adequate pressure in the arteries. As long as arterial blood pressure is adequate, local control of blood flow is appropriately matched to tissues' metabolic needs. Blood flow through tissues

cannot be adequate if arterial blood pressure is too low. Inadequate blood flow throughout the body due to the failure of mechanisms to maintain normal blood pressure is **circulatory shock.** If normal blood pressure is not maintained, damage to the body tissues can lead to death (see Clinical Impact 21.6). On the other hand, if arterial blood pressure is too high, the heart and blood vessels may be damaged (see Clinical Impact 21.3).

Mean arterial pressure (MAP) is slightly less than the average of systolic and diastolic pressures because diastole lasts longer than systole. MAP changes over a person's lifetime. It is approximately 70 mm Hg at birth, slightly less than 100 mm Hg from adolescence to middle age, and 110–130 mm Hg in healthy older persons.

MAP is proportional to cardiac output times peripheral resistance. **Cardiac output (CO)** is the volume of blood pumped by the heart each minute. It is equal to the **heart rate (HR)** times the **stroke volume (SV). Peripheral resistance (PR)** is the resistance to blood flow in all the blood vessels. MAP is mathematically represented as

$$\text{MAP} = \text{CO} \times \text{PR} \text{ or } \text{MAP} = \text{HR} \times \text{SV} \times \text{PR} \qquad (21.9)$$

As indicated by equation (21.9), blood pressure is influenced by three factors: (1) heart rate, (2) stroke volume, and (3) peripheral resistance. An increase in any one of these elevates blood pressure. Conversely, a decrease in any one of them reduces blood pressure.

Because stroke volume depends on the amount of blood entering the heart, regulatory mechanisms that control blood volume also affect blood pressure. For example, an increase in blood volume increases venous return, which increases preload, and the increased preload increases stroke volume.

When blood pressure suddenly drops because of hemorrhage or some other cause, the control systems respond by increasing blood pressure to a value consistent with life and by increasing blood volume to its normal value. Two major types of control systems operate to achieve these responses: (1) those that respond in the short term and (2) those that respond in the long term. The short-term regulatory mechanisms respond quickly but begin to lose their capacity to regulate blood pressure a few hours to a few days after blood pressure is maintained at homeostatic values. This occurs because sensory receptors adapt to the altered pressures. Long-term regulation of blood pressure is controlled primarily by mechanisms that influence kidney function. Those mechanisms do not adapt rapidly to altered blood pressures.

Short-Term Regulation of Blood Pressure

The short-term, rapidly acting mechanisms controlling blood pressure involve neural and hormonal control mechanisms. These mechanisms include (1) the baroreceptor reflexes, (2) the adrenal medullary mechanism, (3) chemoreceptor reflexes, and (4) the central nervous system's ischemic response. Some of these reflex mechanisms operate on a minute-to-minute basis and help regulate blood pressure within a narrow range of values. Other mechanisms respond primarily to emergency situations (see figures 21.41 and 21.43).

Baroreceptor Reflexes

Baroreceptor reflexes are very important in regulating blood pressure on a minute-to-minute basis. They detect even small changes in blood pressure and respond quickly. However, they are not as important as other mechanisms in regulating blood pressure over long periods of time.

Baroreceptors, or *pressoreceptors,* are sensory receptors sensitive to stretch. They are scattered along the walls of most of the large arteries of the neck and thorax and are most numerous in the area of the carotid sinus at the base of the internal carotid artery and in the walls of the aortic arch. Action potentials travel from the carotid sinus baroreceptors through the glossopharyngeal (IX) nerves to the cardioregulatory and vasomotor centers in the medulla oblongata and from the aortic arch through the vagus (X) nerves to the medulla oblongata (figure 21.39). Stimulation of baroreceptors in the carotid sinus activates the **carotid sinus reflex,** and stimulation of baroreceptors in the aortic arch activates the **aortic arch reflex.** Both of these reflexes are baroreceptor reflexes, and they help keep blood pressure within homeostatic values.

In the carotid sinus and the aortic arch, the arterial walls are partially stretched by normal blood pressure, so that the baroreceptors produce a constant but low frequency of action potentials. Increased pressure in the blood vessels stretches the vessel walls more, increasing the frequency of action potentials produced by the baroreceptors. Conversely, a decrease in blood pressure reduces the stretch of the arterial wall, causing a decrease in the frequency of action potentials produced by the baroreceptors.

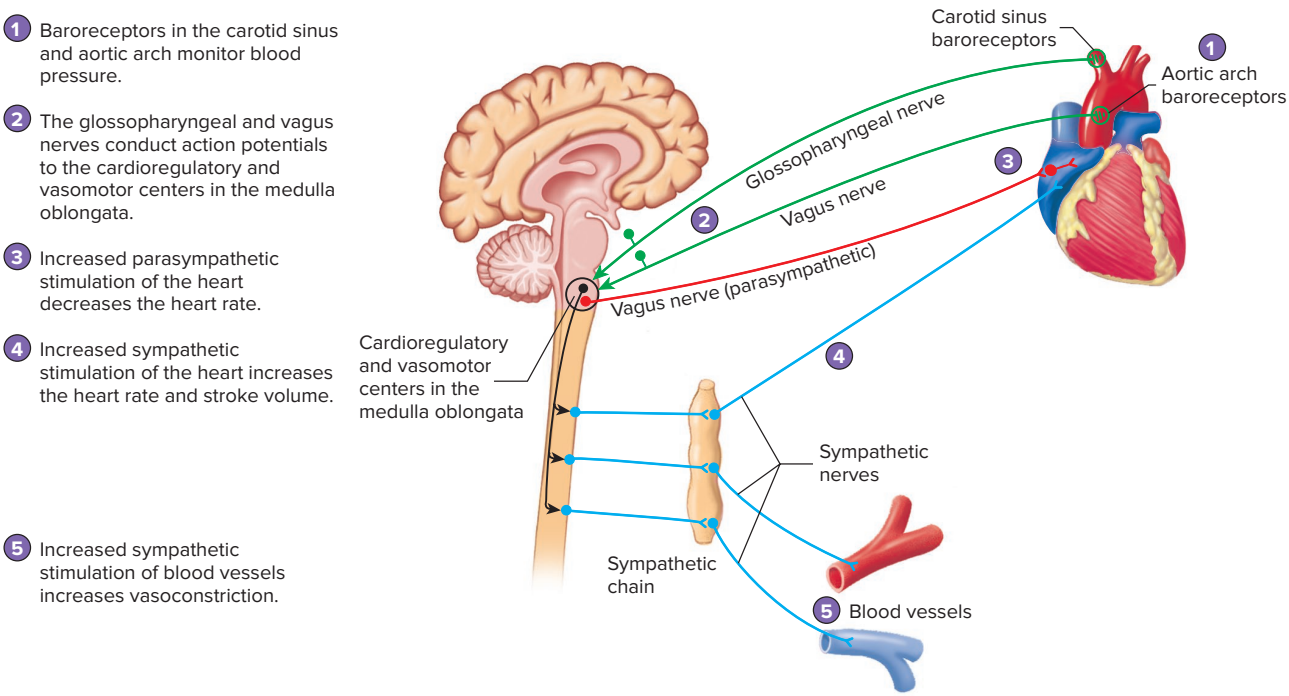
A sudden increase in blood pressure causes the action potential frequency produced in the baroreceptors to also increase. In response to these changes, the vasomotor center in the medulla oblongata of the brain decreases sympathetic stimulation of blood vessels, and the cardioregulatory center, also in the medulla oblongata, increases parasympathetic stimulation of the heart. As a result, peripheral blood vessels dilate, heart rate decreases, and blood pressure decreases (figure 21.40).

Similarly, a sudden decrease in blood pressure causes the action potential frequency produced by the baroreceptors to also decrease. In response, the vasomotor center increases sympathetic stimulation of the blood vessels, and the cardioregulatory center increases sympathetic stimulation and decreases parasympathetic stimulation of the heart. As a result, peripheral blood vessels constrict, heart rate and stroke volume increase, and blood pressure increases (see figures 21.39 and 21.40).

The carotid sinus and aortic arch baroreceptor reflexes are important in regulating blood pressure moment to moment. When a person rises rapidly from sitting or lying to a standing position, blood pressure in the neck and thoracic regions drops dramatically because of the pull of gravity on the blood. This reduction can cause blood flow to the brain to become so sluggish that dizziness or loss of consciousness results. The falling blood pressure activates the baroreceptor reflexes, which reestablish normal blood pressure within a few seconds. A healthy person may experience only a temporary sensation of dizziness.

Predict 7

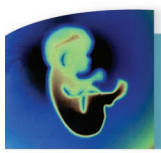
Explain how the baroreceptor reflexes respond when a person does a headstand.



PROCESS FIGURE 21.39 Baroreceptor Reflex Control of Blood Pressure

An increase in blood pressure increases parasympathetic stimulation of the heart and decreases sympathetic stimulation of the heart and blood vessels, resulting in a decrease in blood pressure. A decrease in blood pressure decreases parasympathetic stimulation of the heart and increases sympathetic stimulation of the heart and blood vessels, resulting in an increase in blood pressure.

