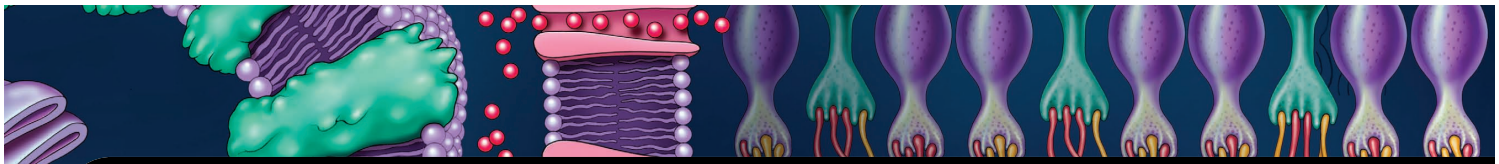


CHAPTER

13

Blood, Heart, and Circulation

Refresh Your Memory

Before you begin this chapter, you may want to review these concepts from previous chapters:

- Action Potentials 174
- Functions of the Autonomic Nervous System 251
- Mechanisms of Contraction 363
- Cardiac and Smooth Muscle 391

CHAPTER OUTLINE

Clinical Investigation

Jessica went to her physician complaining of fatigue and mentioned that she had been experiencing heavier menstruations over the past several months. He mentioned that she had mitral valve prolapse, but didn't think that was the cause of her fatigue and advised her take more iron in her diet while they waited for the blood test results. However, a subsequent ECG revealed that she had atrial fibrillation, which he said might also explain her fatigue. The physician prescribed a drug called rivaroxaban, and told Jessica that she should perhaps exercise more moderately and that she should definitely stop smoking.

Some of the new terms and concepts you will encounter include:

- Anemia, blood clotting factors, heart valves and heart sounds
- Electrocardiogram and heart arrhythmias
- Atherosclerosis, thrombosis, and cardiovascular diseases

13.1 FUNCTIONS AND COMPONENTS OF THE CIRCULATORY SYSTEM

Blood serves numerous functions, including the transport of respiratory gases, nutritive molecules, metabolic wastes, and hormones. Blood travels through the body in a system of vessels leading from and returning to the heart.

LEARNING OUTCOMES

After studying this section, you should be able to:

1. Identify the functions and components of the circulatory system.
2. Describe the relationship between interstitial fluid, plasma, and lymph.

A unicellular organism can provide for its own maintenance and continuity by performing the wide variety of functions needed for life. By contrast, the complex human body is composed of specialized cells that depend on one another. Because most are firmly implanted in tissues, their oxygen and nutrients must be brought to them, and their waste products removed. Therefore, a highly effective means of transporting materials within the body is needed.

The blood serves this transportation function. An estimated 60,000 miles of vessels throughout the body of an adult ensure that continued sustenance reaches each of the trillions of living cells. But the blood can also transport disease-causing viruses, bacteria, and their toxins. To guard against this, the circulatory system has protective mechanisms—the white blood cells and the lymphatic system. In order to perform its various functions, the circulatory system works together with the respiratory, urinary, digestive, endocrine, and integumentary systems in maintaining homeostasis.

Functions of the Circulatory System

The functions of the circulatory system can be divided into three broad areas: transportation, regulation, and protection.

1. **Transportation.** All of the substances essential for cellular metabolism are transported by the circulatory system. These substances can be categorized as follows:
   - **a.** *Respiratory.* Red blood cells, or *erythrocytes,* transport oxygen to the cells. In the lungs, oxygen from the inhaled air attaches to hemoglobin molecules within the erythrocytes and is transported to the cells for aerobic respiration. Carbon dioxide produced by cell respiration is carried by the blood to the lungs for elimination in the exhaled air.
   - **b.** *Nutritive.* The digestive system is responsible for the mechanical and chemical breakdown of food so that it can be absorbed through the intestinal wall into the blood and lymphatic vessels. The blood then carries these absorbed products of digestion through the liver to the cells of the body.
   - **c.** *Excretory.* Metabolic wastes (such as urea), excess water and ions, and other molecules not needed by the body are carried by the blood to the kidneys and excreted in the urine.
2. **Regulation.** The circulatory system contributes to both hormonal and temperature regulation.
   - **a.** *Hormonal.* The blood carries hormones from their site of origin to distant target tissues where they perform a variety of regulatory functions.
   - **b.** *Temperature.* Temperature regulation is aided by the diversion of blood from deeper to more superficial cutaneous vessels or vice versa. When the ambient temperature is high, diversion of blood from deep to superficial vessels helps cool the body; when the ambient temperature is low, the diversion of blood from superficial to deeper vessels helps keep the body warm.
3. **Protection.** The circulatory system protects against blood loss from injury and against pathogens, including foreign microbes and toxins introduced into the body.
   - **a.** *Clotting.* The clotting mechanism protects against blood loss when vessels are damaged.
   - **b.** *Immune.* The immune function of the blood is performed by the *leukocytes* (white blood cells) that protect against many disease-causing agents (pathogens).

Major Components of the Circulatory System

The **circulatory system** consists of two subdivisions: the cardiovascular system and the lymphatic system. The **cardiovascular system** consists of the heart and blood vessels, and the **lymphatic system,** which includes lymphatic vessels and lymphoid tissues within the spleen, thymus, tonsils, and lymph nodes.

The **heart** is a four-chambered double pump. Its pumping action creates the pressure head needed to push blood through

the vessels to the lungs and body cells. At rest, the heart of an adult pumps about 5 liters of blood per minute. At this rate, it takes about 1 minute for blood to be circulated to the most distal extremity and back to the heart.

Blood vessels form a tubular network that permits blood to flow from the heart to all the living cells of the body and then back to the heart. *Arteries* carry blood away from the heart, whereas *veins* return blood to the heart. Arteries and veins are continuous with each other through smaller blood vessels.

Arteries branch extensively to form a "tree" of progressively smaller vessels. The smallest of the arteries are called *arterioles.* Blood passes from the arterial to the venous system in microscopic *capillaries,* which are the thinnest and most numerous of the blood vessels. All exchanges of fluid, nutrients, and wastes between the blood and tissues occur across the walls of capillaries. Blood flows through capillaries into microscopic veins called *venules,* which deliver blood into progressively larger veins that eventually return the blood to the heart.

As blood *plasma* (the fluid portion of the blood) passes through capillaries, the hydrostatic pressure of the blood forces some of this fluid out of the capillary walls. Fluid derived from plasma that passes out of capillary walls into the surrounding tissues is called *tissue fluid,* or *interstitial fluid.* Some of this fluid returns directly to capillaries, and some enters into **lymphatic vessels** located in the connective tissues around the blood vessels. Fluid in lymphatic vessels is called *lymph.* This fluid is returned to the venous blood at specific sites. **Lymph nodes,** positioned along the way, cleanse the lymph prior to its return to the venous blood. The lymphatic system is thus considered a part of the circulatory system and is discussed in section 13.8.

CHECKPOINT

1a. State the components of the circulatory system that function in oxygen transport, in the transport of nutrients from the digestive system, and in protection.

1b. Describe the functions of arteries, veins, and capillaries.

2. Define the terms *interstitial fluid* and *lymph.* How do these fluids relate to blood plasma?

13.2 COMPOSITION OF THE BLOOD

Blood consists of formed elements that are suspended and carried in a fluid called plasma. The formed elements—erythrocytes, leukocytes, and platelets—function respectively in oxygen transport, immune defense, and blood clotting.

LEARNING OUTCOMES

After studying this section, you should be able to:

3. Distinguish between the different formed elements of the blood.

4. Describe the regulation of red and white blood cell production.

5. Explain blood typing and blood clotting.

The total blood volume in the average-size adult is about 5 liters, constituting about 8% of the total body weight. Blood leaving the heart is referred to as *arterial blood.* Arterial blood, with the exception of that going to the lungs, is bright red because of a high concentration of oxyhemoglobin (the combination of oxygen and hemoglobin) in the red blood cells. *Venous blood* is blood returning to the heart. Except for the venous blood from the lungs, it contains less oxygen and is therefore a darker red than the oxygen-rich arterial blood.

Blood is composed of a cellular portion, called *formed elements,* and a fluid portion, called *plasma.* When a blood sample is centrifuged, the heavier formed elements are packed into the bottom of the tube, leaving plasma at the top (fig. 13.1). The formed elements constitute approximately 45% of the total blood volume, and the plasma accounts for the remaining 55%. Red blood cells compose most of the formed elements; the percentage of red blood cell volume to total blood volume in a centrifuged blood sample (a measurement called the *hematocrit*) is 36% to 46% in women and 41% to 53% in men (table 13.1).

Plasma

Plasma is a straw-colored liquid consisting of water and dissolved solutes. The major solute of the plasma in terms of its

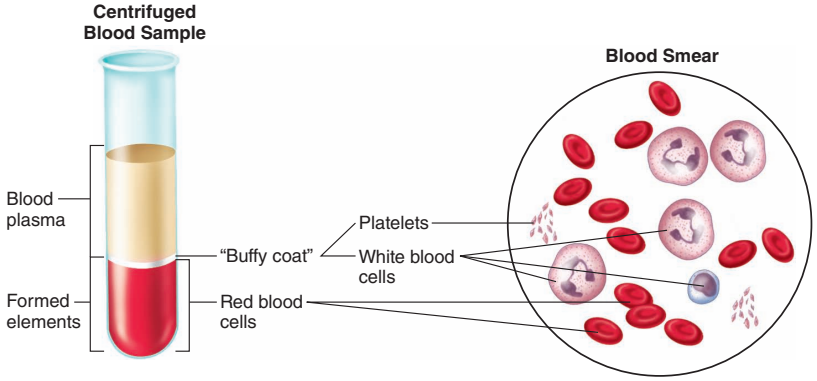


Figure 13.1 The constituents of blood. Blood cells become packed at the bottom of the test tube when whole blood is centrifuged, leaving the fluid plasma at the top of the tube. Red blood cells are the most abundant of the blood cells—white blood cells and platelets form only a thin, light-colored "buffy coat" at the interface between the packed red blood cells and the plasma. AP|R

Table 13.1 | Representative Normal Plasma Values

Measurement	Normal Range
Blood volume	80–85 ml/kg body weight
Blood osmolality	285–295 mOsm
Blood pH	7.38–7.44
Enzymes	
Creatine phosphokinase (CPK)	Female: 10–79 U/L
	Male: 17–148 U/L
Lactic dehydrogenase (LDH)	45–90 U/L
Phosphatase (acid)	Female: 0.01–0.56 Sigma U/ml
	Male: 0.13–0.63 Sigma U/ml
Hematology Values	
Hematocrit	Female: 36%–46%
	Male: 41%–53%
Hemoglobin	Female: 12–16 g/100 ml
	Male: 13.5–17.5 g/100 ml
Red blood cell count	4.50–5.90 million/mm^3
White blood cell count	4,500–11,000/mm^3
Hormones	
Testosterone	Male: 270–1,070 ng/100 ml
	Female: 6–86 ng/100 ml
Adrenocorticotrophic hormone (ACTH)	6–76 pg/ml
Growth hormone	Children: over 10 ng/ml
	Adult male: below 5 ng/ml
Insulin	2–20 µU/ml (fasting)
Ions	
Bicarbonate	24–30 mmol/l
Calcium	9.0–10.5 mg/dl
Chloride	98–106 mEq/L
Potassium	3.5–5.0 mEq/L
Sodium	135–145 mEq/L
Organic Molecules (Other)	
Cholesterol, desirable	under 200 mg/dl
Glucose	75–115 mg/dl (fasting)
Lactic acid	5–15 mg/dl
Protein (total)	5.5–8.0 g/dl
Triglyceride	under 160 mg/dl
Urea nitrogen	10–20 mg/dl
Uric acid	Male 2.5–8.0 mg/dl
	Female 1.5–6.0 mg/dl

Source: Excerpted from material appearing in *The New England Journal of Medicine,* "Case Records of the Massachusetts General Hospital," 302:37–38, 314:39–49, 351:1548–1563. 1980, 1986, 2004.

concentration is Na^+. In addition to Na^+, plasma contains many other ions, as well as organic molecules such as metabolites, hormones, enzymes, antibodies, and other proteins. The concentrations of some of these plasma constituents are shown in table 13.1.

Plasma Proteins

Plasma proteins constitute 7% to 9% of the plasma. The three types of proteins are albumins, globulins, and fibrinogen. **Albumins** account for most (60% to 80%) of the plasma proteins and are the smallest in size. They are produced by the liver and provide the osmotic pressure needed to draw water from the surrounding tissue fluid into the capillaries. This action is needed to maintain blood volume and pressure. **Globulins** are grouped into three subtypes: **alpha globulins, beta globulins,** and **gamma globulins.** The alpha and beta globulins are produced by the liver and function in transporting lipids and fat-soluble vitamins. Gamma globulins are antibodies produced by lymphocytes (one of the formed elements found in blood and lymphoid tissues) and function in immunity. **Fibrinogen,** which accounts for only about 4% of the total plasma proteins, is an important clotting factor produced by the liver. During the process of clot formation (described later in this section), fibrinogen is converted into insoluble threads of *fibrin.* Thus, the fluid from clotted blood, called **serum,** does not contain fibrinogen but is otherwise identical to plasma.

Plasma Volume

A number of regulatory mechanisms in the body maintain homeostasis of the plasma volume. If the body should lose water, the remaining plasma becomes excessively concentrated—its osmolality (chapter 6) increases. This is detected by osmoreceptors in the hypothalamus, resulting in a sensation of thirst and the release of antidiuretic hormone (ADH) from the posterior pituitary (chapter 11, section 11.3). This hormone promotes water retention by the kidneys, which—together with increased intake of fluids—helps compensate for the dehydration and lowered blood volume. This regulatory mechanism, together with others that influence plasma volume, are very important in maintaining blood pressure (chapter 14, section 14.6).

The Formed Elements of Blood

The **formed elements** of blood include two types of blood cells: *erythrocytes,* or *red blood cells,* and *leukocytes,* or *white blood cells.* Erythrocytes are by far the more numerous of the two. A cubic millimeter of blood normally contains 5.1 million to 5.8 million erythrocytes in males and 4.3 million to 5.2 million erythrocytes in females. By contrast, the same volume of blood contains only 5,000 to 9,000 leukocytes.