? *A vasovagal response is when a person feels light-headed or even faints in response to a particular trigger, such as pain or, in some individuals, swallowing. It is due to a reduction in heart rate and drop in blood pressure. Which step in the above diagram is likely the most important to a vasovagal response? Explain your choice.*



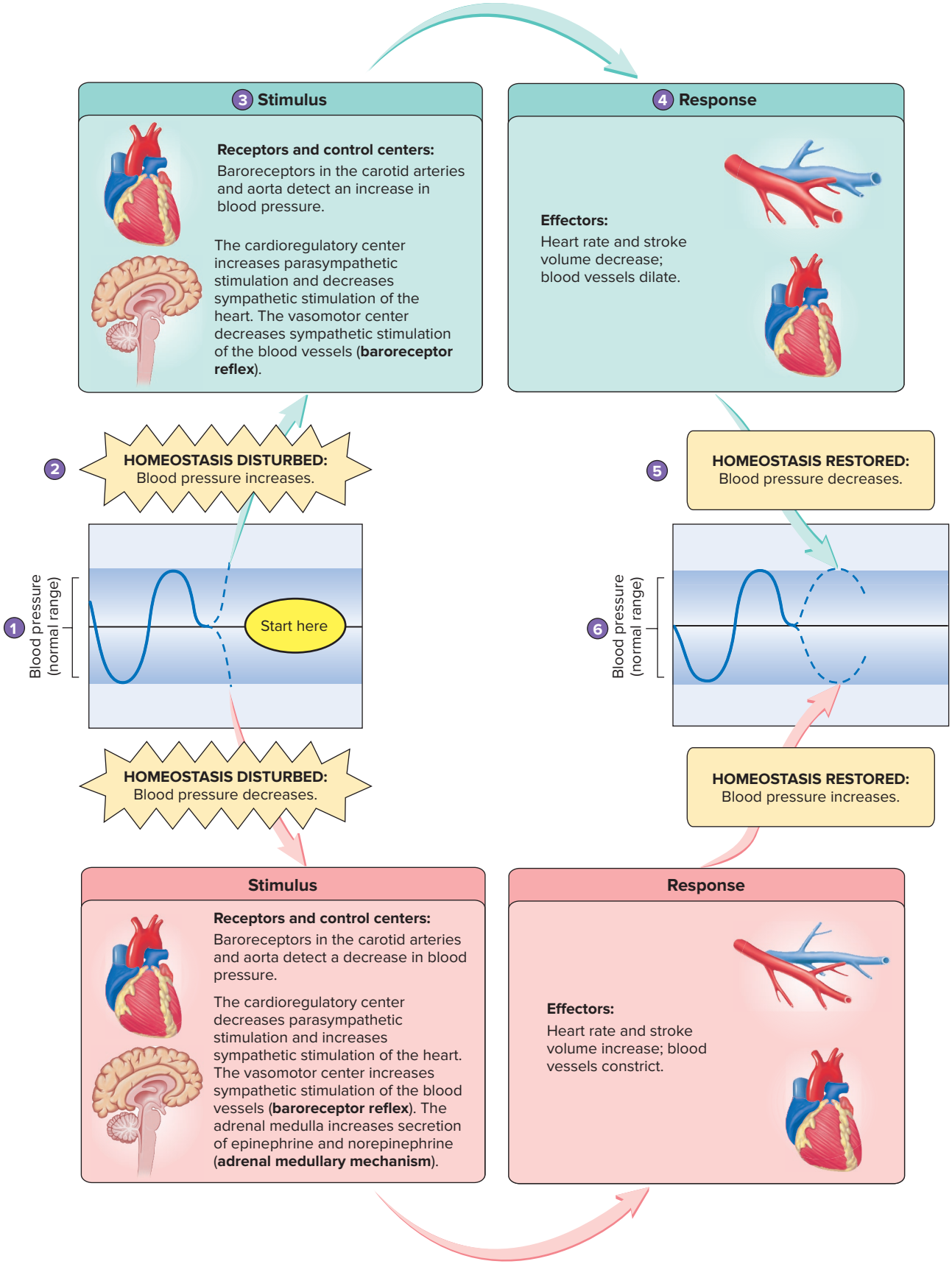
Clinical IMPACT 21.5 Blood Flow Through Tissues During Exercise

Exercise greatly increases blood flow through muscles and keeps blood flow through other organs at a value just adequate to supply their metabolic needs. During exercise, blood flow through skeletal muscles can be 15–20 times greater than through resting muscles. The increase in blood flow ensures that the skeletal muscles receive adequate O_2 and nutrients to sustain activity and remove metabolic waste. Local, nervous, and hormonal regulatory mechanisms are responsible for the increased blood flow. When skeletal muscle is resting, only 20–25% of the capillaries in the skeletal muscle are open, whereas during exercise 100% of the capillaries are open.

Low blood oxygen levels resulting from greatly increased muscular activity and the release of vasodilator substances, such as lactate, CO_2, and K^+, cause the dilation of precapillary sphincters. Increased sympathetic stimulation and epinephrine released from the adrenal medulla cause vasoconstriction in the blood vessels of the skin and viscera, but only some vasoconstriction in the blood vessels of skeletal muscles. Even though some vasoconstriction in skeletal muscle blood vessels occurs, the total resistance to blood flow in skeletal muscle decreases because all the capillaries are open. Blood flow through the skeletal muscles is also enhanced because the increased resistance to blood flow in the skin and viscera causes blood to be shunted from these areas to the skeletal muscles.

The movement of skeletal muscles compresses veins in a cyclic fashion and greatly increases venous return to the heart. In addition, veins undergo some constriction, which reduces the total volume of blood in the veins without dramatically increasing resistance to blood flow. The resulting increase in the preload and increased sympathetic stimulation of the heart lead to elevated heart rate and stroke volume, which increases cardiac output. As a consequence, blood pressure usually increases by 20–60 mm Hg, which also helps sustain the increased blood flow through skeletal muscle blood vessels.

As previously mentioned, blood flow through the skin decreases at the beginning of exercise in response to sympathetic stimulation. However, as body temperature increases in response to increased muscular activity, temperature receptors in the hypothalamus are stimulated. As a result, action potentials in sympathetic nerve fibers causing vasoconstriction decrease, allowing vasodilation of blood vessels in the skin. As a consequence, the skin turns a red or pinkish color, and a great deal of excess heat is lost as blood flows through the dilated blood vessels.



HOMEOSTASIS FIGURE 21.40 Summary of the Baroreceptor Effects on Blood Pressure

(1) Blood pressure is within its normal range. (2) Blood pressure increases outside the normal range, which causes homeostasis to be disturbed. (3) Baroreceptors detect the increase in blood pressure. The cardioregulatory and vasomotor centers in the brain respond to changes in blood pressure. (4) Nervous and hormonal changes alter the activity of cardiac muscle of the heart and smooth muscle of the blood vessels (effectors), causing heart rate and stroke volume to decrease and blood vessels to dilate. (5) These changes cause blood pressure to decrease. (6) Blood pressure returns to its normal range, and homeostasis is restored. Observe the responses to a decrease in blood pressure outside its normal range by following the *red arrows*. For more information on the baroreceptor reflex, see figure 21.39; for the adrenal medullary mechanism, see figure 21.41.

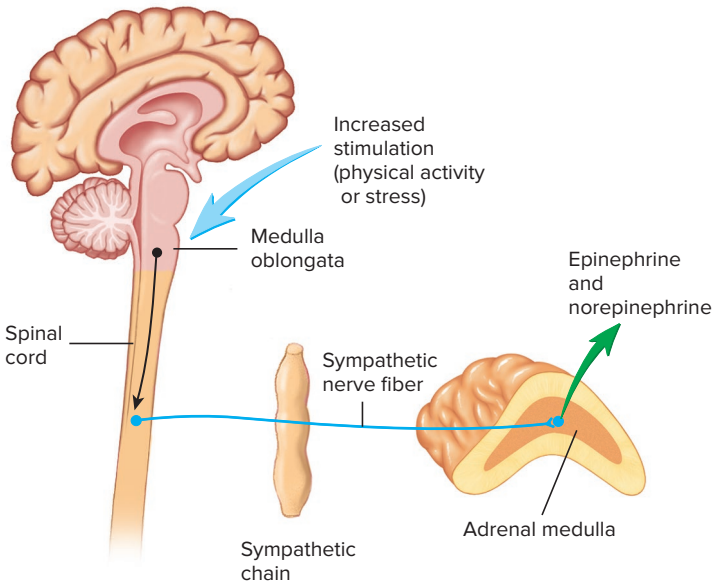


FIGURE 21.41 Adrenal Medullary Mechanism
Stimuli that increase sympathetic stimulation of the heart and blood vessels also result in increased sympathetic stimulation of the adrenal medulla and result in epinephrine and some norepinephrine secretion.

The baroreceptor reflexes are short-term and rapid-acting; however they are adaptable, meaning they do not change the average blood pressure in the long run. The baroreceptors adapt within 1–3 days to any new, sustained blood pressure to which they are exposed. If blood pressure is elevated for more than a few days, as is the case in a person with hypertension, the baroreceptors adapt to the elevated pressure, and the baroreceptor reflexes do not reduce blood pressure to its original value.

Adrenal Medullary Mechanism

The adrenal medullary mechanism is activated by a substantial increase in sympathetic stimulation of the heart and blood vessels (figure 21.41; see figure 21.40). Examples of times when this mechanism is activated include large decreases in blood pressure, sudden and substantial increases in physical activity, and other stressful conditions. The adrenal medullary mechanism results from stimulation of the adrenal medulla by the sympathetic nerve fibers. The adrenal medulla releases epinephrine and smaller amounts of norepinephrine into the bloodstream (figure 21.41; see figure 21.40). These neurohormones affect the cardiovascular system in a fashion similar to direct sympathetic stimulation, causing increased heart rate, increased stroke volume, and vasoconstriction in blood vessels to the skin and viscera. Epinephrine also causes vasodilation of blood vessels of the heart. The adrenal medullary mechanism is short-term and rapid-acting. It responds within seconds to minutes and is usually active for minutes to hours. Other hormonal mechanisms are long-term and slow-acting. They respond within minutes to hours and continue to function for many hours to days.

Chemoreceptor Reflexes

The **chemoreceptor** (kē′mō-rē-sep′tor) **reflexes** help maintain homeostasis by responding to changes in blood composition. Specifically, these reflexes are stimulated by decreases in blood O_2 levels or increases in blood CO_2 levels. Changes in blood CO_2 levels cause changes in blood pH. As blood CO_2 levels increase, blood pH decreases. Conversely, as blood CO_2 levels decrease, blood pH increases. So chemoreceptor reflexes are also stimulated by decreases in blood pH (figures 21.42 and 21.43). Chemoreceptors are located in **carotid bodies,** small organs approximately 1–2 mm in diameter, which lie near the carotid sinuses, and in several **aortic bodies** lying adjacent to the aorta. Afferent nerve fibers pass to the medulla oblongata through the glossopharyngeal nerve (IX) from the carotid bodies and through the vagus nerve (X) from the aortic bodies.

The chemoreceptors receive an abundant blood supply. However, when O_2 availability decreases in the chemoreceptor cells, the frequency of action potentials increases and stimulates the vasomotor center, resulting in increased vasomotor tone. The chemoreceptors act under emergency conditions and do not regulate the cardiovascular system under resting conditions. They normally do not respond strongly unless blood O_2 decreases markedly. The chemoreceptor cells are also stimulated by increased CO_2 and decreased blood pH to increase vasomotor tone, which causes the mean arterial pressure to rise. The elevated mean arterial pressure increases blood flow through tissues in which blood vessels do not constrict, such as the brain and cardiac muscle. Thus, the reflex helps provide adequate O_2 to the brain and the heart when blood O_2 levels in the blood decrease.

Central Nervous System's Ischemic Response

The **central nervous system (CNS) ischemic response** is the increase in blood pressure in response to lack of blood flow to the medulla oblongata of the brain. The CNS ischemic response does not play an important role in regulating blood pressure under normal conditions. It functions primarily in response to emergency situations, as when blood flow to the brain is severely restricted or when blood pressure falls below approximately 50 mm Hg.

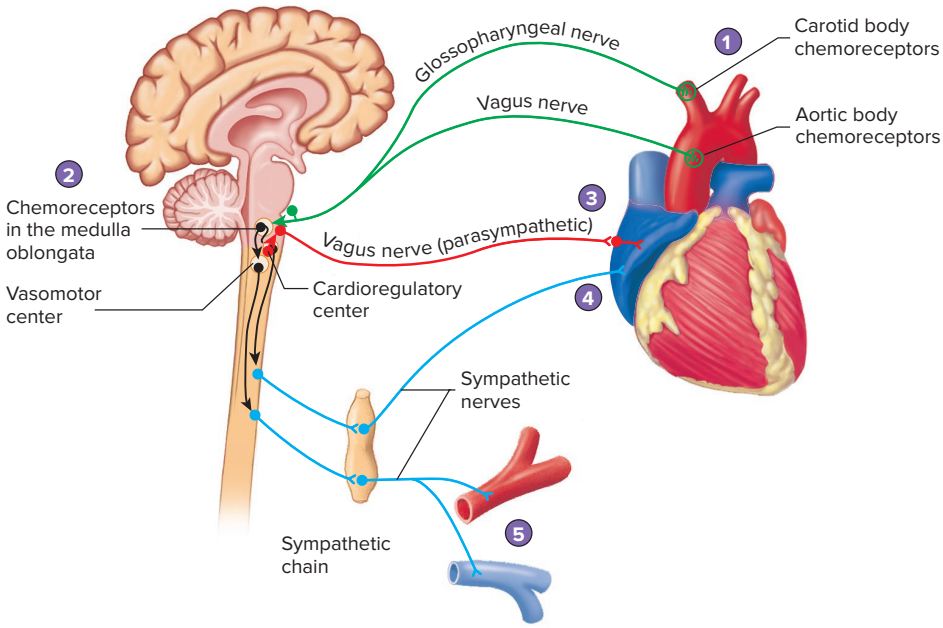
Reduced blood flow results in decreased O_2, increased CO_2, and decreased pH within the medulla oblongata. Neurons of the vasomotor center are strongly stimulated. As a result, the vasomotor center stimulates vasoconstriction, and blood pressure rises dramatically.

The increase in blood pressure that occurs in response to CNS ischemia increases blood flow to the CNS, provided the blood vessels are intact. However, if severe ischemia lasts longer than a few minutes, metabolism in the brain fails because of the lack of O_2. The vasomotor center becomes inactive, and extensive vasodilation occurs in the periphery as vasomotor tone decreases. Prolonged ischemia of the medulla oblongata leads to a massive decline in blood pressure and ultimately death.

Summary of Short-Term Regulation of Blood Pressure

Each of the four short-term regulatory mechanisms of blood pressure are important for specific circumstances. In most circumstances throughout the day, the baroreceptor reflex is the most important short-term regulatory mechanism for maintaining blood pressure. The adrenal medullary mechanism plays a role during exercise and emergencies. The chemoreceptor mechanism is more important when blood O_2 levels are reduced, such as at high altitudes or when CO_2 is elevated or pH is reduced. Thus, it is more important in emergency situations. The CNS ischemic response is activated only in rare, emergency conditions when the brain receives too little O_2.

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



PROCESS FIGURE 21.42 Chemoreceptor Reflex

An increase in blood CO_2 and a decrease in pH and O_2 result in an increased heart rate and vasoconstriction. A decrease in blood CO_2 and an increase in blood pH result in a decreased heart rate and vasodilation.

? *How would holding your breath affect blood pressure?*

ASSESS YOUR PROGRESS

63. *Explain the relationship among mean arterial pressure, cardiac output, and peripheral resistance.*
64. *What are the two major control systems that provide homeostasis of blood pressure? Give a definition of each.*
65. *Where are baroreceptors located? Describe the response of the baroreceptor reflexes when blood pressure increases and decreases.*
66. *Elaborate on the adrenal medullary control mechanism.*
67. *Where are the chemoreceptors for O_2, CO_2, and pH levels located? Discuss what happens when O_2 levels in the blood decrease markedly.*
68. *Describe the CNS ischemic response. Under what conditions does this mechanism operate?*
69. *What mechanism is most important for short-term regulation of blood pressure under resting conditions?*

Long-Term Regulation of Blood Pressure

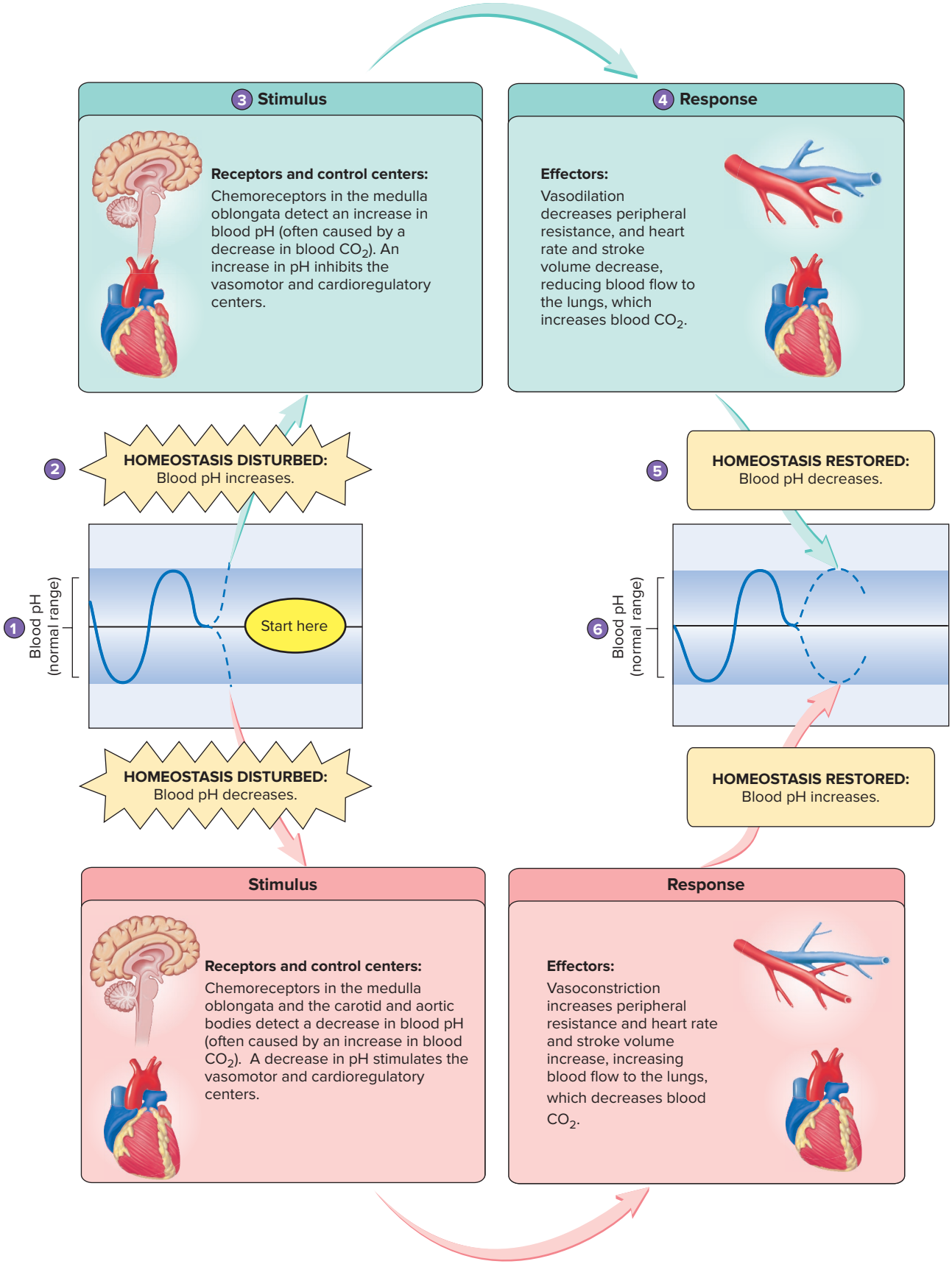
Long-term (slow-acting) regulation of blood pressure involves the regulation of blood concentration and volume by the kidneys, the movement of fluid across the wall of blood vessels, and alterations in the volume of the blood vessels. Some of the long-term regulatory mechanisms begin to respond in minutes, but they continue to function for hours, days, or longer. They adjust blood pressure precisely and keep it within a narrow range of values for years. Major regulatory mechanisms include (1) the renin-angiotensin-aldosterone mechanism, (2) the antidiuretic hormone (vasopressin) mechanism, (3) the atrial natriuretic mechanism, (4) the fluid shift mechanism, and (5) the stress-relaxation response.