Erythrocytes

Erythrocytes are flattened, biconcave discs about 7 µm in diameter and 2.2 µm thick. Their unique shape relates to their function of transporting oxygen; it provides an increased

surface area through which gas can diffuse (fig. 13.2). Erythrocytes lack nuclei and mitochondria (they obtain energy through anaerobic metabolism). Partly because of these deficiencies, erythrocytes have a relatively short circulating life span of only about 120 days. Older erythrocytes are removed from the circulation by phagocytic cells in the liver, spleen, and bone marrow.

Each erythrocyte contains approximately 280 million **hemoglobin** molecules, which give blood its red color. Each hemoglobin molecule consists of four protein chains called *globins,* each of which is bound to one *heme,* a red-pigmented molecule that contains iron. The iron group of heme is able to combine with oxygen in the lungs and release oxygen in the tissues.

The heme iron is recycled from senescent (old) red blood cells (see chapter 18, fig. 18.22) by phagocytes in the liver and spleen. This iron travels in the blood to the bone marrow attached to a protein carrier called **transferrin.** This recycled heme iron supplies most of the body's need for iron. The balance of the requirement for iron, though relatively small, must be made up for in the diet. Dietary iron is absorbed mostly in the duodenum (the first part of the small intestine) and transported from the intestine bound to transferrin in the blood. The transferrin with its bound iron is taken out of the blood by cells of the bone marrow and liver by endocytosis, which is triggered by binding of transferrin to its membrane receptors.

Although the bone marrow produces about 200 billion red blood cells each day, and erythrocytes contain about 2 to 3 g of iron, we normally need only a small amount of iron in the diet to compensate for the small amount lost from the body. However, if there is a dietary iron deficiency that reduces the ability of the bone marrow to produce hemoglobin, an *iron-deficiency anemia* may result. Anemia can also result from a deficiency in vitamin B_{12} due to lack of a stomach secretion called *intrinsic factor* (discussed in the next Clinical Application box).

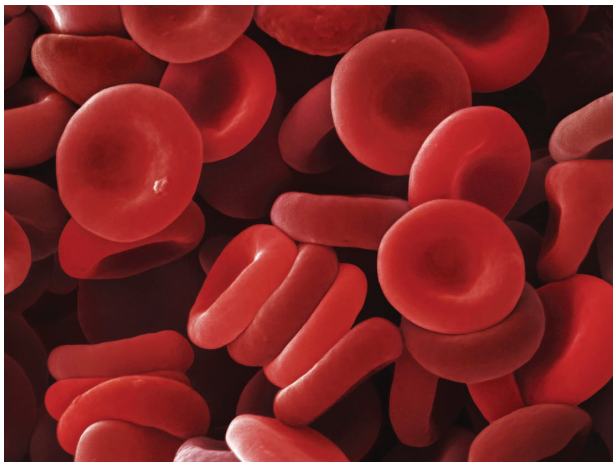


Figure 13.2 A colorized scanning electron micrograph of red blood cells. The shape of the red blood cells is described as a "biconcave disc." In reality, individual red blood cells do not look red when viewed under a microscope. AP|R

CLINICAL APPLICATION

Iron-deficiency anemia, the most common form of *anemia* (low red blood cell and/or hemoglobin concentration), results when there is insufficient iron for the production of normal amounts of hemoglobin. This is most often caused by blood loss due to heavy menstruation, peptic ulcers, or other sources of bleeding in the gastrointestinal tract. It can also be caused by the inability of absorb iron (in *celiac disease,* for example) or from pregnancy due to the requirements of the fetus. **Pernicious anemia** is due to a lack of *intrinsic factor,* a molecule produced by the stomach epithelium and needed for the intestinal absorption of vitamin B_{12} (which is required for hemoglobin production). This can result from autoimmune attack of the gastric epithelium. The most serious anemia is **aplastic anemia,** produced by damage to the bone marrow from a variety of causes, including radiation and chemotherapy for cancer.

Clinical Investigation CLUES

Jessica experienced heavy menstruations and fatigue, and her blood was tested.

- How might heavy menstruation and fatigue be related?
- How might a blood test help to diagnose the cause of Jessica's fatigue?

Leukocytes

Leukocytes differ from erythrocytes in several respects. Leukocytes contain nuclei and mitochondria and can move in an amoeboid fashion. Because of their amoeboid ability, leukocytes can squeeze through pores in capillary walls and move to a site of infection, whereas erythrocytes usually remain confined within blood vessels. The movement of leukocytes through capillary walls is referred to as *diapedesis* or *extravasation.*

White blood cells are almost invisible under the microscope unless they are stained; therefore, they are classified according to their staining properties. Those leukocytes that have granules in their cytoplasm are called **granular leukocytes;** those without clearly visible granules are called **agranular** (or **nongranular**) **leukocytes.**

The stain used to identify white blood cells is usually a mixture of a pink-to-red stain called *eosin* and a blue-to-purple stain (methylene blue), which is called a "basic stain." Granular leukocytes with pink-staining granules are therefore called **eosinophils,** and those with blue-staining granules are called **basophils.** Those with granules that have little affinity for either stain are **neutrophils** (fig. 13.3). Neutrophils are the most abundant type of leukocyte, accounting for 50% to 70% of the leukocytes in the blood. Immature neutrophils have sausage-shaped nuclei and are called *band cells.* As the band cells mature, their

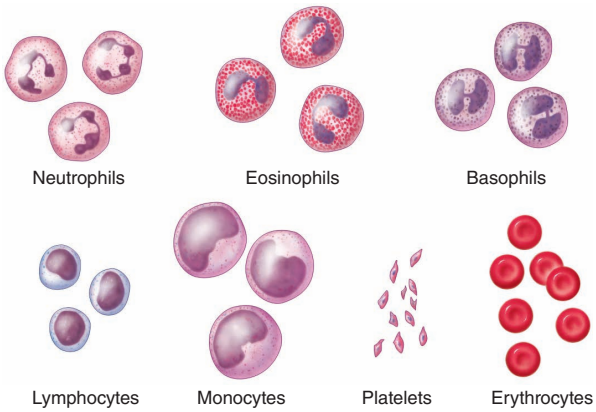


Figure 13.3 The blood cells and platelets. The white blood cells depicted above are granular leukocytes; the lymphocytes and monocytes are nongranular leukocytes. AP|R

nuclei become lobulated, with two to five lobes connected by thin strands. At this stage, the neutrophils are also known as *polymorphonuclear leukocytes (PMNs).*

There are two types of agranular leukocytes: lymphocytes and monocytes. **Lymphocytes** are usually the second most numerous type of leukocyte; they are small cells with round nuclei and little cytoplasm. **Monocytes,** by contrast, are the largest of the leukocytes and generally have kidney- or horseshoe-shaped nuclei. In addition to these two cell types, there are smaller numbers of *plasma cells,* which are derived from lymphocytes. Plasma cells produce and secrete large amounts of antibodies. The immune functions of the different white blood cells are described in more detail in chapter 15.

CLINICAL APPLICATION

Whereas **anemia** refers to an abnormally low red blood cell count (as previously discussed), **polycythemia** is an abnormally high red blood cell count. This can have many causes, including the low oxygen of life at high altitudes (discussed in chapter 16). **Leukopenia** is an abnormally low white blood cell count, which may be produced by radiation for cancer, among other causes. **Leukocytosis** is the opposite—an abnormally high white blood cell count, which may be caused by cytokines released from an inflammation during an infection. **Leukemia** is cancer of the bone marrow that causes a high number of abnormal and immature white blood cells to appear in the blood.

Platelets

Platelets, or **thrombocytes,** are the smallest of the formed elements and are actually fragments of large cells called *megakaryocytes,* which are found in bone marrow. (This is why the term *formed elements* is used instead of *blood cells* to describe erythrocytes, leukocytes, and platelets.) The fragments that enter the circulation as platelets lack nuclei but, like leukocytes, are capable of amoeboid movement. The platelet count per cubic millimeter of blood ranges from 130,000 to 400,000, but this count can vary greatly under different physiological conditions. Platelets survive for about five to nine days before being destroyed by the spleen and liver.

Platelets play an important role in blood clotting. They constitute most of the mass of the clot, and phospholipids in their cell membranes activate the clotting factors in plasma that result in threads of fibrin, which reinforce the platelet plug. Platelets that attach together in a blood clot release *serotonin,* a chemical that stimulates constriction of blood vessels, thus reducing the flow of blood to the injured area. Platelets also secrete growth factors (autocrine regulators—chapter 11, section 11.7), which are important in maintaining the integrity of blood vessels. These regulators also may be involved in the development of atherosclerosis, as described in section 13.7.

The formed elements of the blood are illustrated in figure 13.3, and their characteristics are summarized in table 13.2.

Hematopoiesis

Blood cells are constantly formed through a process called **hematopoiesis** (also called **hemopoiesis**). The **hematopoietic stem cells**—those that give rise to blood cells—originate in the yolk sac of the human embryo and then migrate in sequence to regions around the aorta, to the placenta, and then to the liver of a fetus. The liver is the major hematopoietic organ of the fetus, but then the stem cells migrate to the bone marrow and the liver ceases to be a source of blood cell production shortly after birth. Scientists estimate that the hematopoietic tissue of the bone marrow produces about 500 billion cells each day. The hematopoietic stem cells form a population of relatively undifferentiated, multipotent adult stem cells (chapter 20, section 20.6) that give rise to all of the specialized blood cells. The hematopoietic stem cells are self-renewing, duplicating themselves by mitosis so that the parent stem cell population will not become depleted as individual stem cells differentiate into the mature blood cells. Hematopoietic stem cells are rare, but they proliferate in response to the proinflammatory cytokines released during infection (chapter 15, section 15.3) and in response to the depletion of leukocytes during infection. Hematopoietic stem cells are the only cells capable of restoring complete hematopoietic ability (producing all blood cell lines) upon transplantation into the depleted bone marrow of a recipient.

The term **erythropoiesis** refers to the formation of erythrocytes, and **leukopoiesis** to the formation of leukocytes. These processes occur in two classes of tissues after birth, myeloid and lymphoid. **Myeloid tissue** is the red bone marrow of the long bones, ribs, sternum, pelvis, bodies of the vertebrae, and portions of the skull. **Lymphoid tissue** includes the lymph nodes, tonsils, spleen, and thymus. The bone marrow produces all of the different types of blood cells; the lymphoid tissue produces lymphocytes derived from cells that originated in the bone marrow.

Table 13.2 | Formed Elements of the Blood

Component	Description	Number Present	Function
Erythrocyte (red blood cell)	Biconcave disc without nucleus; contains hemoglobin; survives 100 to 120 days	4,000,000 to 6,000,000 / mm^3	Transports oxygen and carbon dioxide
Leukocytes (white blood cells)		5,000 to 10,000 / mm^3	Aid in defense against infections by microorganisms
Granulocytes	About twice the size of red blood cells; cytoplasmic granules present; survive 12 hours to 3 days		
1. Neutrophil	Nucleus with 2 to 5 lobes; cytoplasmic granules stain slightly pink	54% to 62% of white cells present	Phagocytic
2. Eosinophil	Nucleus bilobed; cytoplasmic granules stain red in eosin stain	1% to 3% of white cells present	Helps to detoxify foreign substances; secretes enzymes that dissolve clots; fights parasitic infections
3. Basophil	Nucleus lobed; cytoplasmic granules stain blue in hematoxylin stain	Less than 1% of white cells present	Releases anticoagulant heparin
Agranulocytes	Cytoplasmic granules not visible; survive 100 to 300 days (some much longer)		
1. Monocyte	2 to 3 times larger than red blood cell; nuclear shape varies from round to lobed	3% to 9% of white cells present	Phagocytic
2. Lymphocyte	Only slightly larger than red blood cell; nucleus nearly fits cell	25% to 33% of white cells present	Provides specific immune response (including antibodies)
Platelet (thrombocyte)	Cytoplasmic fragment; survives 5 to 9 days	130,000 to 400,000 / mm^3	Enables clotting; releases serotonin, which causes vasoconstriction

As the cells become differentiated during erythropoiesis and leukopoiesis, they develop membrane receptors for chemical signals that cause further development along particular lines. The earliest cells that can be distinguished under a microscope are the *erythroblasts* (which become erythrocytes), *myeloblasts* (which become granular leukocytes), *lymphoblasts* (which form lymphocytes), and *monoblasts* (which form monocytes).

Erythropoiesis is an extremely active process. It is estimated that about 2.5 million erythrocytes are produced every second in order to replace those that are continuously destroyed by the spleen and liver. The life span of an erythrocyte is approximately 120 days. Agranular leukocytes remain functional for 100 to 300 days under normal conditions. Granular leukocytes, by contrast, have an extremely short life span of 12 hours to 3 days.

The production of different subtypes of leukocytes is stimulated by chemicals called **cytokines.** These are autocrine regulators secreted by various cells of the immune system. The production of red blood cells is stimulated by the hormone **erythropoietin,** which is secreted by the kidneys. The gene for erythropoietin has been commercially cloned so that this hormone is now available for treatment of anemia, including the anemia that results from kidney disease in patients undergoing dialysis. Injections with recombinant erythropoietin significantly improve aerobic physical performance, probably because of increased hemoglobin allowing the blood to carry an increased amount of oxygen. The World Anti-Doping Code bans the use of recombinant erythropoietin for this reason, and urine from athletes is tested for erythropoietin by World Anti-Doping Agency (WADA) laboratories.

Scientists have identified a specific cytokine that stimulates proliferation of megakaryocytes and their maturation into platelets. By analogy with erythropoietin, they named this regulatory molecule **thrombopoietin.** The gene that codes for thrombopoietin

CLINICAL APPLICATION

Thrombocytosis is an abnormally elevated platelet count. This occurs when conditions such as acute blood loss, inflammation, cancer, and others stimulate the liver to produce an excess of thrombopoietin. However, the production of thrombopoietin is normally adjusted to maintain homeostasis of the platelet count. Because both megakaryocytes in the bone marrow and circulating platelets have receptors that bind to thrombopoietin, a decrease in platelets makes more thrombopoietin available to stimulate the megakaryocytes, raising the platelet count. Conversely, an increase in the number of platelets results in less thrombopoietin that is free to enter the bone marrow and stimulate the megakaryocytes, reducing the platelet count to normal.

also has been cloned, so that recombinant thrombopoietin is now available for medical research and applications. In clinical trials, thrombopoietin has been used to treat the *thrombocytopenia* (low platelet count) that occurs as a result of bone marrow depletion in patients undergoing chemotherapy for cancer.