Renin-Angiotensin-Aldosterone Mechanism

The kidneys increase urine output as the blood volume and arterial pressure increase, and they decrease urine output as the blood volume and arterial pressure decrease. Increased urine output reduces blood volume and blood pressure, and decreased urine output resists a further decrease in blood volume and blood pressure. Controlling urine output is an important means by which blood pressure is regulated, and it continues to operate until blood pressure is precisely within its normal range of values. The **renin-angiotensin-aldosterone mechanism** helps regulate blood pressure by altering blood volume.

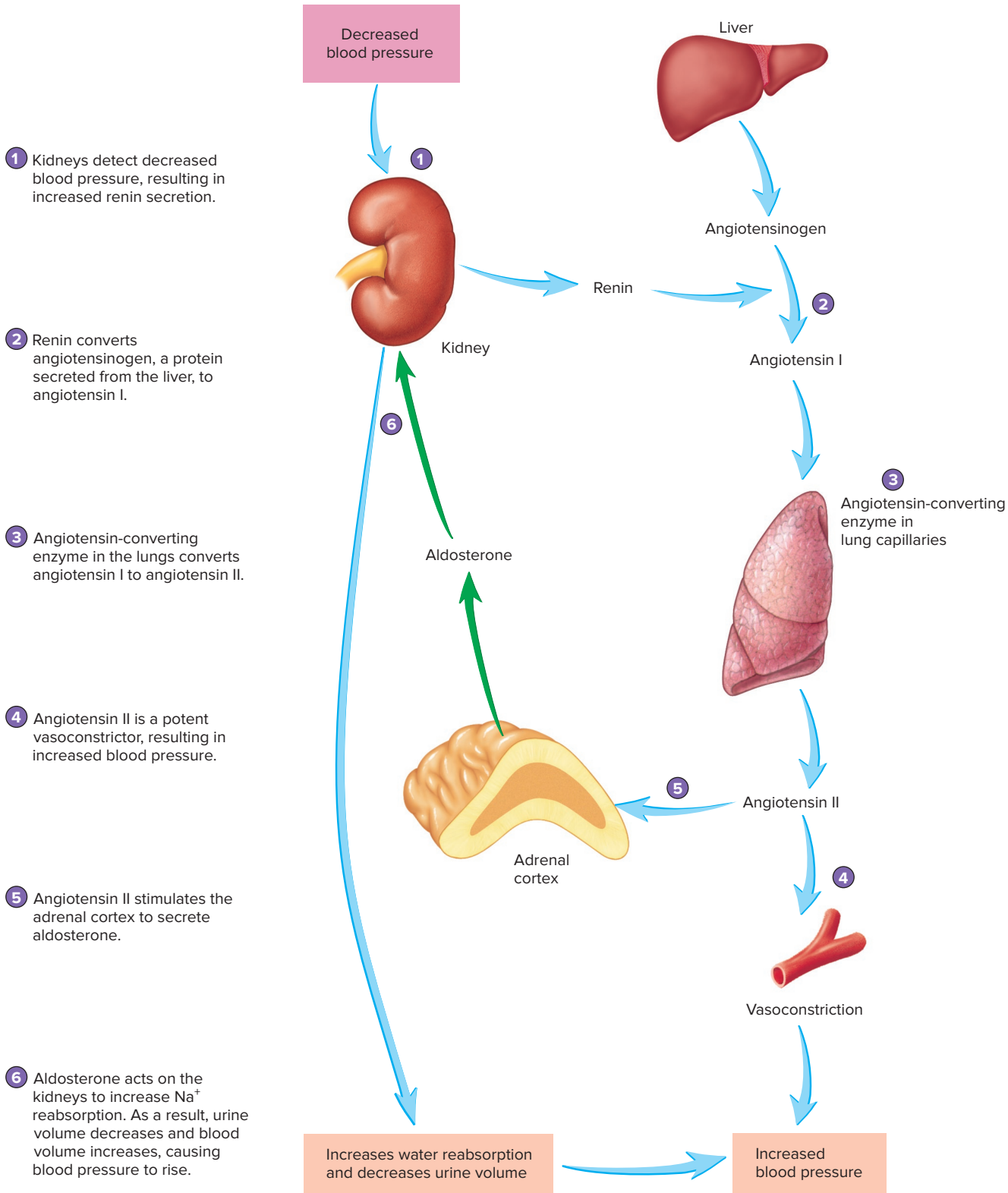
The kidneys release an enzyme, called **renin** (rē′nin), into the blood (figure 21.44; see chapter 26) from specialized structures called the **juxtaglomerular** (jŭks′tă-glŏ-mer′ū-lăr) **apparatuses.** Renin acts on a plasma protein, synthesized by the liver, called **angiotensinogen** (an′jē-ō-ten-sin′ō-jen) to split a fragment off one end. The fragment, called **angiotensin** (an-jē-ō-ten′sin) **I,** contains 10 amino acids. Another enzyme, called **angiotensin-converting enzyme,** found primarily in small blood vessels of the lungs, cleaves 2 additional amino acids from angiotensin I to produce a fragment consisting of 8 amino acids, called **angiotensin II,** or *active angiotensin*.

Angiotensin II causes vasoconstriction in arterioles and, to some degree, in veins. As a result, it increases peripheral resistance and venous return to the heart, both of which raise blood pressure. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex. **Aldosterone** (al-dos′ter-ōn) acts on the kidneys to increase the reabsorption of Na^+ and Cl^- from the filtrate into the extracellular fluid. If antidiuretic hormone (ADH; see chapter 18) is present, water



HOMEOSTASIS FIGURE 21.43 Summary of the Effects of pH and Gases on Blood Pressure

(1) Blood pH is within its normal range. (2) Blood pH increases outside the normal range, which causes homeostasis to be disturbed. (3) Chemoreceptors detect the increase in blood pH. The cardioregulatory and vasomotor centers in the brain are inhibited. (4) Nervous and hormonal changes alter the activity of cardiac muscle of the heart and smooth muscle of the blood vessels (effectors), causing heart rate and stroke volume to decrease and blood vessels to dilate, reducing blood flow to the lungs, which increases blood CO_2. (5) These changes cause blood pH to decrease. (6) Blood pH returns to its normal range, and homeostasis is restored. Observe the responses to a decrease in blood pH outside its normal range by following the *red arrows*. For more information on the chemoreceptor reflex, see figure 21.42; for the central nervous system ischemic response, see the text.



PROCESS FIGURE 21.44 Renin-Angiotensin-Aldosterone Mechanism

The kidneys detect decreased blood pressure and increase renin secretion. The result is vasoconstriction, increased water reabsorption, and decreased urine volume, changes that maintain blood pressure.

? *Why does increased Na+ reabsorption cause increased water reabsorption at the kidneys?*

moves by osmosis with the Na^+ and Cl^-. Consequently, aldosterone causes the kidneys to retain solutes, such as Na^+ and Cl^-, and water. The result is increased blood volume by decreasing the production of urine and conserving water (see chapter 26). Angiotensin II also increases salt appetite, thirst, and ADH secretion.

Secretion of renin is dependent on changes in blood pressure. Decreased blood pressure stimulates renin secretion, and increased blood pressure decreases renin secretion. The renin-angiotensin-aldosterone mechanism is important in maintaining blood pressure on a daily basis. It also reacts strongly under conditions of circulatory shock, but it requires many hours to become maximally effective. Its onset is not as fast as that of nervous reflexes or the adrenal medullary response, but its duration is longer. Once renin is secreted, it remains active for approximately 1 hour, and the effect of aldosterone lasts much longer (many hours).

Angiotensin-converting enzyme (ACE) inhibitors are a class of drugs that inhibit angiotensin-converting enzyme, which converts angiotensin I to angiotensin II. These drugs were first identified as components of the venom of pit vipers. Subsequently, several ACE inhibitors were synthesized. ACE inhibitors are commonly administered to combat hypertension.

Angiotensin II is not the only stimulus for aldosterone secretion. Other stimuli can directly stimulate aldosterone secretion. For example, an increased plasma ion concentration of K^+ and a reduced plasma concentration of Na^+ directly stimulate aldosterone secretion from the adrenal cortex (see chapters 18 and 27). Aldosterone regulates the concentration of these ions in the plasma. A decreased blood pressure and an elevated K^+ concentration occur during plasma loss, during dehydration, and in response to tissue damage, such as burns and crushing injuries.

Antidiuretic Hormone (Vasopressin) Mechanism

The **antidiuretic hormone (vasopressin) mechanism** works in harmony with the renin-angiotensin-aldosterone mechanism in response to changes in blood pressure (figure 21.45). Baroreceptors are sensitive to changes in blood pressure. Decreases in blood pressure detected by the baroreceptors result in the release of antidiuretic hormone (ADH) from the posterior pituitary, although the blood pressure must decrease substantially before the mechanism is activated.

ADH acts directly on blood vessels to cause vasoconstriction, although it is not as potent as other vasoconstrictors. Within minutes after a rapid and substantial decline in blood pressure, ADH is released in sufficient quantities to help reestablish normal blood pressure. ADH also decreases the rate of urine production by the kidneys, thereby helping maintain blood volume and blood pressure.

Neurons of the hypothalamus are sensitive to changes in the solute concentration of the plasma. Even small increases in solute concentrations directly stimulate hypothalamic neurons that increase ADH secretion (figure 21.45; see chapter 26). Increases in the concentration of the plasma, as occur during dehydration, and decreases in blood pressure, as happens after plasma loss, such as in extensive burns or crushing injuries, stimulate ADH secretion.

Atrial Natriuretic Mechanism

A polypeptide called **atrial natriuretic** (ā′trē-ăl nā′trē-ū-ret′ik) **hormone (ANH)** is released from cells in the atria of the heart.