Regulation of Leukopoiesis

A variety of cytokines stimulate different stages of leukocyte development. The cytokines known as *multipotent growth factor-1, interleukin-1,* and *interleukin-3* have general effects, stimulating the development of different types of white blood cells. *Granulocyte colony-stimulating factor (G-CSF)* acts in a highly specific manner to stimulate the development of neutrophils, whereas *granulocyte-monocyte colony-stimulating factor (GM-CSF)* stimulates the development of monocytes and eosinophils. The genes for the cytokines G-CSF and GM-CSF have been cloned, making these cytokines available for medical applications.

CLINICAL APPLICATION

Hematopoietic stem cell transplants help to restore bone marrow function when the bone marrow stem cell population has been depleted because of chemotherapy or radiation therapy for cancer, or from other causes. These stem cells can be obtained from aspiration of the marrow from the iliac crest, but are now more commonly obtained from peripheral blood after the person has been injected with G-CSF and GM-CSF, which stimulate the marrow to release more stem cells. *Autologous transplants* are obtained from the same patient (before treatments that deplete the bone marrow), whereas *allogeneic transplants* are obtained from a different person, usually a sibling or someone else who is genetically closely matched.

Regulation of Erythropoiesis

The primary regulator of erythropoiesis is *erythropoietin,* produced by the kidneys in response to tissue hypoxia when the blood oxygen levels are decreased. One of the possible causes of decreased blood oxygen levels is a decreased red blood cell count. Because of erythropoietin stimulation, the daily production of new red blood cells compensates for the daily destruction of old red blood cells, preventing a decrease in the blood oxygen content. An increased secretion of erythropoietin and production of new red blood cells occurs when a person is at a high altitude or has lung disease, which are conditions that reduce the oxygen content of the blood.

Erythropoietin acts by binding to membrane receptors on cells that will become erythroblasts (fig. 13.4). The erythropoietin-stimulated cells undergo cell division and differentiation, leading to the production of erythroblasts. These are transformed into *normoblasts,* which lose their nuclei to become *reticulocytes.* The reticulocytes then change into fully mature erythrocytes. This process takes 3 days; the reticulocyte

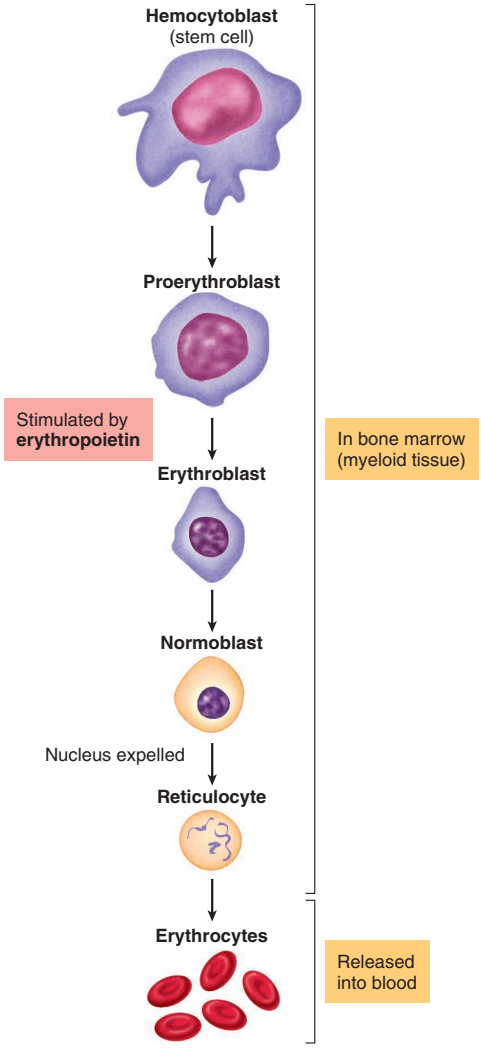


Figure 13.4 The stages of erythropoiesis. The proliferation and differentiation of cells that will become mature erythrocytes (red blood cells) occurs in the bone marrow and is stimulated by the hormone erythropoietin, secreted by the kidneys. AP|R

normally stays in the bone marrow for the first 2 days and then circulates in the blood on the third day. At the end of the erythrocyte life span of 120 days, the old red blood cells are removed by the liver and by macrophages (phagocytic cells) of the spleen and bone marrow. Most of the iron contained in the hemoglobin molecules of the destroyed red blood cells is recycled back to the myeloid tissue to be used in the production of hemoglobin for new red blood cells (see chapter 18, fig. 18.22). The production of red blood cells and synthesis of hemoglobin depends on the supply of iron, along with that of vitamin B_{12} and folic acid.

Iron in food is absorbed in the duodenum (first region of the small intestine) and passes into *enterocytes* (intestinal epithelial cells), where it can be either stored or secreted into the plasma through **ferroportin** membrane channels. Similarly, the iron derived from the heme in old red blood cells that were destroyed by macrophages can be stored in the macrophages or released into the blood through ferroportin channels. Iron travels in the blood is bound to a plasma protein called *transferrin,* where it may be used by the bone marrow in erythropoiesis or stored, primarily in the liver. Iron is eliminated from the body only by the shedding of intestinal epithelial cells and through menstruation. Thus, the intestinal absorption of iron must be highly regulated so that only the amount needed to maintain iron homeostasis is absorbed.

The major regulator of iron homeostasis is **hepcidin,** a polypeptide hormone secreted by the liver. Hepcidin acts on the enterocytes of the small intestine and the macrophages where iron is stored to cause the ferroportin channels to be removed from the plasma membrane and destroyed. Hepcidin thereby inhibits the intestinal absorption of iron and the release of iron from cellular storage, lowering the plasma iron concentration. This completes a negative feedback loop in which the liver's production of hepcidin is decreased by iron deficiency and most anemias, and increased by excessive iron intake.

Because the dietary requirements for iron are quite small, iron-deficiency anemia in adults is usually due not to a dietary deficiency but rather to blood loss, which reduces the amount of iron that can be recycled. The normal dietary requirement for men is about 10 mg/day, whereas women with average menstrual blood loss need about 15 mg/day and pregnant women require about 30 mg/day.

Red Blood Cell Antigens and Blood Typing

There are certain molecules on the surfaces of all cells in the body that can be recognized as foreign by the immune system of another individual. These molecules are known as *antigens.* As part of the immune response, particular lymphocytes secrete a class of proteins called *antibodies* that bond in a specific fashion with antigens. The specificity of antibodies for antigens is analogous to the specificity of enzymes for their substrates, and of receptor proteins for neurotransmitters and hormones. A complete description of antibodies and antigens is provided in chapter 15.

ABO System

The distinguishing antigens on other cells are far more varied than the antigens on red blood cells. Red blood cell antigens, however, are of extreme clinical importance because their types must be matched between donors and recipients for blood transfusions. There are several groups of red blood cell antigens, but the major group is known as the **ABO system.** In terms of the antigens present on the red blood cell surface, a person may be *type A* (with only A antigens), *type B* (with only B antigens), *type AB* (with both A and B antigens), or *type O* (with neither A nor B antigens). Each person's blood type—A, B, or O—denotes the antigens present on the red blood cell surface, which are the products of the genes (located on chromosome number 9) that code for these antigens.

Each person inherits two genes (one from each parent) that control the production of the ABO antigens. The genes for A or B antigens are dominant to the gene for O. The O gene is recessive, simply because it doesn't code for either the A or the B red blood cell antigens. The genes for A and B are often shown as I^A and I^B, and the recessive gene for O is shown as the lower-case i. A person who is type A, therefore, may have inherited the A gene from each parent (may have the genotype I^AI^A), or the A gene from one parent and the O gene from the other parent (and thus have the genotype I^Ai). Likewise, a person who is type B may have the genotype I^BI^B or IBi. It follows that a type O person inherited the O gene from each parent (has the genotype ii), whereas a type AB person inherited the A gene from one parent and the B gene from the other (there is no dominant-recessive relationship between A and B).

The immune system exhibits tolerance to its own red blood cell antigens. People who are type A, for example, do not produce anti-A antibodies. Surprisingly, however, they do make antibodies against the B antigen and, conversely, people with blood type B make antibodies against the A antigen (fig. 13.5). This is believed to result from the fact that antibodies made in response to some common bacteria cross-react with the A or B antigens. People who are type A, therefore, acquire antibodies that can react with B antigens by exposure to these bacteria, but they do not develop antibodies that can react with A antigens because tolerance mechanisms prevent this.

People who are type AB develop tolerance to both of these antigens, and thus do not produce either anti-A or anti-B antibodies. Those who are type O, by contrast, do not develop tolerance to either antigen; therefore, they have both anti-A and anti-B antibodies in their plasma (table 13.3).

Transfusion Reactions

Before transfusions are performed, a *major crossmatch* is made by mixing serum from the recipient with blood cells from the donor. If the types do not match—if the donor is type A, for example, and the recipient is type B—the recipient's antibodies attach to the donor's red blood cells and form bridges that cause the cells to clump together, or **agglutinate** (figs. 13.5 and 13.6). Because of this agglutination reaction, the A and B antigens are sometimes called *agglutinogens,* and the antibodies against them are called *agglutinins.* Transfusion errors that result in such agglutination can lead to blockage of small blood vessels and cause hemolysis (rupture of red blood cells), which may damage the kidneys and other organs.

In emergencies, type O blood has been given to people who are type A, B, AB, or O. Because type O red blood cells lack A and B antigens, the recipient's antibodies cannot cause agglutination of the donor red blood cells. Type O is, therefore, a *universal donor*—but only as long as the volume of plasma

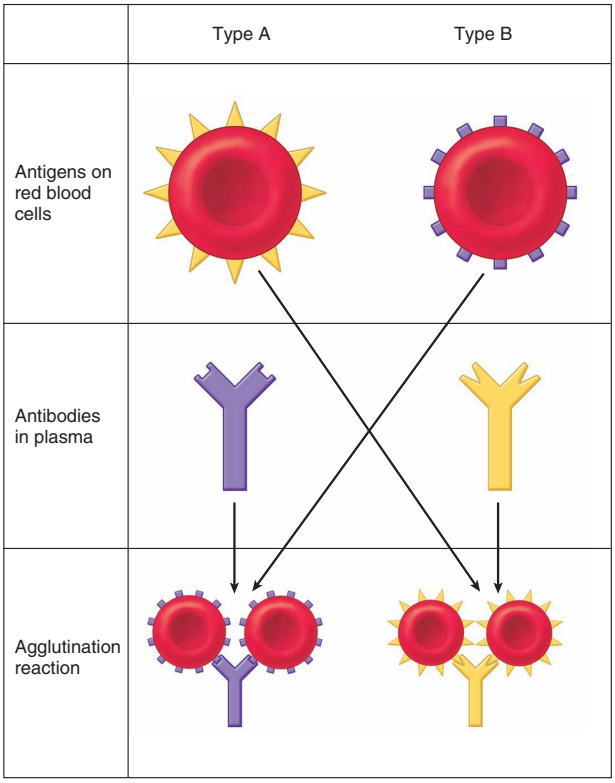


Figure 13.5 **Agglutination reaction.** People with type A blood have type A antigens on their red blood cells and antibodies in their plasma against the type B antigen. People with type B blood have type B antigens on their red blood cells and antibodies in their plasma against the type A antigen. Therefore, if red blood cells from one blood type are mixed with antibodies from the plasma of the other blood type, an agglutination reaction occurs. In this reaction, red blood cells stick together because of antigen-antibody binding.

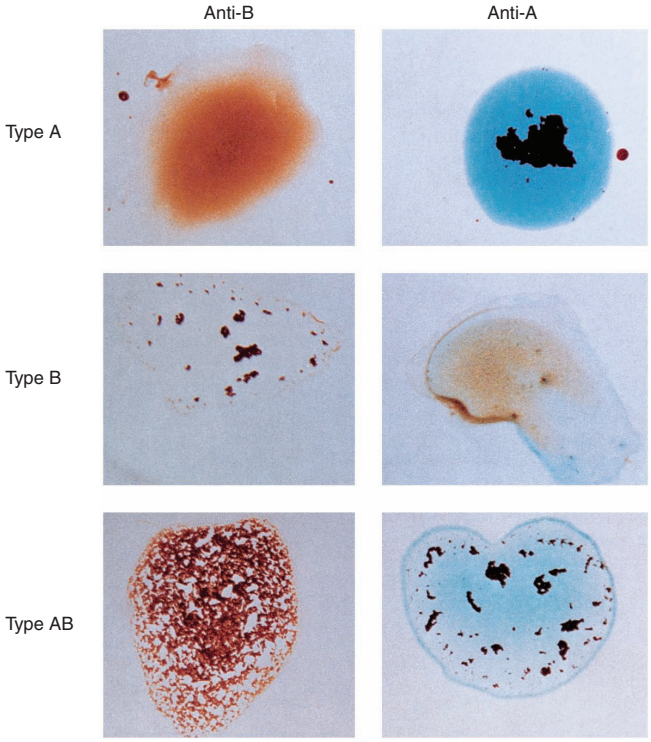


Figure 13.6 **Blood typing.** Agglutination (clumping) of red blood cells occurs when cells with A-type antigens are mixed with anti-A antibodies and when cells with B-type antigens are mixed with anti-B antibodies. No agglutination would occur with type O blood (not shown).

Table 13.3 | The ABO System of Red Blood Cell Antigens

Genotype	Antigen on RBCs	Antibody in Plasma
I^AI^A; I^Ai	A	Anti-B
I^BI^B; I^Bi	B	Anti-A
ii	O	Anti-A and anti-B
I^AI^B	AB	Neither anti-A nor anti-B

donated is small, since plasma from a type O person would agglutinate type A, type B, and type AB red blood cells. Likewise, type AB people are *universal recipients* because they lack anti-A and anti-B antibodies, and thus cannot agglutinate donor red blood cells. (Donor plasma could agglutinate recipient red blood cells if the transfusion volume were too large.) Because of the dangers involved, use of the universal donor and recipient concept is strongly discouraged in practice.

Rh Factor

Another group of antigens found on the red blood cells of most people is the **Rh factor** (named for the rhesus monkey, in which these antigens were first discovered). There are a number of different antigens in this group, but one stands out because of its medical significance. This Rh antigen is termed D, and is often indicated as Rho(D). If this Rh antigen is present on a person's red blood cells, the person is **Rh positive;** if it is absent, the person is **Rh negative.** The Rh-positive condition is by far the more common (with a frequency of 85% in the Caucasian population, for example).

The Rh factor is of particular significance when Rh-negative mothers give birth to Rh-positive babies. The fetal and maternal blood are normally kept separate across the placenta (chapter 20, section 20.6), and so the Rh-negative mother is not usually exposed to the Rh antigen of the fetus during

the pregnancy. At the time of birth, however, a variable degree of exposure may occur, and the mother's immune system may become sensitized and produce antibodies against the Rh antigen. This does not always occur, however, because the exposure may be minimal and because Rh-negative women vary in their sensitivity to the Rh factor. If the woman does produce antibodies against the Rh factor, these antibodies could cross the placenta in subsequent pregnancies and cause hemolysis of the Rh-positive red blood cells of the fetus. Therefore, the baby could be born anemic with a condition called *erythroblastosis fetalis,* or *hemolytic disease of the newborn.*

Erythroblastosis fetalis can be prevented by injecting the Rh-negative mother with an antibody preparation against the Rh factor (a trade name for this preparation is RhoGAM—the GAM is short for gamma globulin, the class of plasma proteins in which antibodies are found) within 72 hours after the birth of each Rh-positive baby. This is a type of passive immunization in which the injected antibodies inactivate the Rh antigens and thus prevent the mother from becoming actively immunized to them. Some physicians now give RhoGAM throughout the Rh-positive pregnancy of any Rh-negative woman.

Blood Clotting

When a blood vessel is injured, a number of physiological mechanisms are activated that promote **hemostasis,** or the cessation of bleeding (*hemo* = blood; *stasis* = standing). Breakage of the endothelial lining of a vessel exposes collagen proteins from the subendothelial connective tissue to the blood. This initiates three separate, but overlapping, hemostatic mechanisms: (1) vasoconstriction, (2) the formation of a platelet plug, and (3) the production of a web of fibrin proteins that penetrates and surrounds the platelet plug.

Platelets and Blood Vessel Walls

In the absence of blood vessel damage, platelets are repelled from each other and from the endothelium of blood vessels. The endothelium is a simple squamous epithelium that overlies connective tissue collagen and other proteins that are capable of activating platelets to begin clot formation. Thus, an intact endothelium physically separates the blood from collagen and other platelet activators in the vessel wall. In addition, the endothelial cells secrete *prostacyclin* (or *PGI_2*, a type of prostaglandin—see chapter 11, fig. 11.34) and *nitric oxide (NO),* which (1) act as vasodilators and (2) act on the platelets to inhibit platelet aggregation. In addition, the plasma membrane of endothelial cells contains an enzyme known as *CD39,* which has its active site facing the blood. The CD39 enzyme breaks down ADP in the blood to AMP and P_i (ADP is released by activated platelets and promotes platelet aggregation, as described shortly). These protective mechanisms are needed to ensure that platelets don't stick to the vessel wall and to each other, so that the flow of blood is not impeded when the endothelium is intact (fig. 13.7*a*).

When a blood vessel is injured and the endothelium is broken, glycoproteins in the platelet's plasma membrane are now able to bind to the exposed collagen fibers. The force of blood flow might pull the platelets off the collagen, however, were it not for another protein produced by endothelial cells known as *von Willebrand's factor* (fig. 13.7*b*), which binds to both collagen and the platelets.

Platelets contain secretory granules; when platelets stick to collagen, they *degranulate* as the secretory granules release their products. These products include *adenosine diphosphate (ADP), serotonin,* and a prostaglandin called *thromboxane A_2* (chapter 11; see fig. 11.34). This event is known as the **platelet release reaction.** The ADP and thromboxane A_2 released from activated platelets recruits new platelets to the vicinity and makes them "sticky," so that they adhere to those stuck on the collagen (fig. 13.7*b*). The second layer of platelets, in turn, undergoes a platelet release reaction, and the ADP and thromboxane A_2 that are secreted cause additional platelets to aggregate at the site of the injury. This produces a **platelet plug** (fig. 13.7*c*) in the damaged vessel.

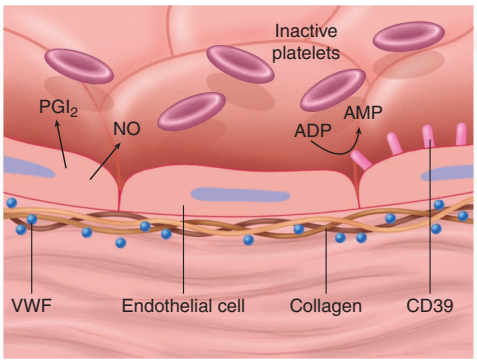
The activated platelets also help to activate plasma clotting factors, leading to the conversion of a soluble plasma protein known as *fibrinogen* into an insoluble fibrous protein, *fibrin.* There are binding sites on the platelet's plasma membrane for fibrinogen and fibrin, so that these proteins help join platelets together and strengthen the platelet plug (fig. 13.7*c*). The clotting sequence leading to fibrin formation is discussed in the next topic.

CLINICAL APPLICATION

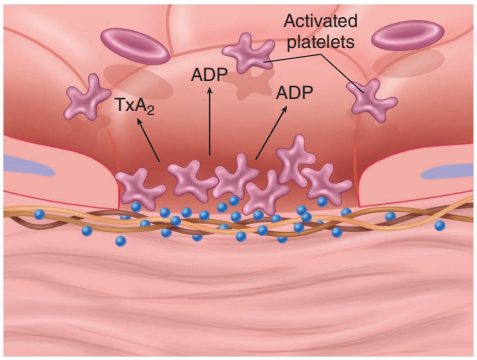
Platelet aggregation inhibitors are medically useful to prevent clot formation and **coronary thrombosis,** a major cause of *myocardial infarction* ("heart attack"; see section 13.7). *Aspirin* irreversibly inhibits the enzyme cyclooxygenase, which is required for prostaglandin formation (chapter 11; see fig. 11.34). Aspirin thereby inhibits the ability of platelets to produce the prostaglandin thromboxane A_2, which is needed for platelet aggregation. Since platelets are not complete cells, they cannot regenerate new enzymes; aspirin thus inhibits cyclooxygenase for the life of the platelets. Other drugs that operate by different mechanisms to affect platelet function are also available. For example, *Clopidogrel* (*Plavix*) inhibits the ability of ADP to promote platelet aggregation, and *dipyridamole* interferes with the ability of platelets to produce ADP. *Glycoprotein IIb/IIIa drugs* are monoclonal antibodies that block the platelet plasma membrane receptors needed for platelets to bind to collagen and to Von Willebrand factor (fig. 13.7), preventing platelets from sticking to the wound site.

Clotting Factors: Formation of Fibrin

The platelet plug is strengthened by a meshwork of insoluble protein fibers known as **fibrin** (fig. 13.8). Blood clots therefore are composed of platelets and fibrin, and they usually contain trapped red blood cells that give the clot a red color



(a)



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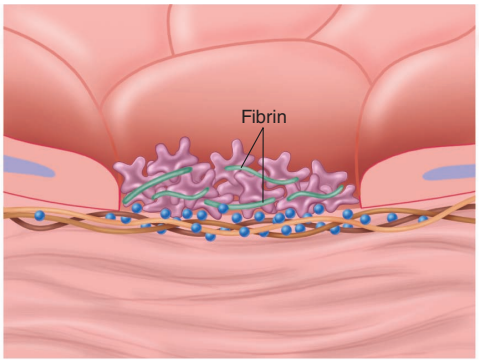


(c)

Figure 13.7 Platelet aggregation. (*a*) Platelet aggregation is prevented in an intact endothelium because it separates the blood from collagen, a potential platelet activator. Also, the endothelium secretes nitric oxide (*NO*) and prostaglandin I2 (*PGI2*), which inhibit platelet aggregation. An enzyme called *CD39* breaks down *ADP* in the blood, which would otherwise promote platelet aggregation. (*b*) When the endothelium is broken, platelets adhere to collagen and to von Willebrand's factor (*V WF*), which helps anchor the platelets that are activated by this process and by the secretion of ADP and thromboxane A2 (*Tx A2*), a prostaglandin. (*c*) A platelet plug is formed and reinforced with fibrin proteins.

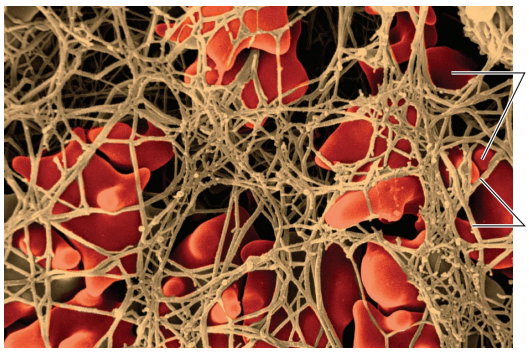


Figure 13.8 Colorized scanning electron micrograph of a blood clot. The threads of fibrin have trapped red blood cells in this image.

(clots formed in arteries, where the blood flow is more rapid, generally lack red blood cells and thus appear gray). Finally, contraction of the platelet mass in the process of *clot retraction* forms a more compact and effective plug. Fluid squeezed from the clot as it retracts is called **serum,** which is plasma without fibrinogen, the soluble precursor of fibrin. (Serum is obtained in laboratories by allowing blood to clot in a test tube and then centrifuging the tube so that the clot and blood cells become packed at the bottom of the tube.)

The conversion of fibrinogen into fibrin may occur via either of two pathways. Blood left in a test tube will clot without the addition of any external chemicals. Because all of the components are present in the blood, this clotting pathway is called the **intrinsic pathway.** Damaged tissues, however, release a chemical that initiates a "shortcut" to the formation of fibrin. Because this chemical is not part of blood, the shorter pathway is called the **extrinsic pathway.**

The intrinsic pathway is initiated by exposure to hydrophilic surfaces *in vitro* (such as the glass of a test tube) or to negatively charged structures such as collagen, polyphosphates, and neutrophil extracellular traps (NETS; chapter 15, section 15.1) in the exposed tissues of a wound *in vivo*. This *contact pathway* activates a plasma protein called factor XII (table 13.4), which is a protein-digesting enzyme (a protease). Active factor XII in turn activates another clotting factor, which activates yet another. The plasma clotting factors are numbered in order of their discovery, which does not reflect the actual sequence of reactions.

The next steps in the sequence require the presence of Ca^{2+} and phospholipids, the latter provided by platelets. These

steps result in the conversion of an inactive glycoprotein, called **prothrombin,** into the active enzyme **thrombin.** Thrombin converts the soluble protein **fibrinogen** into **fibrin** monomers. These monomers are joined together to produce the insoluble fibrin polymers that form a meshwork supporting the platelet plug. The intrinsic clotting sequence is shown on the right side of figure 13.9.

The extrinsic pathway of clot formation is initiated by **tissue factor** (or *tissue thromboplastin,* also known as *factor III*), a membrane glycoprotein found inside the walls

Table 13.4 | The Plasma Clotting Factors

Factor	Name	Function	Pathway
I	Fibrinogen	Converted to fibrin	Common
II	Prothrombin	Converted to thrombin (enzyme)	Common
III	Tissue thromboplastin	Cofactor	Extrinsic
IV	Calcium ions (Ca^{2+})	Cofactor	Intrinsic, extrinsic, and common
V	Proaccelerin	Cofactor	Common
VII*	Proconvertin	Enzyme	Extrinsic
VIII	Antihemophilic factor	Cofactor	Intrinsic
IX	Plasma thromboplastin component; Christmas factor	Enzyme	Intrinsic
X	Stuart-Prower factor	Enzyme	Common
XI	Plasma thromboplastin antecedent	Enzyme	Intrinsic
XII	Hageman factor	Enzyme	Intrinsic
XIII	Fibrin stabilizing factor	Enzyme	Common

*Factor VI is no longer referenced; it is now believed to be the same substance as activated factor V.

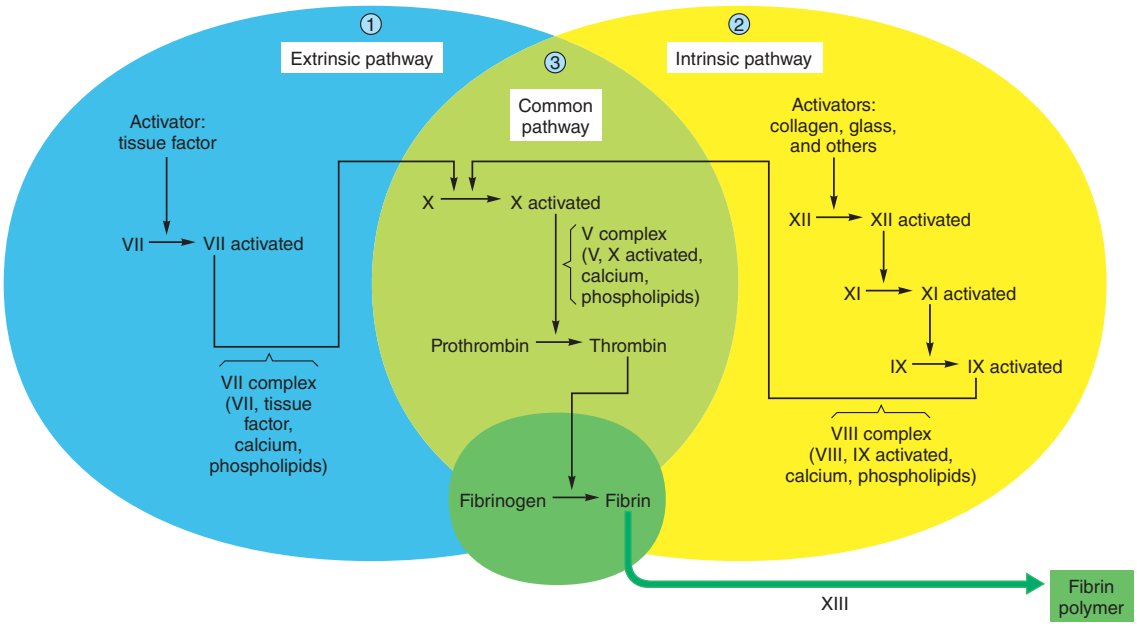


Figure 13.9 **The clotting pathways.** (1) The extrinsic clotting pathway is initiated by the release of tissue factor. (2) The intrinsic clotting pathway is initiated by the activation of factor XII by contact with collagen or glass. (3) Extrinsic and intrinsic clotting pathways converge when they activate factor X, eventually leading to the formation of fibrin.

of blood vessels (in the tunica media and tunica externa; see fig. 13.26) and the cells of the surrounding tissues. When a blood vessel is injured, tissue factor then becomes exposed to factor VII and VIIa in the blood and forms a complex with factor VIIa. By forming this complex, tissue factor greatly increases (by a factor of two million) the ability of factor VIIa to activate factor X and factor IX.