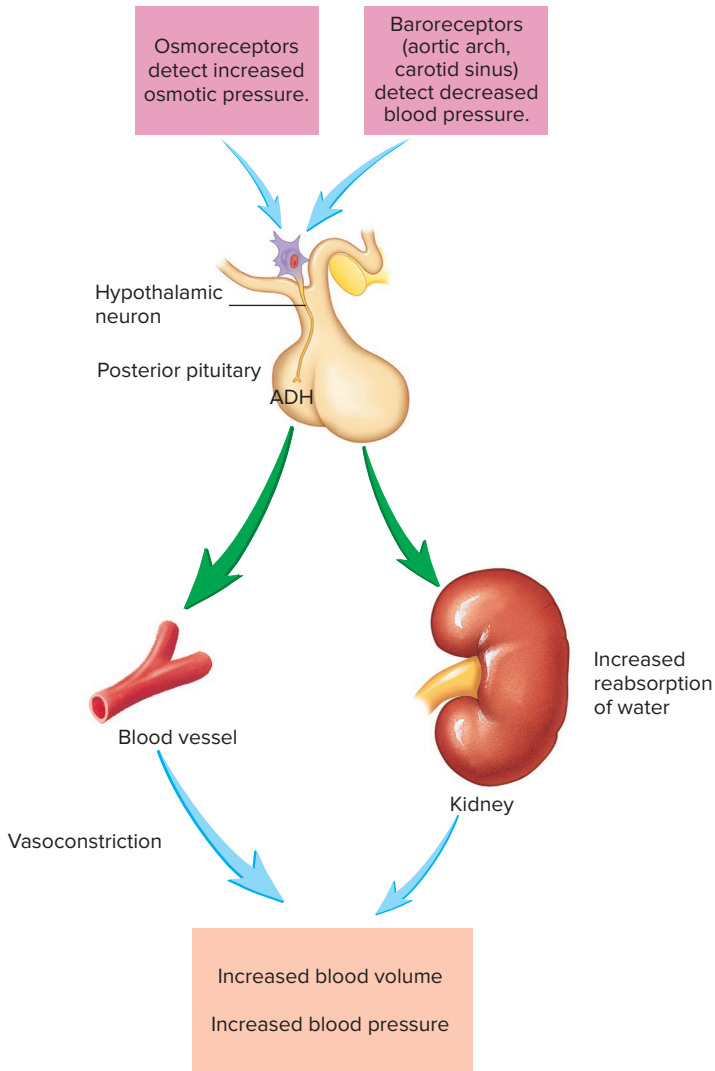
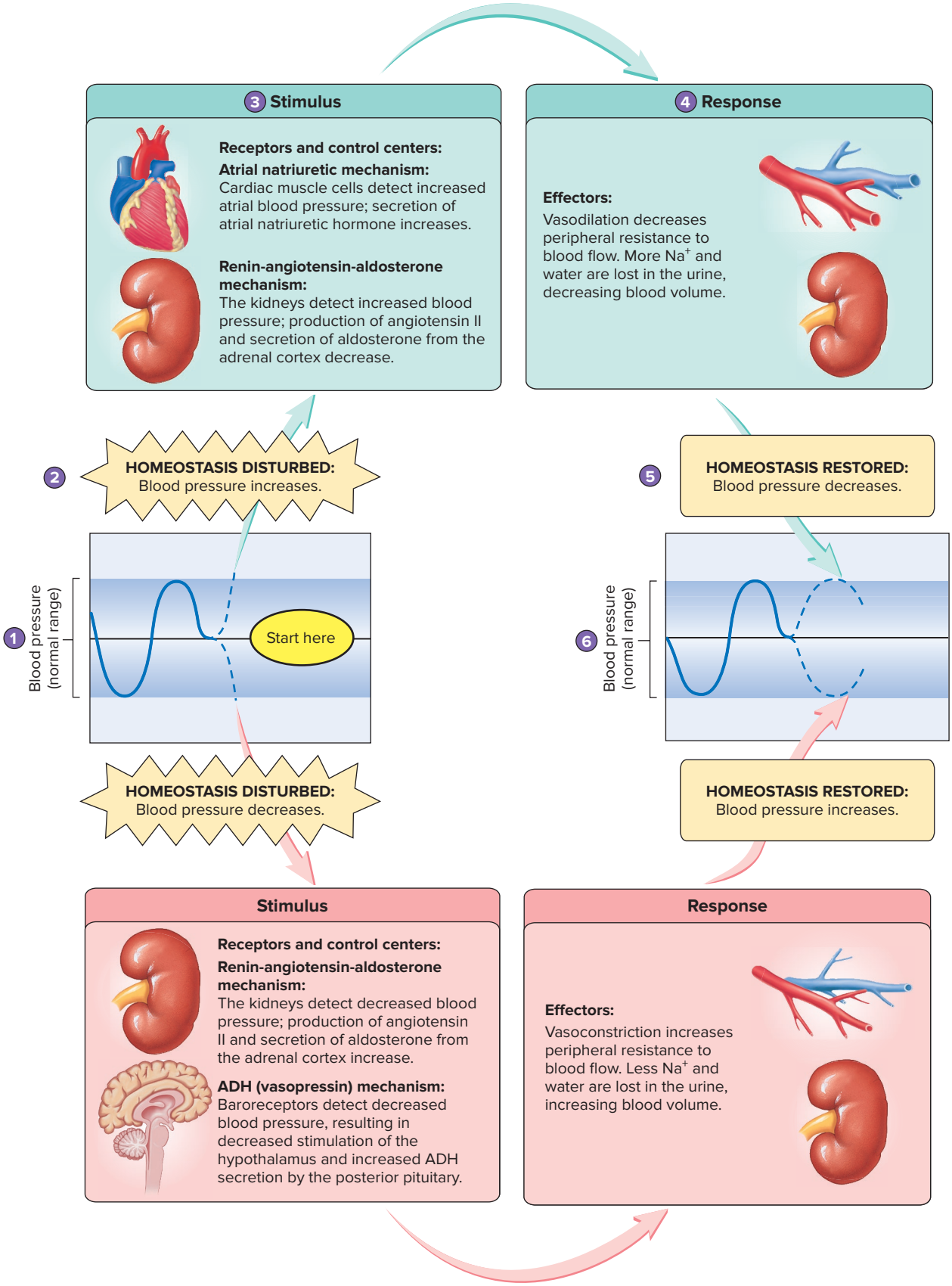


FIGURE 21.45 Antidiuretic Hormone (Vasopressin) Mechanism
Increases in the osmolality of blood or decreases in blood pressure result in antidiuretic hormone (ADH) secretion. ADH increases water reabsorption by the kidneys, and large amounts of ADH result in vasoconstriction. These changes maintain blood pressure.

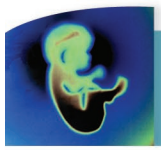
A major stimulus for its release is increased venous return, which stretches atrial cardiac muscle cells. Atrial natriuretic hormone acts on the kidneys to increase the rate of urine production and Na^+ loss in the urine. It also dilates arteries and veins. Loss of water and Na^+ in the urine causes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

The renin-angiotensin-aldosterone, ADH, and atrial natriuretic mechanisms work simultaneously to help regulate blood pressure by controlling urine production by the kidneys. If blood pressure drops below 50 mm Hg, the volume of urine produced by the kidneys is reduced to nearly zero. If blood pressure is increased to 200 mm Hg, the urine volume produced is approximately six to eight times greater than normal. The mechanisms that regulate blood pressure in the long term are summarized in figure 21.46.



HOMEOSTASIS FIGURE 21.46 Summary of Long-Term (Slow-Acting) Blood Pressure Control Mechanisms

(1) Blood pressure is within its normal range. (2) Blood pressure increases outside the normal range, which causes homeostasis to be disturbed. (3) Increased blood pressure is detected by cardiac muscle cells and the kidneys (receptors). The heart and kidneys (control center) respond to increased blood pressure by secretion of hormones. (4) Blood vessels of the body and the kidneys (effectors) respond to the hormones by dilating or adjusting blood volume through urine formation. (5) These changes cause blood pressure to decrease. (6) Blood pressure returns to its normal range, and homeostasis is restored. Observe the responses to a decrease in blood pressure outside its normal range by following the *red arrows*. For more information on the renin-angiotensin-aldosterone mechanism, see figure 21.44; for the antidiuretic hormone mechanism, see figure 21.45; for the atrial natriuretic mechanism, see figure 27.6.



Clinical IMPACT 21.6 Circulatory Shock

Circulatory shock is inadequate blood flow throughout the body due to the failure of the mechanisms that maintain normal blood pressure. As a consequence, tissues suffer damage due to lack of O_2. Severe shock can damage vital body tissues to the extent that the patient dies.

Depending on its severity, circulatory shock can be divided into three stages: (1) compensated shock, (2) progressive shock, and (3) irreversible shock. All types of circulatory shock exhibit one or more of these stages, regardless of their cause. Several causes of circulatory shock exist. Hemorrhagic, or hypovolemic, shock, caused by excessive blood loss, is used here to illustrate the characteristics of each stage.

In **compensated shock,** blood pressure decreases only a moderate amount, and the mechanisms that regulate blood pressure successfully reestablish normal blood pressure and blood flow. The baroreceptor reflexes, chemoreceptor reflexes, and ischemia within the medulla oblongata initiate strong sympathetic responses that result in intense vasoconstriction and increased heart rate. As blood volume decreases, the stress-relaxation response of blood vessels causes them to contract and helps sustain blood pressure. In response to reduced blood flow through the kidneys, increased amounts of renin are released. The elevated renin release causes a greater rate of angiotensin II formation, resulting in vasoconstriction and increased aldosterone release from the adrenal cortex. Aldosterone, in turn, promotes water and salt retention by the kidneys, thereby conserving water. In addition, ADH is released from the posterior pituitary gland and enhances the kidneys' retention of water. Because of the fluid shift mechanism, water also moves from the interstitial spaces and the intestinal lumen to restore normal blood volume. An intense sensation of thirst increases water intake, also helping elevate normal blood volume. In mild cases of compensated shock, baroreceptor reflexes can compensate for blood loss until blood volume is restored but, in more severe cases, all the mechanisms described are required to compensate for the blood loss.