The extrinsic clotting pathway (shown on the left side of fig. 13.9) is now believed to initiate clot formation *in vivo.* Current evidence suggests that the intrinsic clotting pathway plays an amplification role, increasing the clotting cascade initiated by the extrinsic pathway. This function is aided by activated platelets. As platelets become activated and form a platelet plug, a molecule called *phosphatidylserine* becomes exposed at their surfaces. The phosphatidylserine anchors factor VIII and factor V complexes (fig. 13.9) to the platelet surface, which greatly increases the formation of thrombin.

CLINICAL APPLICATION

Hemophilia A is a hereditary disease, inherited as an X-linked recessive trait, which has been prevalent in the royal families of Europe. In hemophilia A, a defect in one subunit of factor VIII prevents this factor from participating in the intrinsic clotting pathway. **Von Willebrand's disease,** involving a defect in another subunit of factor VIII, is also inherited as an X-linked recessive trait. This produces defective von Willebrand factor, a large glycoprotein needed for rapidly circulating platelets to adhere to collagen at the site of vascular injury (see fig. 13.7), which contributes to difficulty in clot formation. **Hemophilia B,** also known as *Christmas disease,* is caused by a deficiency of factor IX and, like factor VIII deficiency in hemophilia A, is inherited as an X-linked trait. This disorder has recently been successfully treated with gene therapy. Some acquired and inherited defects in the clotting system are summarized in table 13.5.

Dissolution of Clots

As the damaged blood vessel wall is repaired, activated factor XII promotes the conversion of an inactive molecule in plasma into the active form called *kallikrein.* Kallikrein, in turn, catalyzes the conversion of inactive *plasminogen* into the active molecule **plasmin.** Plasmin is an enzyme that digests fibrin into "split products," thus promoting dissolution of the clot.

CLINICAL APPLICATION

Thrombolytic agents are drugs that function as protease enzymes to convert plasminogen to plasmin, thereby promoting the dissolution of blood clots. Recombinant DNA technology has allowed the production of *tissue plasminogen activator* (*t-PA,* or *alteplase;* there is also *r-PA*, or *reteplase*), but products derived from *Streptococcus* bacteria—*urokinase* and *streptokinase*—are also used. These can promote the dissolution of blood clots in the treatment of such conditions as **deep vein thrombosis, stroke, coronary thrombosis,** and **pulmonary embolism.** Thrombolytic agents must be used carefully because of the risk of hemorrhage.

Table 13.5 | Some Acquired and Inherited Clotting Disorders and a Listing of Anticoagulant Drugs

Category	Cause of Disorder	Comments
Acquired clotting disorders	Vitamin K deficiency	Inadequate formation of prothrombin and other clotting factors in the liver
Inherited clotting disorders	Hemophilia A (defective factor $VIII_{AHF}$)	Recessive trait carried on X chromosome; results in delayed formation of fibrin
	von Willebrand's disease (defective factor $VIII_{vWF}$)	Dominant trait carried on autosomal chromosome; impaired ability of platelets to adhere to collagen in subendothelial connective tissue
	Hemophilia B (defective factor IX); also called Christmas disease	Recessive trait carried on X chromosome; results in delayed formation of fibrin
Anticoagulants		
Aspirin	Inhibits prostaglandin production, resulting in a defective platelet release reaction	
Coumarin	Inhibits activation of vitamin K	
Heparin	Inhibits activity of thrombin	
Citrate	Combines with Ca^{2+}, and thus inhibits the activity of many clotting factors	

Anticoagulants

Clotting of blood in test tubes can be prevented by the addition of *sodium citrate* or *ethylenediaminetetraacetic acid (EDTA),* both of which chelate (bind to) calcium. By this means, Ca^{2+} levels in the blood that can participate in the clotting sequence are lowered, and clotting is inhibited. A mucoprotein called **heparin** can also be added to the tube to prevent clotting. Heparin activates *antithrombin III,* a plasma protein that combines with and inactivates thrombin. Heparin is also given intravenously during certain medical procedures to prevent clotting. **Warfarin (coumadin)** blocks the cellular activation of vitamin K by inhibiting the enzyme *vitamin K epoxide reductase.* Because vitamin K is required for blood clotting, as described next, this drug serves as an anticoagulant and is the only clinically used oral anticoagulant.

Vitamin K is needed for the conversion of glutamate, an amino acid found in many of the clotting factor proteins, into a derivative called *gamma-carboxyglutamate.* This derivative is more effective than glutamate at bonding to Ca^{2+} and such bonding is needed for proper function of clotting factors II, VII, IX, and X. Because of the indirect action of vitamin K on blood clotting, warfarin must be given to a patient for several days before it becomes effective as an anticoagulant.

Clinical Investigation CLUES

Jessica was prescribed rivaroxaban, a drug that inactivates factor X.

- What is the action of factor X?
- Would the drug interfere with the intrinsic or extrinsic clotting pathway?

CHECKPOINT

3. Distinguish between the different types of formed elements of the blood in terms of their origin, appearance, and function.
4. Describe how the rate of erythropoiesis is regulated.

5a. Explain what is meant by "type A positive" and describe what can happen in a blood transfusion if donor and recipient are not properly matched.

5b. Explain the meaning of *intrinsic* and *extrinsic* as applied to the clotting pathways. How do the two pathways differ from each other? Which steps are common to both?

13.3 STRUCTURE OF THE HEART

The heart contains four chambers: two atria, which receive venous blood, and two ventricles, which eject blood into arteries. The right ventricle pumps blood to the lungs, where the blood becomes oxygenated; the left ventricle pumps oxygenated blood to the entire body.

LEARNING OUTCOMES

After studying this section, you should be able to:

6. Distinguish between the systemic and the pulmonary circulation.
7. Describe the structure of the heart and its components.

About the size of a fist, the hollow, cone-shaped **heart** is divided into four chambers. The right and left **atria** (singular, *atrium*) receive blood from the venous system; the right and left **ventricles** pump blood into the arterial system. The right atrium and ventricle (sometimes called the *right pump*) are separated from the left atrium and ventricle (the *left pump*) by a muscular wall, or *septum.* This septum normally prevents mixture of the blood from the two sides of the heart.

Between the atria and ventricles, there is a layer of dense connective tissue known as the **fibrous skeleton** of the heart. Bundles of myocardial cells (chapter 12, section 12.6) in the atria attach to the upper margin of this fibrous skeleton and form a single functioning unit, or *myocardium.* The myocardial cell bundles of the ventricles attach to the lower margin and form a different myocardium. As a result, the myocardia of the atria and ventricles are structurally and functionally separated from each other, and special conducting tissue is needed to carry action potentials from the atria to the ventricles. The connective tissue of the fibrous skeleton also forms rings, called *annuli fibrosi,* around the four heart valves, providing a foundation for the support of the valve flaps.

Pulmonary and Systemic Circulations

Blood whose oxygen content has become partially depleted and whose carbon dioxide content has increased as a result of tissue metabolism returns to the right atrium. This blood then enters the right ventricle, which pumps it into the *pulmonary trunk* and *pulmonary arteries.* The pulmonary arteries branch to transport blood to the lungs, where gas exchange occurs between the lung capillaries and the air sacs (alveoli) of the lungs. Oxygen diffuses from the air to the capillary blood, while carbon dioxide diffuses in the opposite direction.

The blood that returns to the left atrium by way of the *pulmonary veins* is therefore enriched in oxygen and partially depleted of carbon dioxide. The path of blood from the heart (right ventricle), through the lungs, and back to the heart (left atrium) completes one circuit: the **pulmonary circulation.**

Oxygen-rich blood in the left atrium enters the left ventricle and is pumped into a very large, elastic artery—the *aorta.* The aorta ascends for a short distance, makes a U-turn, and then descends through the thoracic (chest) and abdominal cavities. Arterial branches from the aorta supply oxygen-rich blood

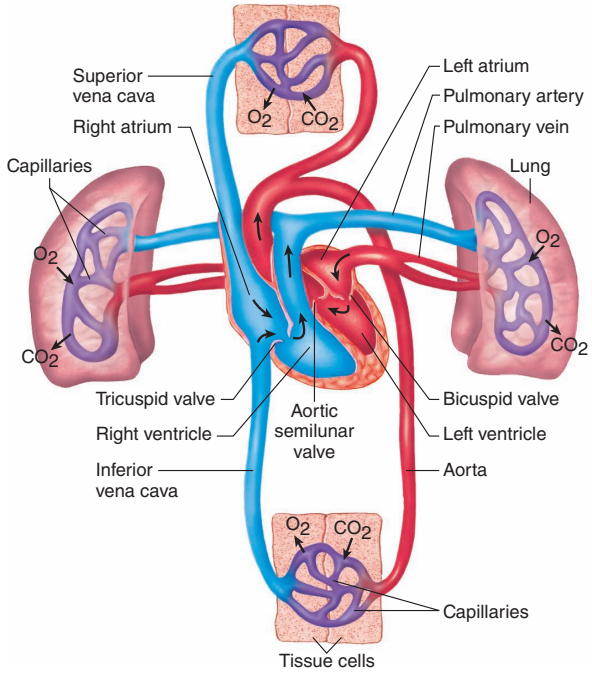


Figure 13.10 A diagram of the circulatory system. The systemic circulation includes the aorta and venae cavae; the pulmonary circulation includes the pulmonary arteries and pulmonary veins. AP|R

to all of the organ systems and are thus part of the **systemic circulation.**

As a result of cellular respiration, the oxygen concentration is lower and the carbon dioxide concentration is higher in the tissues than in the capillary blood. Blood that drains from the tissues into the systemic veins is thus partially depleted of oxygen and increased in carbon dioxide content. These veins ultimately empty into two large veins—the *superior* and *inferior venae cavae*—that return the oxygen-poor blood to the right atrium. This completes the systemic circulation: from the heart (left ventricle), through the organ systems, and back to the heart (right atrium). The systemic and pulmonary circulations are illustrated in figure 13.10, and their characteristics are summarized in table 13.6.

The numerous small muscular arteries and arterioles of the systemic circulation present greater resistance to blood flow than that in the pulmonary circulation. Despite the differences in resistance, the rate of blood flow through the systemic circulation must be matched to the flow rate of the pulmonary circulation. Because the amount of work performed by the left ventricle is greater (by a factor of 5 to 7) than that performed by the right ventricle, it is not surprising that the muscular wall of the left ventricle is thicker (8 to 10 mm) than that of the right ventricle (2 to 3 mm).

Atrioventricular and Semilunar Valves

Although adjacent myocardial cells are joined together mechanically and electrically by intercalated discs (chapter 12; see figs. 12.32 and 12.33), the atria and ventricles are separated into two functional units by a sheet of connective tissue—the fibrous skeleton previously mentioned. Embedded within this sheet of tissue are one-way **atrioventricular (AV) valves.** The AV valve located between the right atrium and right ventricle has three flaps, and is therefore called the *tricuspid valve.* The AV valve between the left atrium and left ventricle has two flaps and is thus called the *bicuspid valve,* or, alternatively, the *mitral valve* (fig. 13.11).

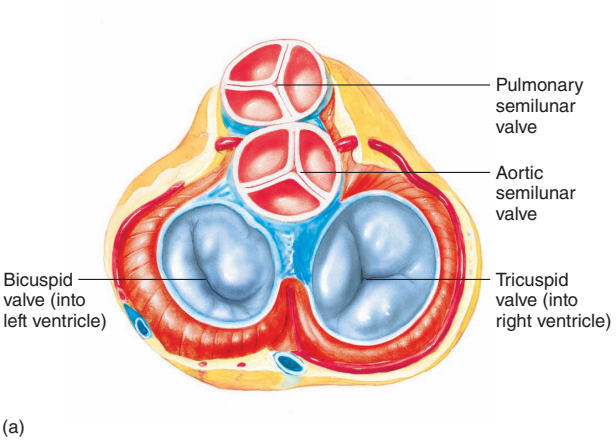
The AV valves allow blood to flow from the atria to the ventricles, but they normally prevent the backflow of blood into the atria. Opening and closing of these valves occur as a result of pressure differences between the atria and ventricles. When the ventricles are relaxed, the venous return of blood to the atria causes the pressure in the atria to exceed that in the ventricles. The AV valves therefore open, allowing blood to enter the ventricles. As the ventricles contract, the intraventricular pressure rises above the pressure in the atria and pushes the AV valves closed.

There is a danger, however, that the high pressure produced by contraction of the ventricles could push the valve flaps too much and evert them. This is normally prevented by contraction of the *papillary muscles* within the ventricles, which are connected to the AV valve flaps by strong tendinous cords called the *chordae tendineae* (fig. 13.11). Contraction of the papillary muscles occurs at the same time as contraction of the muscular walls of the ventricles and serves to keep the valve flaps tightly closed.

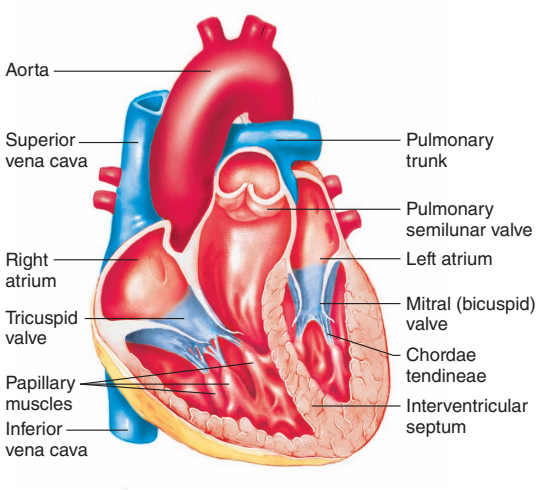
Table 13.6 | Summary of the Pulmonary and Systemic Circulations

	Source	Arteries	O_2 Content of Arteries	Veins	O_2 Content of Veins	Termination
Pulmonary Circulation	Right ventricle	Pulmonary arteries	Low	Pulmonary veins	High	Left atrium
Systemic Circulation	Left ventricle	Aorta and its branches	High	Superior and inferior venae cavae and their branches*	Low	Right atrium

*Blood from the coronary circulation does not enter the venae cavae, but instead returns directly to the right atrium via the coronary sinus.



(a)



(b)

Figure 13.11 **The heart valves.** (*a*) A superior view of the heart valves. (*b*) A sagittal section through the heart, showing both AV valves and the pulmonary semilunar valve (the aortic semilunar valve is not visible in this view). AP|R

One-way **semilunar valves** (fig. 13.12) are located at the origin of the pulmonary artery and aorta. These valves open during ventricular contraction, allowing blood to enter the pulmonary and systemic circulations. During ventricular relaxation, when the pressure in the arteries is greater than the pressure in the ventricles, the semilunar valves snap shut, preventing the backflow of blood into the ventricles.

Heart Sounds

Closing of the AV and semilunar valves produces sounds that can be heard by listening through a stethoscope placed on the chest. These sounds are often verbalized as "lub-dub." The "lub," or **first sound,** is produced by closing of the AV valves during isovolumetric contraction of the ventricles (section 13.4). The "dub," or **second sound,** is produced by closing of the semilunar valves when the pressure in the ventricles falls below the pressure in the arteries. The first sound is thus heard when the ventricles contract at *systole,* and the second sound is heard when the ventricles relax at the beginning of *diastole.* (Systole and diastole are discussed in section 13.4.)

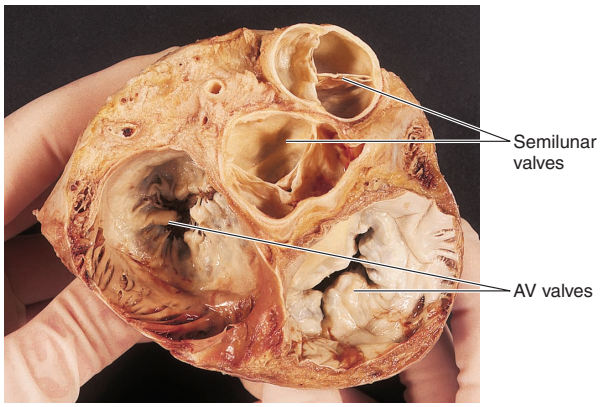


Figure 13.12 **Photograph of a sectioned heart showing the valves.** The pulmonic and aortic semilunar valves are seen toward the top of the photograph. The mitral and tricuspid AV valves are also visible.

CLINICAL APPLICATION

Different **auscultatory chest positions** allow the closing of the separate valves to be heard, so that the first and second heart sounds may be heard to "split" into their components. Closing of the tricuspid valve is best heard when the stethoscope is placed to either side of the lower sternum, just above the xiphoid process, whereas closing of the mitral valve is best heard at the apex of the heart, in the fifth left intercostal space (fig. 13.13). Closing of the pulmonary and aortic semilunar valves is heard best at the second left and right intercostal spaces, respectively. However, these auscultatory positions are affected by obesity, pregnancy, and other conditions.

Heart Murmurs

Murmurs are abnormal heart sounds produced by abnormal patterns of blood flow in the heart. Many murmurs are caused by defective heart valves. Defective heart valves may be congenital, or they may occur as a result of *rheumatic endocarditis,* associated with rheumatic fever. In this disease, the valves become damaged by antibodies made in response to an infection caused by streptococcus bacteria (the bacteria that produce strep throat). Many

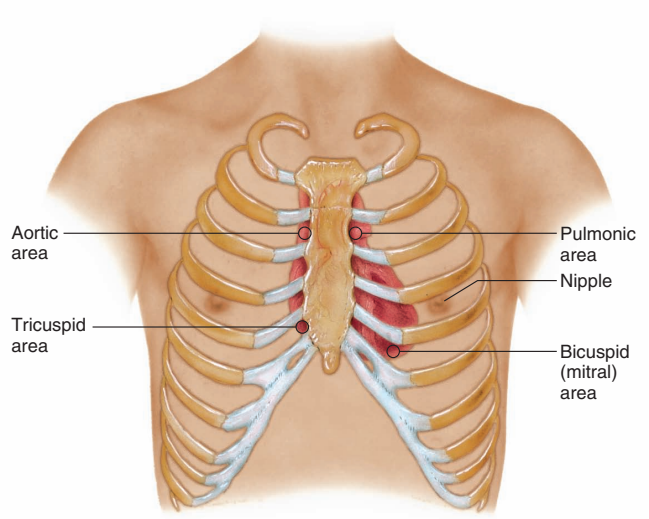


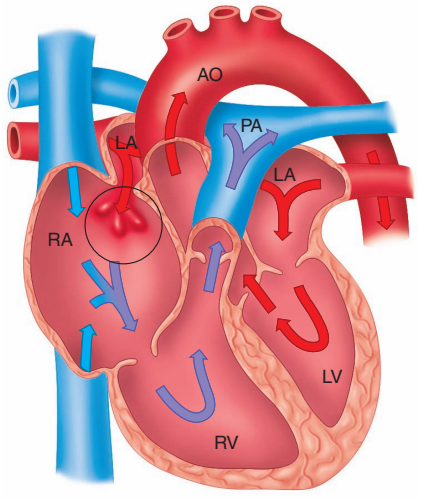
Figure 13.13 Routine stethoscope positions for listening to the heart sounds. The first heart sound is caused by closing of the AV valves; the second by closing of the semilunar valves. AP|R

people have small defects that produce detectable murmurs but do not seriously compromise the pumping ability of the heart. Larger defects, however, may have dangerous consequences and thus may require surgical correction.

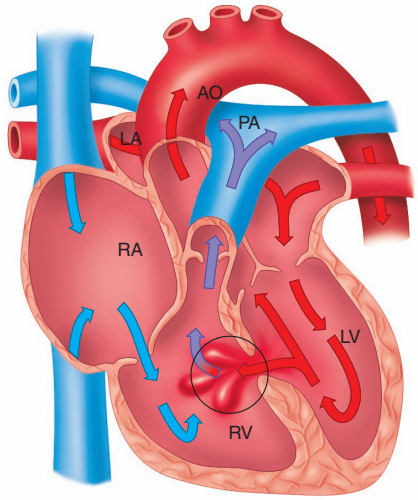
In *mitral stenosis,* for example, the mitral valve becomes thickened and calcified. This can impair the blood flow from the left atrium to the left ventricle. An accumulation of blood in the left atrium may cause a rise in left atrial and pulmonary vein pressure, resulting in pulmonary hypertension. To compensate for the increased pulmonary pressure, the right ventricle grows thicker and stronger.

Mitral valve prolapse (with a prevalence estimated at 2.5%) is the most common cause of chronic mitral regurgitation, where blood flows backward into the left atrium. It has both congenital and acquired forms; in younger people with mitral valve prolapse, it is usually caused by excess valve leaflet material. Although most people with this condition lack symptoms and have an apparently normal lifespan, in some people the condition can progress. Regurgitation can worsen if there is lengthening and rupture of the chordae tendinae extending from the papillary muscles to the valve flaps (see fig. 13.11). In those cases, the mitral valve may be repaired or replaced with a mechanical or biological (pig or cow) valve.

Murmurs also can be produced by the flow of blood through *septal defects*—holes in the septum between the right and left sides of the heart. These are usually congenital and may occur either in the interatrial or interventricular septum (fig. 13.14). When a septal defect is not accompanied by other abnormalities, blood will usually pass through the defect from the left to the right side, due to the higher pressure on the left side. The buildup of blood and pressure on the right side of the heart that results may lead to pulmonary hypertension and edema (fluid in the lungs).



(a) Septal defect in atria



(b) Septal defect in ventricles

Figure 13.14 Abnormal blood flow due to septal defects. Left-to-right shunting of blood is shown (circled areas) because the left pump is at a higher pressure than the right pump in the adult heart. (*a*) Leakage of blood through a defect in the atria (a patent foramen ovale). (*b*) Leakage of blood through a defect in the interventricular septum. (RA = right atrium; RV = right ventricle; LA = left atrium; RA = right atrium; AO = aorta; PA = pulmonary artery.)

CLINICAL APPLICATION

In a fetus, there is an opening called the **foramen ovale** (fig. 13.14) between the left and right atria. Blood flows from the right atrium into the left atrium through this opening, because the pressure is higher in the right side than the left side of the heart. This pressure difference is due to the constriction of arterioles in the fetal lungs in response to hypoxia (low oxygen). Constriction of pulmonary arterioles in the fetus also causes a higher pressure in the pulmonary trunk than in the aorta, which shunts (diverts) blood from the pulmonary trunk through a connection called the **ductus arteriosus** into the aorta (fig. 13.15).

After the baby is born and starts breathing, the pulmonary oxygen levels rise. This causes pulmonary arterioles to dilate and the pressure in the right side of the heart to lower below the pressure in the left side, promoting the closing of the foramen ovale. The rise in blood oxygen also stimulates smooth muscle contraction in the ductus arteriosus, causing it to close. If these fetal structures remain open postnatally, they are referred to as a *patent foramen ovale* or a *patent ductus arteriosus* and can produce heart murmurs.

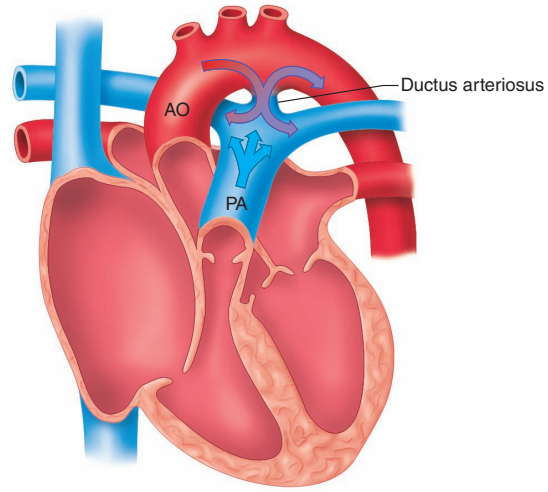


Figure 13.15 **The flow of blood through a patent (open) ductus arteriosus.** The ductus is normally open in a fetus but closes after birth, eventually becoming the ligamentum arteriosum. (AO = aorta; PA = pulmonary arteries.)

Clinical Investigation CLUES

Jessica was told that she has a mitral valve prolapse.

- What is a mitral valve prolapse, and where on the chest might it best be heard?
- Is it likely that Jessica's fatigue is due to her mitral valve prolapse?

CHECKPOINT

6a. Using a flow diagram (arrows), describe the pathway of the pulmonary circulation. Indicate the relative amounts of oxygen and carbon dioxide in the vessels involved.

6b. Use a flow diagram to describe the systemic circulation and indicate the relative amounts of oxygen and carbon dioxide in the blood vessels.

6c. List the AV valves and the valves of the pulmonary artery and aorta. How do these valves ensure a oneway flow of blood?

7a. Discuss how defective valves affect blood flow within the heart and produce heart murmurs.

7b. Describe the patterns of blood flow in interatrial and interventricular septal defects, and in a patent foramen ovale in both a fetus and an adult.

13.4 CARDIAC CYCLE

The two atria fill with blood and then contract simultaneously. This is followed by simultaneous contraction of both ventricles, which sends blood through the pulmonary and systemic circulations. Pressure changes in the atria and ventricles as they go through the cardiac cycle are responsible for the flow of blood through the heart chambers and out into the arteries.

LEARNING OUTCOMES

After studying this section, you should be able to:

8. Describe the cardiac cycle in terms of systole and diastole of the atria and ventricles.

9. Explain how the pressure differences within the heart chambers are responsible for blood flow during the cardiac cycle.

The **cardiac cycle** refers to the repeating pattern of contraction and relaxation of the heart. The phase of contraction is called **systole,** and the phase of relaxation is called **diastole.** When these terms are used without reference to specific chambers, they refer to contraction and relaxation of the ventricles. It should be noted, however, that the atria also contract and relax. There is an atrial systole and diastole. Atrial contraction occurs toward the end of diastole, when the ventricles are relaxed; when the ventricles contract during systole, the atria are relaxed (fig. 13.16).

The heart thus has a two-step pumping action. The right and left atria contract almost simultaneously, followed by contraction of the right and left ventricles 0.1 to 0.2 second later. During the time when both the atria and ventricles are relaxed, the venous return of blood fills the atria. The buildup of pressure that results causes the AV valves to open and blood to flow from atria to ventricles. It has been estimated that the ventricles are about 80% filled with blood even before the atria contract. Contraction of the atria adds the final 20% to the *end-diastolic volume,* which is the total volume of blood in the ventricles at the end of diastole.

Contraction of the ventricles in systole ejects about two-thirds of the blood they contain—an amount called the *stroke volume*—leaving one-third of the initial amount left in the ventricles as the *end-systolic volume.* The ventricles then fill with blood during the next cycle. At an average *cardiac rate* of 75 beats per minute, each cycle lasts 0.8 second; 0.5 second is spent in diastole, and systole takes 0.3 second (fig. 13.16).