In **progressive shock,** the regulatory mechanisms are inadequate to compensate for the reduction in blood volume. As a consequence, a positive-feedback cycle develops. As circulatory shock worsens, regulatory mechanisms become even less able to compensate for the increasing severity. The cycle proceeds until the next stage of shock is reached or until medical treatment assists the regulatory mechanisms in reestablishing adequate blood flow to the tissues.

During progressive shock, blood pressure declines to a level that is inadequate for maintaining blood flow to cardiac muscle; thus, the heart begins to deteriorate. Tissues subject to severe ischemia release substances that are toxic to the heart. When blood pressure declines to a very low level, blood begins to clot in the small vessels. Eventually, blood vessels begin to dilate due to decreased sympathetic activity and a lack of O_2 in capillary beds. Capillary permeability increases under ischemic conditions, allowing fluid to leave the blood vessels and enter the interstitial spaces. Finally, intense tissue deterioration begins in response to inadequate blood flow.

Without medical intervention, progressive shock leads to **irreversible shock,** which results in death, regardless of the medical treatment applied. In this stage, the damage to tissues, including cardiac muscle, is so extensive that the patient is destined to die, even if adequate blood volume is reestablished and blood pressure is elevated to its normal value. Irreversible shock is characterized by decreasing heart function and progressive dilation of and increased permeability of peripheral blood vessels.

Patients suffering from circulatory shock are normally placed in a horizontal position, usually with the head slightly lower than the feet. Oxygen is often supplied. **Replacement therapy,** which includes transfusions of whole blood, plasma, artificial solutions called plasma substitutes, and physiological saline solutions, is administered to increase blood volume. In some circumstances, drugs that enhance vasoconstriction are also administered. Patients in anaphylactic (an′ă-fĭ-lak′tik; allergic) shock are given anti-inflammatory substances, such as glucocorticoids and antihistamines. The basic objective in treating shock is to reverse the condition and prevent it from progressing to the irreversible stage, as well as to reestablish normal blood flow through tissues.

Several types of shock can be classified by cause:

- **Hemorrhagic shock** is caused by external or internal bleeding that reduces blood volume.
- **Plasma loss shock** is reduced blood volume due to loss of plasma into the interstitial spaces and greatly increased blood viscosity. Causes of plasma loss shock include intestinal obstruction, in which a large amount of plasma moves from the blood into the intestines, and severe burns, which cause large amounts of plasma to be lost from the burned surface.
- **Dehydration** results from a severe and prolonged shortage of fluid intake.
- **Severe diarrhea** or **vomiting** causes a loss of plasma through the intestinal wall.
- **Neurogenic shock** is a rapid loss of vasomotor tone, leading to vasodilation so extensive that blood pressure declines severely.
- **Anesthesia** includes deep general anesthesia and spinal anesthesia that decrease the activity of the medullary vasomotor center or the sympathetic nerve fibers.
- **Brain damage** leads to an ineffective medullary vasomotor function.
- **Emotional shock** (*vasovagal syncope*) stems from emotions that cause strong parasympathetic stimulation of the heart and results in vasodilation in skeletal muscles and in the viscera.
- **Anaphylactic shock** results from an allergic response in which the release of inflammatory substances increases vasodilation and capillary permeability.
- **Septic shock** results from peritoneal, systemic, and gangrenous infections that cause the release of toxic substances into the blood (*blood poisoning*), depressing the activity of the heart and leading to vasodilation and increased capillary permeability.
- **Cardiogenic shock** occurs when the heart stops pumping in response to various conditions, such as heart attack or electrocution.

Fluid Shift Mechanism

The **fluid shift mechanism** occurs in response to small changes in pressures across capillary walls. As blood pressure increases, some fluid is forced from the capillaries into the interstitial spaces. This movement of fluid helps prevent the development of high blood pressure. As blood pressure falls, interstitial fluid moves into capillaries, and this fluid movement resists a further decline in blood pressure. Fluid shift is a powerful mechanism by which blood pressure is maintained, because the interstitial volume acts as a reservoir and is in equilibrium with the large volume of intercellular fluid.

The fluid shift mechanism begins to act within a few minutes of a stimulus, but it requires hours to achieve its full functional capacity. It plays a very important role when dehydration develops over several hours, or when a large volume of saline is administered over several hours.

Stress-Relaxation Response

A **stress-relaxation response** is characteristic of smooth muscle cells (see chapter 9). When blood volume suddenly declines, blood pressure also decreases, reducing the force applied to smooth muscle cells in blood vessel walls. As a result, during the next few minutes to an hour, the smooth muscle cells contract, reducing the volume of the blood vessels, and thus resisting a further decline in blood pressure. Conversely, when blood volume increases rapidly, as occurs during a transfusion, blood pressure increases, and smooth muscle cells of the blood vessel walls relax, resulting in a more gradual increase in blood pressure. The stress-relaxation mechanism is most effective when changes in blood pressure occur over a period of many minutes.

Predict 8

Explain the various mechanisms that regulate blood pressure in response to the rapid loss of a large volume of blood, compared with the loss of the same volume of blood over a period of several hours.

ASSESS YOUR PROGRESS

70. *What stimulates renin secretion in the kidneys?*

71. *For each of these chemicals—angiotensin II, aldosterone, antidiuretic hormone, and atrial natriuretic hormone—state where each is produced and how each affects the circulatory system.*

72. *What is fluid shift, and what does it accomplish?*

73. *Describe the stress-relaxation response of a blood vessel.*

Answer

Learn to Predict

After reading the Clinical Impact, "Circulatory Shock," in this chapter, we learned that circulatory shock is inadequate blood flow throughout the body. More specifically, septic shock results from infections that cause the release of toxic substances into the circulatory system that depress heart activity, cause vasodilation, and increase capillary permeability. After T.J. developed septic shock, we would expect his blood volume to decrease as fluid moved from the more permeable capillaries to the interstitial spaces. The reduction in blood volume would lead to a drop in his blood pressure, stimulating the baroreceptor reflex mechanism and subsequently an increase in heart rate. We would also expect T.J.'s stroke volume to decrease with a drop in blood volume. Increased sympathetic stimulation would cause vasoconstriction of blood vessels as T.J.'s body tried to maintain normal blood pressure. With the reduction in blood flow through the skin, T.J. would appear very pale. If T.J.'s blood pressure is not maintained, he could progress to irreversible shock, which is lethal.

Answers to odd-numbered Predict questions from this chapter appear in appendix E.

Summary

21.1 Functions of the Circulatory System

1. The circulatory system carries blood from the heart to the tissues of the body and returns the blood to the heart.
2. The circulatory system allows for nutrient, waste, and gas exchange with the tissues.
3. The circulatory system transports other substances (hormones, enzymes, etc.) through the body.
4. The circulatory system regulates blood pressure and blood flow to the tissues.

21.2 Structural Features of Blood Vessels

1. Blood flows from the heart through elastic arteries, muscular arteries, and arterioles to the capillaries.
2. Blood returns to the heart from the capillaries through venules, small veins, and large veins.

Structure of Blood Vessels

Except for capillaries and venules, blood vessels have three layers.

1. The inner tunica intima consists of endothelium, a basement membrane, and an internal elastic lamina.
2. The tunica media, the middle layer, contains circular smooth muscle and elastic fibers.
3. The outer tunica adventitia is connective tissue.

Types of Arteries

1. Large elastic arteries are thin-walled with large diameters. The tunica media has many elastic fibers and little smooth muscle.
2. Muscular arteries are thick-walled with small diameters. The tunica media has abundant smooth muscle and some elastic fibers.
3. Arterioles are the smallest arteries. The tunica media consists of smooth muscle cells and a few elastic fibers.

Capillaries

1. The entire circulatory system is lined with simple squamous epithelium called endothelium. Capillaries consist only of endothelium.
2. Capillaries are surrounded by loose connective tissue, the adventitia, that contains pericapillary cells.
3. Three types of capillaries exist.
   - The walls of continuous capillaries have no gaps between the endothelial cells.
   - Fenestrated capillaries have pores, called fenestrae, that extend completely through the cell.
   - Sinusoidal capillaries are large-diameter capillaries with large fenestrae.
4. Materials pass through the capillaries in several ways: between the endothelial cells, through the fenestrae, and through the plasma membrane.
5. Blood flows from arterioles through metarterioles and then through the capillary network. Venules drain the capillary network.
   - Smooth muscle in the arterioles, metarterioles, and precapillary sphincters regulates blood flow into the capillaries.
   - Blood can pass rapidly through the thoroughfare channel.
6. Arteriovenous anastomoses allow blood to flow from arteries to veins without passing through the capillaries. They function in temperature regulation.

Types of Veins

1. Venules are composed of endothelium surrounded by a few smooth muscle cells.
2. Small veins are venules covered with a layer of smooth muscle.
3. Medium-sized veins and large veins contain less smooth muscle and fewer elastic fibers than arteries of the same size.
4. Valves prevent the backflow of blood in the veins.
5. Vasa vasorum are blood vessels that supply the tunica adventitia and tunica media.

Neural Innervation of Blood Vessels

Sympathetic nerve fibers supply the smooth muscle of the tunica media.

Aging of the Arteries

Arteriosclerosis results from a loss of elasticity in the aorta, large arteries, and coronary arteries.

21.3 Pulmonary Circulation

The pulmonary circulation moves blood to and from the lungs. The pulmonary trunk arises from the right ventricle and divides to form the pulmonary arteries, which project to the lungs. From the lungs, the pulmonary veins return to the left atrium.

21.4 Systemic Circulation: Arteries

Arteries carry blood from the left ventricle of the heart to all parts of the body.

Aorta

The aorta leaves the left ventricle to form the ascending aorta, aortic arch, and descending aorta (consisting of the thoracic and abdominal aortae).

Coronary Arteries

Coronary arteries supply the heart.