FITNESS APPLICATION

The atria fail to contract when a person has **atrial fibrillation,** yet the amount of blood that fills the ventricles and that the ventricles eject is often sufficient to allow the person to live without obvious symptoms. However, the person may experience fatigue and difficulty exercising due to an inability to sufficiently increase the cardiac output. More seriously, the pooling of blood in the atria increases the chances of blood clot formation, causing a four- to fivefold increase in the risk of stroke. This may be prevented with anticoagulants including *aspirin, warfarin* (which blocks the activation of vitamin K; section 13.2), and *rivaroxaban* (*Xarelto*), which inhibits factor X activity in the clotting sequence (see fig. 13.9).

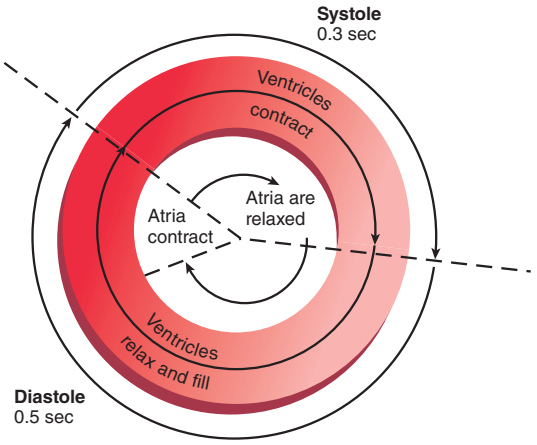


Figure 13.16 The cardiac cycle of ventricular systole and diastole. Contraction of the atria occurs in the last 0.1 second of ventricular diastole. Relaxation of the atria occurs during ventricular systole. The durations given for systole and diastole relate to a cardiac rate of 75 beats per minute.

Clinical Investigation CLUES

Jessica was told that she has atrial fibrillation and experienced fatigue, and the physician prescribed rivaroxaban.

- How might atrial fibrillation explain Jessica's fatigue?
- What is the major danger of atrial fibrillation, and how does rivaroxaban help?

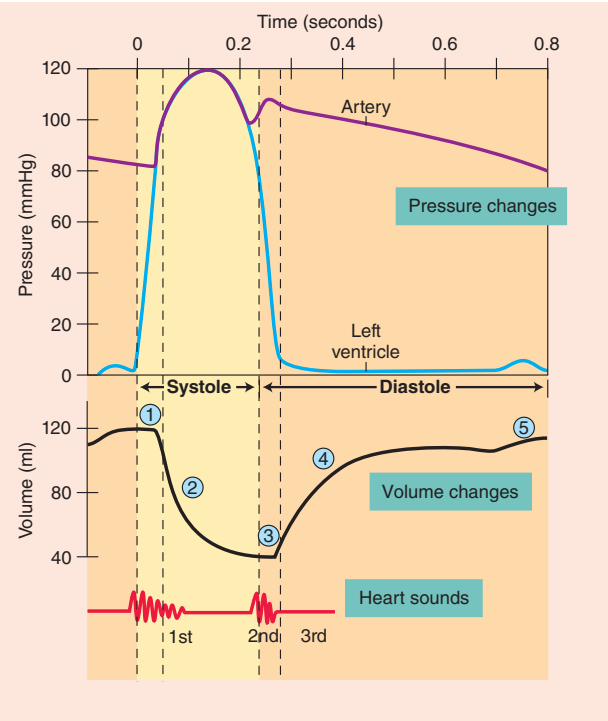
Pressure Changes During the Cardiac Cycle

When the heart is in diastole, the pressure in the systemic arteries averages about 80 mmHg (millimeters of mercury). These events in the cardiac cycle then occur (fig. 13.17):

1. As the ventricles begin their contraction, the intraventricular pressure rises, causing the AV valves to snap shut and produce the first heart sound. At this time, the ventricles are neither being filled with blood (because the AV valves are closed) nor ejecting blood (because the intraventricular pressure has not risen sufficiently to open the semilunar valves). This is the phase of *isovolumetric contraction.*
2. When the pressure in the left ventricle becomes greater than the pressure in the aorta, the phase of *ejection* begins as the semilunar valves open. The pressure in the left ventricle and aorta rises to about 120 mmHg (fig. 13.17) when ejection begins and the ventricular volume decreases.
3. As the pressure in the ventricles falls below the pressure in the arteries, the back pressure causes the semilunar valves to snap shut and produce the second heart sound. The pressure in the aorta falls to 80 mmHg, while pressure in the left ventricle falls to 0 mmHg. During *isovolumetric relaxation,* the AV and semilunar valves are closed. This phase lasts until the pressure in the ventricles falls below the pressure in the atria.
4. When the pressure in the ventricles falls below the pressure in the atria, the AV valves open and a phase of *rapid filling* of the ventricles occurs.
5. *Atrial contraction (atrial systole)* delivers the final amount of blood into the ventricles immediately prior to the next phase of isovolumetric contraction of the ventricles.

Similar events occur in the right ventricle and pulmonary circulation, but the pressures are lower. The maximum pressure produced at systole in the right ventricle is 25 mmHg, which falls to a low of 8 mmHg at diastole.

The arterial pressure rises as a result of ventricular systole (due to blood ejected into the arterial system) and falls during ventricular diastole (fig. 13.17). Because of this, a person's cardiac cycle can be followed by measuring the systolic and diastolic arterial pressures, and by palpating (feeling) the pulse (chapter 14, section 14.6). A pulse is felt (for example, in the radial artery of the wrist) when the arterial pressure rises from diastolic to systolic levels and pushes against the examiner's finger. Figure 13.17



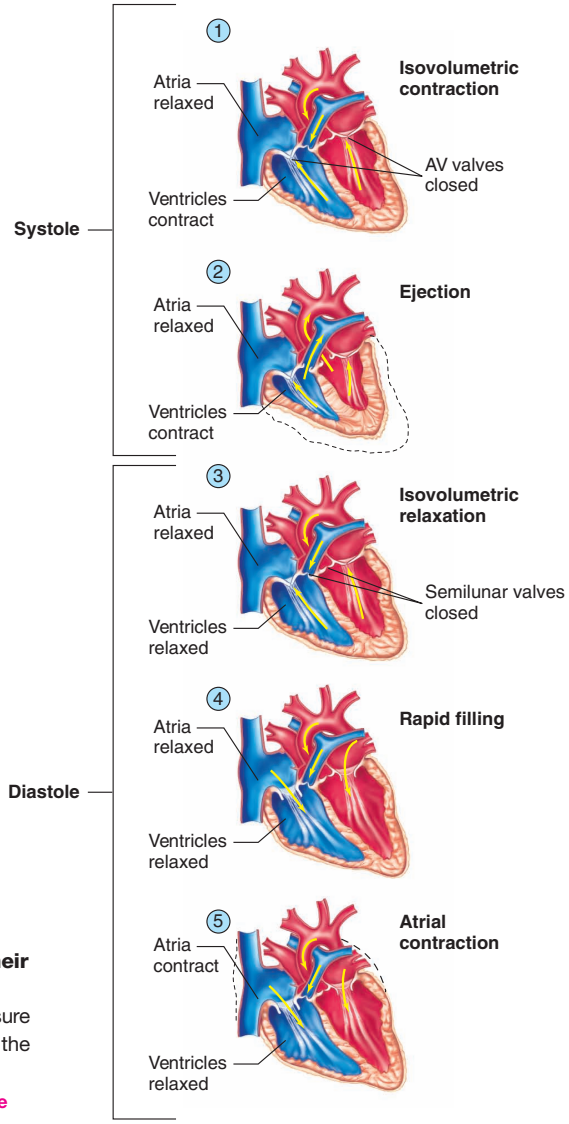


Figure 13.17 Pressure changes in the left ventricle and their effects during the cardiac cycle. The figure shows the effects of left ventricular pressure changes on left ventricular volume and arterial pressure and the correlation of these with the heart sounds. The numbers refer to the events described in the text. AP|R

See the *Test Your Quantitative Ability* section of the Review Activities at the end of this chapter.

reveals an inflection in the descending portion of the arterial pressure graph, which cannot be felt on palpation. This inflection is called the *dicrotic notch* and is produced by closing of the aortic and pulmonic semilunar valves. Closing of these valves produces the second heart sound and the dicrotic notch during the phase of isovolumetric relaxation at the beginning of diastole.

An electrocardiogram (ECG) also allows an examiner to follow the cardiac cycle of systole and diastole (see fig. 13.25). This is because myocardial contraction occurs in response to the depolarization stimulus of an action potential and myocardial relaxation begins during repolarization. The relationships between the electrical activity of the heart, the electrocardiogram, and the cardiac cycle are described in the next section.

CHECKPOINT

8a. Using a drawing or flow chart, describe the sequence of events that occurs during the cardiac cycle. Indicate when atrial and ventricular filling occur and when atrial and ventricular contraction occur.

8b. Describe how the pressure in the left ventricle and in the systemic arteries varies during the cardiac cycle.

9. Draw a figure to illustrate the pressure variations described in question 8b, and indicate in your figure when the AV and semilunar valves close.

13.5 ELECTRICAL ACTIVITY OF THE HEART AND THE ELECTROCARDIOGRAM

The pacemaker region of the heart (SA node) exhibits a spontaneous depolarization that causes action potentials, resulting in the automatic beating of the heart. Action potentials are conducted by myocardial cells in the atria and are transmitted to the ventricles by specialized conducting tissue. Electrocardiogram waves correspond to these events in the heart.

LEARNING OUTCOMES

After studying this section, you should be able to:

10. Describe the pacemaker potential and the myocardial action potential, and explain how the latter correlates with myocardial contraction and relaxation.

11. Describe the components of the ECG and their relationships to the cardiac cycle.

As described in chapter 12, myocardial cells are short, branched, and interconnected by gap junctions. Gap junctions function as electrical synapses, and have been described in chapter 7 (see fig. 7.21) and chapter 12 (see fig. 12.32). The entire mass of cells interconnected by gap junctions is known as a *myocardium.* A myocardium is a single functioning unit, or *functional syncytium,* because action potentials that originate in any cell in the mass can be transmitted to all the other cells. The myocardia of the atria and ventricles are separated from each other by the fibrous skeleton of the heart, as previously described. Impulses normally originate in the atria, so the atrial myocardium is excited before that of the ventricles.

Electrical Activity of the Heart

If the heart of a frog is removed from the body and all neural innervations are severed, it will still continue to beat as long as the myocardial cells remain alive. The automatic nature of the heartbeat is referred to as *automaticity.* As a result of experiments with isolated myocardial cells and of observations of patients with blocks in the conductive tissues of the heart, scientists have learned that there are three regions that can spontaneously generate action potentials and thereby function as pacemakers. In the normal heart, only one of these, the **sinoatrial node (SA node),** functions as the pacemaker. The SA node is located in the right atrium near the opening of the superior vena cava, and serves as the primary (normal) pacemaker of the heart. The two potential, or secondary, pacemaker regions—the *AV node* and *Purkinje fibers* (parts of the conduction network; see fig. 13.20)—are normally suppressed by action potentials originating in the SA node.

Pacemaker Potential

The cells of the SA node do not maintain a resting membrane potential in the manner of resting neurons or skeletal muscle cells. Instead, during the period of diastole, the SA node exhibits a slow *spontaneous depolarization* called the **pacemaker potential.** Because this pacemaker potential occurs during diastole, it is also called a **diastolic depolarization.** The SA node cells produce this spontaneous, diastolic depolarization in a clocklike manner through the interaction of different membrane ion channels and transporters.

The production of the spontaneous depolarization, and thus of the automatic heartbeat, involves ion channels in the plasma membrane and in the sarcoplasmic reticulum. One type in the plasma membrane is known as **HCN channels,** which are unique to pacemaker cells. The "H" in the name stands for hyperpolarization; these channels—unlike all other voltage-gated ion channels—open in response to hyperpolarization rather than to depolarization. When they open, they allow the entry of Na^+ to produce a depolarization. Because of its unusual cause, the inward flow of Na^+ though HCN channels is called a "funny current." The "CN" part of the HCN channel name stands for cyclic nucleotide; these channels also open to cyclic AMP (cAMP), produced in response to stimulation of beta-adrenergic receptors by epinephrine and norepinephrine.

The "funny current" entry of Na^+ through the HCN channels is important in producing the diastolic depolarization, but a clocklike entry of Ca^{2+} into the cytoplasm also contributes significantly. Once the diastolic depolarization reaches a threshold value (about −40 mV), it causes the opening of voltage-gated Ca^{2+} channels in the plasma membrane. It is the influx of Ca^{2+} at this time—rather than the more usual inflow of Na^+—that produces the upward phase of the action potential in the pacemaker cells (fig. 13.18). While this upward phase of the action potential is occurring, the Ca^{2+} that has entered stimulates the opening of Ca^{2+} release

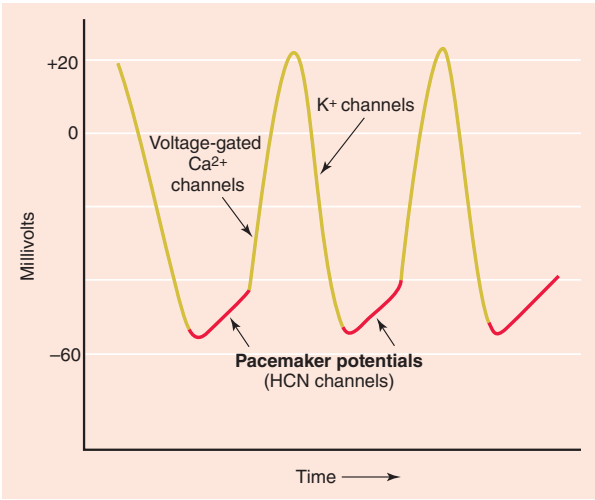


Figure 13.18 Pacemaker potentials and action potentials in the SA node. The pacemaker potentials are spontaneous depolarizations. When they reach threshold, they trigger action potentials.

channels in the sarcoplasmic reticulum (also called ryanodine receptors; chapter 12, section 12.2) in a process of *Ca^{2+}-induced Ca^{2+} release* (chapter 12; see fig. 12.34). This produces a massive release of Ca^{2+} from the sarcoplasmic reticulum that causes contraction of the myocardial cells. Repolarization is then produced by the opening of voltage-gated K^+ channels (fig. 13.18).