Arteries of the Head and Neck

1. The brachiocephalic, left common carotid, and left subclavian arteries branch from the aortic arch to supply the head and the upper limbs. The brachiocephalic artery divides to form the right common carotid and the right subclavian arteries. The vertebral arteries branch from the subclavian arteries.
2. The common carotid arteries and the vertebral arteries supply the head.
   - The common carotid arteries divide to form the external carotids, which supply the face and mouth, and the internal carotids, which supply the brain.
   - The vertebral arteries join within the cranial cavity to form the basilar artery, which supplies the brain.

Arteries of the Upper Limb

1. The subclavian artery continues (without branching) as the axillary artery and then as the brachial artery. The brachial artery divides into the radial and ulnar arteries.
2. The radial artery supplies the deep palmar arch, and the ulnar artery supplies the superficial palmar arch. Both arches give rise to the digital arteries.

Thoracic Aorta and Its Branches

The thoracic aorta has visceral branches that supply the thoracic organs and parietal branches that supply the thoracic wall.

Abdominal Aorta and Its Branches

1. The abdominal aorta has visceral branches that supply the abdominal organs and parietal branches that supply the abdominal wall.
2. The visceral branches are paired and unpaired. The paired arteries supply the kidneys, adrenal glands, and gonads. The unpaired arteries supply the stomach, spleen, and liver (celiac trunk); the small intestine and upper part of the large intestine (superior mesenteric); and the lower part of the large intestine (inferior mesenteric).

Arteries of the Pelvis

1. The common iliac arteries arise from the abdominal aorta, and the internal iliac arteries branch from the common iliac arteries.
2. The visceral branches of the internal iliac arteries supply the pelvic organs, and the parietal branches supply the pelvic wall and floor and the external genitalia.

Arteries of the Lower Limb

1. The external iliac arteries branch from the common iliac arteries.
2. The external iliac artery continues (without branching) as the femoral artery and then as the popliteal artery. The popliteal artery divides to form the anterior and posterior tibial arteries.
3. The posterior tibial artery gives rise to the fibular (peroneal) and plantar arteries. The plantar arteries form the plantar arch from which the digital arteries arise.

21.5 Systemic Circulation: Veins

1. The three major veins returning blood to the heart are the superior vena cava (head, neck, thorax, and upper limbs), the inferior vena cava (abdomen, pelvis, and lower limbs), and the coronary sinus (heart).
2. Veins are of three types: superficial, deep, and sinuses.

Veins Draining the Heart

Coronary veins enter the coronary sinus or the right atrium.

Veins of the Head and Neck

1. The internal jugular veins drain the venous sinuses of the anterior head and neck.
2. The external jugular veins and the vertebral veins drain the posterior head and neck.

Veins of the Upper Limb

1. The deep veins are the small ulnar and radial veins of the forearm, which join the brachial veins of the arm. The brachial veins drain into the axillary vein.
2. The superficial veins are the basilic, cephalic, and median cubital. The basilic vein becomes the axillary vein, which then becomes the subclavian vein. The cephalic vein drains into the axillary vein.

Veins of the Thorax

The left and right brachiocephalic veins and the azygos veins return blood to the superior vena cava.

Veins of the Abdomen and Pelvis

1. Ascending lumbar veins from the abdomen join the azygos and hemiazygos veins.
2. Vessels from the kidneys, adrenal gland, and gonads directly enter the inferior vena cava.
3. Vessels from the stomach, intestines, spleen, and pancreas connect with the hepatic portal vein. The hepatic portal vein transports blood to the liver for processing. Hepatic veins from the liver join the inferior vena cava.

Veins of the Lower Limb

1. The deep veins are the fibular (peroneal), anterior and posterior tibial, popliteal, femoral, and external iliac.
2. The superficial veins are the great and small saphenous veins.

21.6 Dynamics of Blood Circulation

The interrelationships among pressure, flow, resistance, and the control mechanisms that regulate blood pressure and blood flow play a critical role in the function of the circulatory system.

Laminar and Turbulent Flow in Vessels

Blood flow through vessels is normally streamlined, or laminar. Turbulent flow is disruption of laminar flow.

Blood Pressure

1. Blood pressure is a measure of the force exerted by blood against the blood vessel wall. Blood moves through vessels because of blood pressure.
2. Blood pressure can be measured by listening for Korotkoff sounds produced by turbulent flow in arteries as pressure is released from a blood pressure cuff.

Blood Flow and Poiseuille's Law

1. Blood flow is the amount of blood that moves through a vessel in a given period. Blood flow is directly proportional to pressure differences and inversely proportional to resistance.
2. Resistance is the sum of all the factors that inhibit blood flow. Resistance increases when viscosity increases and when blood vessels become smaller in diameter or increase in length.
3. Viscosity is the resistance of a liquid to flow. Most of the viscosity of blood results from red blood cells. The viscosity of blood increases when the hematocrit increases.

Critical Closing Pressure and Laplace's Law

1. As pressure in a vessel decreases, the force holding it open decreases, and the vessel tends to collapse. The critical closing pressure is the pressure at which a blood vessel closes.
2. Laplace's law states that the force acting on the wall of a blood vessel is proportional to the diameter of the vessel times blood pressure.

Vascular Compliance

1. Vascular compliance is a measure of the change in volume of blood vessels produced by a change in pressure. The venous system has a large compliance and acts as a blood reservoir.
2. The greatest volume of blood is contained in the veins. The smallest volume is in the arterioles.

21.7 Physiology of the Systemic Circulation

Cross-Sectional Area of Blood Vessels

As the diameter of vessels decreases, their total cross-sectional area increases, and the velocity of blood flow through them decreases.

Pressure and Resistance

Blood pressure averages 100 mm Hg in the aorta and drops to 0 mm Hg in the right atrium. The greatest drop occurs in the arterioles, which regulate blood flow through tissues.

Pulse and Pulse Pressure

1. Pulse pressure is the difference between systolic and diastolic pressures. Pulse pressure increases when stroke volume increases or vascular compliance decreases.
2. Pulse pressure waves travel through the vascular system faster than the blood flows.
3. Pulse pressure can be used to take the pulse, which can serve as an indicator of heart rate and rhythm.

Capillary Exchange and Regulation of Interstitial Fluid Volume

1. Blood pressure, capillary permeability, and osmosis affect the movement of fluid from the capillaries.
2. A net movement of fluid occurs from the blood into the tissues. The fluid gained by the tissues is removed by the lymphatic system.

Functional Characteristics of Veins

Venous return to the heart increases because of an increase in blood volume, venous tone, and arteriole dilation.

Blood Pressure and the Effect of Gravity

In a standing person, hydrostatic pressure caused by gravity increases blood pressure below the heart and decreases pressure above the heart.

21.8 Control of Blood Flow in Tissues

Blood flow through tissues is highly controlled and matched closely to the metabolic needs of tissues.

Local Control of Blood Flow in Tissues

1. Blood flow through a tissue is usually proportional to the tissue's metabolic needs. Exceptions are tissues that perform functions that require additional blood.
2. Control of blood flow by the metarterioles and precapillary sphincters can be regulated by vasodilator substances or by lack of O_2 and nutrients.
3. Only large changes in blood pressure have an effect on blood flow through tissues.
4. If the metabolic activity of a tissue increases, the number and the diameter of capillaries in the tissue increase over time.

Autoregulation of Blood Flow

1. Autoregulation refers to changes in blood flow in response to changes in O_2, nutrients, and metabolic by-products, which alter vasoconstriction and contraction of precapillary sphinters to adjust blood flow through tissues.
2. Long-term regulation of blood flow results in alteration in capillary diameter and number of capillaries in a tissue.

Nervous and Hormonal Control of Blood Flow in Tissues

1. The sympathetic nervous system (vasomotor center in the medulla) controls blood vessel diameter. Other brain areas can excite or inhibit the vasomotor center.
2. Vasomotor tone is a state of partial contraction of blood vessels.
3. The nervous system is responsible for routing the flow of blood and maintaining blood pressure.
4. Sympathetic action potentials stimulate epinephrine and norepinephrine release from the adrenal medulla, and these hormones cause vasoconstriction in most blood vessels.

21.9 Regulation of Mean Arterial Pressure

Mean arterial pressure (MAP) is proportional to cardiac output times peripheral resistance.

Short-Term Regulation of Blood Pressure

1. Baroreceptors are sensory receptors sensitive to stretch.
   - Baroreceptors are located in the carotid sinuses and the aortic arch.
   - The baroreceptor reflex changes peripheral resistance, heart rate, and stroke volume in response to changes in blood pressure.
2. Chemoreceptors are sensory receptors sensitive to O_2, CO_2, and pH levels in the blood.
3. Epinephrine and norepinephrine are released from the adrenal medulla as a result of sympathetic stimulation. They increase heart rate, stroke volume, and vasoconstriction.
4. The CNS ischemic response, which results from high CO_2 or low pH levels in the medulla, increases peripheral resistance.

Long-Term Regulation of Blood Pressure

1. In the renin-angiotensin-aldosterone mechanism, renin is released by the kidneys in response to low blood pressure. Renin promotes the production of angiotensin II, which causes vasoconstriction and an increase in aldosterone secretion.
2. The antidiuretic hormone (vasopressin) mechanism causes ADH release from the posterior pituitary in response to a substantial decrease in blood pressure. ADH acts directly on blood vessels to cause vasoconstriction.
3. The atrial natriuretic mechanism causes atrial natriuretic hormone release from the cardiac muscle cells when atrial blood pressure increases. It stimulates an increase in urine production, causing a decrease in blood volume and blood pressure.
4. The fluid shift mechanism causes fluid shift, which is the movement of fluid between the interstitial spaces and capillaries in response to changes in blood pressure to maintain blood volume.
5. The stress-relaxation response is an adjustment of the smooth muscles of blood vessels in response to a change in blood volume.

REVIEW AND COMPREHENSION

1. Given these blood vessels:
   (1) arteriole (3) elastic artery (5) vein
   (2) capillary (4) muscular artery (6) venule

   Choose the arrangement that lists the blood vessels in the order a red blood cell passes through them as it leaves the heart, travels to a tissue, and returns to the heart.
   a. 3,4,2,1,5,6 c. 4,3,1,2,5,6 e. 4,2,3,5,1,6
   b. 3,4,1,2,6,5 d. 4,3,2,1,6,5

2. Given these structures:
   (1) metarteriole (3) thoroughfare channel
   (2) precapillary sphincter

   Choose the arrangement that lists the structures in the order a red blood cell encounters them as it passes through a tissue.
   a. 1,3,2 b. 2,1,3 c. 2,3,1 d. 3,1,2 e. 3,2,1

3. In which of these blood vessels are elastic fibers present in the largest amounts?
   a. large arteries c. arterioles e. large veins
   b. medium arteries d. venules

4. Comparing and contrasting arteries and veins, veins have
   a. thicker walls.
   b. a greater amount of smooth muscle than arteries.
   c. a tunica media, but arteries do not.
   d. valves, but arteries do not.
   e. All of these are correct.

5. The structures that supply the walls of blood vessels with blood are
   a. venous shunts. d. vasa vasorum.
   b. tunic channels. e. coronary arteries.
   c. arteriovenous anastomoses.

6. Given these arteries:
   (1) basilar (3) internal carotid
   (2) common carotid (4) vertebral

   Which of these arteries have *direct* connections with the cerebral arterial circle (circle of Willis)?
   a. 1,2 b. 2,4 c. 1,3 d. 3,4 e. 2,3

7. Given these blood vessels:
   (1) axillary artery (4) radial artery
   (2) brachial artery (5) subclavian artery
   (3) brachiocephalic artery

   Choose the arrangement that lists the vessels in order, from the aorta to the right hand.
   a. 2,5,4,1 b. 5,2,1,4 c. 5,3,1,4,2 d. 3,5,1,2,4 e. 4,5,1,2,3

8. A branch of the aorta that supplies the liver, stomach, and spleen is the
   a. celiac trunk.
   b. common iliac.
   c. inferior mesenteric.
   d. superior mesenteric.
   e. renal.

9. Given these arteries:
   (1) common iliac (3) femoral
   (2) external iliac (4) popliteal

   Choose the arrangement that lists the arteries in order, from the aorta to the knee.
   a. 1,2,3,4 b. 1,2,4,3 c. 2,1,3,4 d. 2,1,4,3 e. 3,1,2,4

10. Given these veins:
    (1) brachiocephalic (3) superior vena cava
    (2) internal jugular (4) venous sinus

    Choose the arrangement that lists the veins in order, from the brain to the heart.
    a. 1,2,4,3 b. 2,4,1,3 c. 2,4,3,1 d. 4,2,1,3 e. 4,2,3,1

11. Blood returning from the arm to the subclavian vein passes through which of these veins?
    a. cephalic
    b. basilic
    c. brachial
    d. Both a and b are correct.
    e. All of these are correct.

12. Given these blood vessels:
    (1) inferior mesenteric vein (3) hepatic portal vein
    (2) superior mesenteric vein (4) hepatic vein

    Choose the arrangement that lists the vessels in order, from the small intestine to the inferior vena cava.
    a. 1,3,4 b. 1,4,3 c. 2,3,4 d. 2,4,3 e. 3,1,4

13. Given these veins:
    (1) small saphenous (3) fibular (peroneal)
    (2) great saphenous (4) posterior tibial

    Which are superficial veins?
    a. 1,2 b. 1,3 c. 2,3 d. 2,4 e. 3,4

14. Vascular compliance is
    a. greater in arteries than in veins.
    b. the increase in vessel volume divided by the increase in vessel pressure.
    c. the pressure at which blood vessels collapse.
    d. proportional to the diameter of the blood vessel times pressure.
    e. All of these are correct.

15. The resistance to blood flow is greatest in the
    a. aorta.
    b. arterioles.
    c. capillaries.
    d. venules.
    e. veins.

16. Veins
    a. increase their volume because of their large compliance.
    b. increase venous return to the heart when they vasodilate.
    c. vasodilate because of increased sympathetic stimulation.
    d. All of these are correct.

17. Local direct control of blood flow through a tissue
    a. maintains an adequate rate of flow despite large changes in arterial blood pressure.
    b. results from relaxation and contraction of precapillary sphincters.
    c. occurs in response to a buildup in CO_2 in the tissues.
    d. occurs in response to a decrease in oxygen in the tissues.
    e. All of these are correct.

18. An increase in mean arterial pressure can result from
    a. an increase in peripheral resistance.
    b. an increase in heart rate.
    c. an increase in stroke volume.
    d. All of these are correct.

19. When blood O_2 levels markedly decrease, the chemoreceptor reflex causes
    a. peripheral resistance to decrease.
    b. mean arterial blood pressure to increase.
    c. vasomotor tone to decrease.
    d. vasodilation.
    e. All of these are correct.

20. When blood pressure is suddenly decreased a small amount (10 mm Hg), which of these mechanisms are activated to restore blood pressure to normal levels?
    a. chemoreceptor reflexes
    b. baroreceptor reflexes
    c. CNS ischemic responses
    d. All of these are correct.

21. A sudden release of epinephrine from the adrenal medulla
    a. increases heart rate.
    b. increases stroke volume.
    c. causes vasoconstriction in visceral blood vessels.
    d. All of these are correct.

22. In response to a decrease in blood pressure
    a. ADH secretion increases.
    b. the kidneys decrease urine production.
    c. blood volume increases.
    d. All of these are correct.

23. In response to a decrease in blood pressure
    a. more fluid than normal enters the tissues (fluid shift mechanism).
    b. smooth muscles in blood vessels relax (stress-relaxation response).
    c. the kidneys retain more salts and water than normal.
    d. All of these are correct.

24. A patient is found to have severe arteriosclerosis of the renal arteries, which has reduced renal blood pressure. Which of these is consistent with that condition?
    a. hypotension
    b. hypertension
    c. decreased vasomotor tone
    d. exaggerated sympathetic stimulation of the heart
    e. Both a and c are correct.

25. During exercise, the blood flow through skeletal muscle may increase up to 20-fold. However, the cardiac output does not increase that much. This occurs because of
    a. vasoconstriction in the viscera.
    b. vasoconstriction in the skin (at least temporarily).
    c. vasodilation of skeletal muscle blood vessels.
    d. Both a and b are correct.
    e. All of these are correct.

Answers appear in appendix F.

CRITICAL THINKING

1. For each of the following destinations, name all the arteries that a red blood cell would encounter if it started its journey in the left ventricle.
   a. posterior interventricular groove of the heart
   b. anterior neck to the brain (give two ways)
   c. posterior neck to the brain (give two ways)
   d. external skull
   e. tip of the fingers of the left hand (what other blood vessel would be encountered if the trip were through the right upper limb?)
   f. anterior compartment of the leg
   g. liver
   h. small intestine
   i. urinary bladder
2. For each of the following starting places, name all the veins that a red blood cell would encounter on its way back to the right atrium.
   a. anterior interventricular groove of the heart (give two ways)
   b. venous sinus near the brain
   c. external posterior of skull
   d. hand (return deep and superficial)
   e. foot (return deep and superficial)
   f. stomach
   g. kidney
   h. left inferior wall of the thorax
3. In a study of heart valve functions, it is necessary to inject a dye into the right atrium of the heart by inserting a catheter into a blood vessel and moving the catheter into the right atrium. What route would you suggest? If you wanted to do this procedure into the left atrium, what would you do differently?
4. All the blood that passes through the aorta, except the blood that flows into the coronary vessels, returns to the heart through the venae cavae. (*Hint:* The diameter of the aorta is 26 mm, and the diameter of a vena cava is 32 mm.) Explain why the resistance to blood flow in the aorta is greater than the resistance to blood flow in the venae cavae. Because the resistances are different, explain why blood flow can be the same.
5. As blood vessels increase in diameter, the amount of smooth muscle decreases and the amount of connective tissue increases. Explain why. (*Hint:* Remember Laplace's law.)
6. A very short nursing student is asked to measure the blood pressure of a very tall person. She decides to measure the blood pressure at the level of the tall person's foot while he is standing. What artery does she use? After taking the blood pressure, she decides that the tall person is suffering from hypertension because the systolic pressure is 200 mm Hg. Is her diagnosis correct? Why or why not?
7. David was suffering from severe cirrhosis of the liver and hepatitis. Over a period of time, he developed severe edema. Explain how decreased liver function can result in edema.
8. During hyperventilation, CO_2 is "blown off," and CO_2 levels in the blood decrease. What effect does this decrease have on blood pressure? Explain. What symptoms do you expect to see as a result?
9. Epinephrine causes vasodilation of blood vessels in cardiac muscle but vasoconstriction of blood vessels in the skin. Explain why this is a beneficial arrangement.
10. While Jack and Eliza were backpacking on a trail in Yellowstone Park, they encountered a grizzly bear cub that seemed amazingly tame. However, while Jack tried to feed the cub, its mother appeared and attacked him. Eliza escaped by climbing a tree, but Jack received several deep lacerations (cuts) and lost a lot of blood over the next several hours. Eliza helped him reach medical aid, and he survived. Which of the following mechanisms was (were) activated to help keep Jack alive? Explain your choice.
    (1) baroreceptor mechanism
    (2) CNS ischemic response
    (3) renin-angiotensin-aldosterone mechanism
    (4) fluid shift mechanism
    (5) antidiuretic hormone mechanism
    (6) adrenal medullary response
    a. 1,2,3,4,5,6 b. 1,3,4,5,6 c. 1,6 d. 1,4,6 e. 1
11. Mr. Wilson, age 85, lives in a care facility, where he is not very mobile and is often lethargic. One day an aide noticed that he was sitting in his usual chair but appeared to be unconscious. She took his pulse, which was 140 beats/minute and then took his blood pressure, which was 190/130. Which of the following conditions is (are) consistent with these observations?
    a. stroke
    b. activation of the CNS ischemic response
    c. heart attack
    d. shock
    e. Both a and b are correct.

Answers to odd-numbered questions appear in appendix G.