When repolarization is complete, the mechanisms responsible for the next diastolic depolarization begin, leading to the next action potential and the next heartbeat. This produces a cardiac rate that can vary depending on the effects of the autonomic nervous system. Epinephrine and norepinephrine cause the production of cyclic AMP within the pacemaker cells (chapter 11; see fig. 11.8), which opens HCN channels for Na^+ to produce a depolarization. Production of cAMP also promotes the entry of Ca^{2+} into the cytoplasm through Ca^{2+} channels. By these means, sympathoadrenal stimulation increases the rate of diastolic depolarization to help produce a faster cardiac rate (chapter 14; see fig. 14.1), while also increasing the strength of myocardial contraction (chapter 14; see fig. 14.2). Acetylcholine (ACh), released by parasympathetic axons that innervate the pacemaker cells, bind to their muscarinic receptors in the plasma membrane. Acting through G-proteins, this causes the opening of K^+ channels (chapter 9; see fig. 9.11). The outward diffusion of K^+ slows the time required for the diastolic depolarization to reach threshold, slowing the production of action potentials and thereby slowing the cardiac rate.

Recent research suggests that the SA node is not a uniform structure, but instead consists of different pacemaker regions that are electrically separated from each other and from the surrounding myocardial cells of the right atrium. These regions communicate electrically through different *sinoatrial conduction pathways.* Action potentials spread through the sinoatrial conduction pathways to depolarize both atria and, through other conduction pathways (AV node, bundle of His, and Purkinje fibers), to depolarize the ventricles. In this way, a region of the sinoatrial node paces the heart to produce what is called a **normal sinus rhythm.**

As previously mentioned, the AV node and Purkinje fibers can potentially serve as pacemakers but are normally suppressed by action potentials originating in the SA node. This is because when a membrane is producing an action potential, it is in a refractory period (see fig. 13.21). When the membrane of a cell other than a pacemaker cell recovers from its refractory period, it will again be stimulated by action potentials from the SA node. This is because the diastolic depolarization and action potential production in the SA node are faster than in these other sites. If conduction from the SA node is blocked, cells in one of these regions could spontaneously depolarize and produce action potentials. This region would then serve as an abnormal pacemaker, called an *ectopic pacemaker* or *ectopic focus.* Because the normal SA node pacemaker has the fastest spontaneous cycle, the rate set by an ectopic pacemaker would usually be slower than the normal sinus rhythm.

Myocardial Action Potential

Once another myocardial cell has been stimulated by action potentials originating in the SA node, it produces its own action potentials. The majority of myocardial cells have resting membrane potentials of about −85 mV. When stimulated by action potentials from a pacemaker region, these cells become depolarized to threshold, at which point their voltage-regulated Na^+ gates open. The upshoot phase of the action potential of nonpacemaker cells is due to the rapid inward diffusion of Na^+ through *fast Na^+ channels.* Following the rapid reversal of the membrane polarity, the membrane potential quickly declines to about −15 mV. Unlike the action potential of other cells, however, this level of depolarization is maintained for 200 to 300 msec before repolarization (fig. 13.19). This *plateau phase* results from a slow inward diffusion of Ca^{2+} through *slow Ca^{2+} channels,* which balances a slow outward diffusion of K^+. Rapid repolarization at the end of the plateau phase is achieved, as in other cells, by the opening of voltage-gated K^+ channels and the rapid outward diffusion of K^+ that results.

The long plateau phase of the myocardial action potential distinguishes it from the spike-like action potentials in axons

CLINICAL APPLICATION

Arrhythmias are abnormal patterns of electrical activity that result in abnormalities of the heartbeat. Drugs used to treat arrhythmias affect the nature and conduction of cardiac action potentials, and have been classified into four different groups. Group 1 drugs are those that block the fast Na^+ channels (*quinidine, procainamide, lidocaine*); group 2 drugs are beta-blockers, interfering with the ability of catecholamines to stimulate beta-adrenergic receptors (*propranolol, atenolol*); group 3 drugs block K^+ channels (*amiodarone*), slowing repolarization; and group 4 drugs block the slow Ca^{2+} channels (*verapamil, diltiazem*). Different arrhythmias are best treated by the specific actions of each drug.

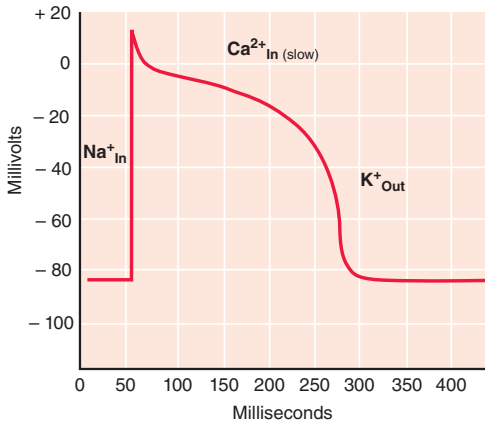


Figure 13.19 An action potential in a myocardial cell from the ventricles. The plateau phase of the action potential is maintained by a slow inward diffusion of Ca^{2+}. The cardiac action potential, as a result, is about 100 times longer in duration than the spike-like action potential in an axon.

and skeletal muscle fibers. The plateau phase is accompanied by the entry of Ca^{2+}, which begins excitation-contraction coupling (as described shortly). Thus, myocardial contraction accompanies the long action potential (see fig. 13.21), and is completed before the membrane recovers from its refractory period. Summation and tetanus, as can occur in skeletal muscles (chapter 12), is thereby prevented from occurring in the myocardium by this long refractory period.

Conducting Tissues of the Heart

Action potentials that originate in the SA node spread to adjacent myocardial cells of the right and left atria through the gap junctions between these cells. Because the myocardium of the atria is separated from the myocardium of the ventricles by the fibrous skeleton of the heart, however, the impulse cannot be conducted directly from the atria to the ventricles. Specialized conducting tissue, composed of modified myocardial cells, is thus required. These specialized myocardial cells form the *AV node, bundle of His,* and *Purkinje fibers.*

Action potentials that have spread from the SA node through the atria pass into the **atrioventricular node (AV node),** which is located on the inferior portion of the interatrial septum (fig. 13.20). From here, action potentials continue through the **atrioventricular bundle,** or **bundle of His** (pronounced "hiss"), beginning at the top of the interventricular septum. This conducting tissue pierces the fibrous skeleton of the heart and continues to descend along the interventricular septum. The atrioventricular bundle divides into right and left bundle branches, which are continuous with the **Purkinje fibers** within the ventricular walls. Within the myocardium of the ventricles, the action potential spreads from the inner (endocardium) to the outer (epicardium) side. This causes both ventricles to contract simultaneously and eject blood into the pulmonary and systemic circulations.

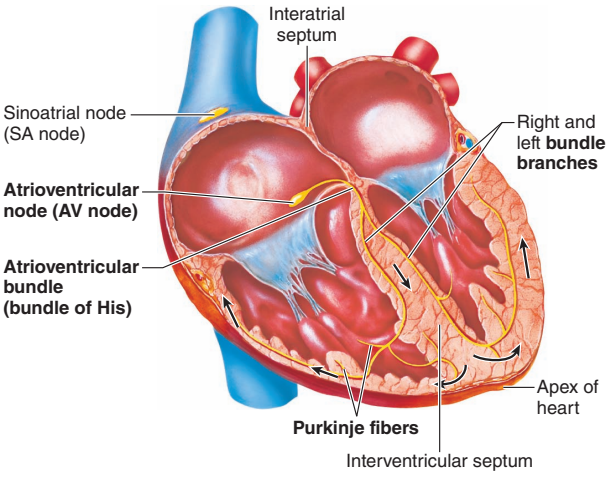


Figure 13.20 The conduction system of the heart. The conduction system consists of specialized myocardial cells that rapidly conduct the impulses from the atria into the ventricles. AP|R

Conduction of the Impulse

Action potentials from the SA node spread very quickly—at a rate of 0.8 to 1.0 meter per second (m/sec)—across the myocardial cells of both atria. The conduction rate then slows considerably as the impulse passes into the AV node. Slow conduction of impulses (0.03 to 0.05 m/sec) through the AV node accounts for over half of the time delay between excitation of the atria and ventricles. After the impulses spread through the AV node, the conduction rate increases greatly in the atrioventricular bundle and reaches very high velocities (5 m/sec) in the Purkinje fibers. As a result of this rapid conduction of impulses, ventricular contraction begins 0.1 to 0.2 second after the contraction of the atria.

Excitation-Contraction Coupling in Heart Muscle

The mechanism of excitation-contraction coupling in myocardial cells, involving *Ca^{2+}-stimulated Ca^{2+} release,* was discussed in chapter 12 (see fig. 12.34). In summary, action potentials conducted by the sarcolemma (chiefly along the transverse tubules) briefly open voltage-gated Ca^{2+} channels in the plasma membrane. This allows Ca^{2+} to diffuse into the cytoplasm from the extracellular fluid, producing a brief "puff" of Ca^{2+} that serves to stimulate the opening of Ca^{2+} release channels in the sarcoplasmic reticulum. The amount of Ca^{2+} released from intracellular stores in the sarcoplasmic reticulum is far greater than the amount that enters from the extracellular fluid through voltage-gated channels in the sarcolemma. Thus, it is mostly the Ca^{2+} from the sarcoplasmic reticulum that binds to troponin and stimulates contraction.

These events occur at *signaling complexes,* which are the regions where the sarcolemma come in very close proximity to the sarcoplasmic reticulum. There are an estimated 20,000 signaling complexes in a myocardial cell, all activated at the

CLINICAL APPLICATION

Digitalis, or **digoxin** (*Lanoxin*), is a "cardiac glycoside" drug often used to treat people with congestive heart failure or atrial fibrillation. Digitalis inactivates the Na^+/K^+–ATPase pumps in the myocardial cell plasma membrane, interfering with their ability to pump Na^+ out of the cell. This increases the activity of the Na^+/Ca^{2+} exchange pumps in the plasma membrane, so that they pump more Na^+ out of the cell and more Ca^{2+} into the cell. As the intracellular concentration of Ca^{2+} rises, so does the amount of Ca^{2+} stored in the sarcoplasmic reticulum. This increases the contractility (strength of contraction) of the myocardium, which helps to treat congestive heart failure, and also slows the conduction of the impulses through the AV node, helping to treat atrial fibrillation.

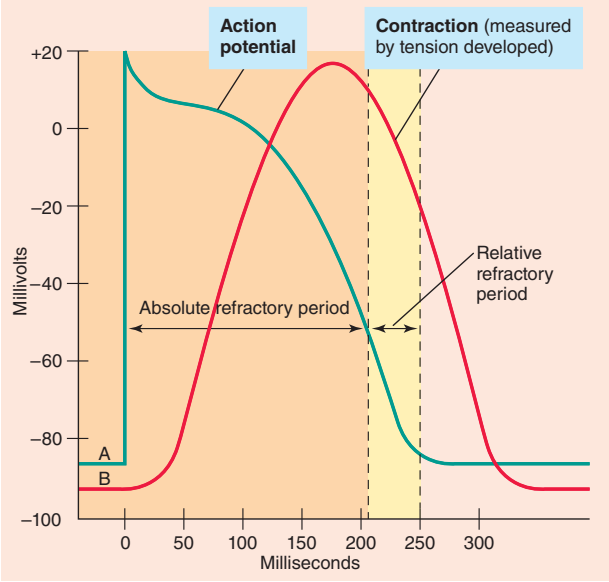


Figure 13.21 Correlation of the myocardial action potential with myocardial contraction. The time course for the myocardial action potential is compared with the duration of contraction. Notice that the long action potential results in a correspondingly long absolute refractory period and relative refractory period. These refractory periods last almost as long as the contraction, so that the myocardial cells cannot be stimulated a second time until they have completed their contraction from the first stimulus.

same time by the depolarization stimulus of the action potential. This results in a myocardial contraction that develops during the depolarization phase of the action potential (fig. 13.21).

During the repolarization phase of the action potential, the concentration of Ca^{2+} within the cytoplasm must be lowered sufficiently to allow myocardial relaxation and diastole. The Ca^{2+} concentration of the cytoplasm is lowered by the *sarcoplasmic reticulum Ca^{2+} ATPase,* or *SERCA, pump,* which actively transports Ca^{2+} into the lumen of the SR. Also, Ca^{2+} is extruded across the sarcolemma into the extracellular fluid by the action of two transporters. One is a *Na^+/Ca^{2+} exchanger* (*NCX*), which functions in secondary active transport where the downhill movement of Na^+ into the cell powers the uphill extrusion of Ca^{2+}. The other is a primary active transport *Ca^{2+} ATPase pump.* These transporters ensure that the myocardium relaxes during and following repolarization (fig. 13.21), so that the heart can fill with blood during diastole.

Unlike skeletal muscles, the heart cannot sustain a contraction. This is because the atria and ventricles behave as if each were composed of only one cell. This is described as a *functional syncytium;* the functional syncytium of the atria (and the functional syncytium of the ventricles) is stimulated as a single unit and contracts as a unit. This contraction, corresponding in time to the long action potential of myocardial cells and lasting almost 300 msec, is analogous to the twitch produced by a single skeletal muscle fiber (which lasts only 20 to 100 msec in comparison). The heart normally cannot be stimulated again until after it has relaxed from its previous contraction because myocardial cells have *long refractory periods* (fig. 13.21) that correspond to the long duration of their action potentials. Summation of contractions is thus prevented, and the myocardium must relax after each contraction. By this means, the rhythmic pumping action of the heart is ensured.

The Electrocardiogram

The body is a good conductor of electricity because tissue fluids have a high concentration of ions that move (creating a current) in response to potential differences. Potential differences generated by the heart are conducted to the body surface, where they can be recorded by surface electrodes placed on the skin. The recording thus obtained is called an **electrocardiogram** (**ECG** or **EKG**); the recording device is called an *electrocardiograph.* Each cardiac cycle produces three distinct ECG waves, designated *P, QRS,* and *T* (fig. 13.22*a*).

Note that the ECG is not a recording of action potentials, but it does result from the production and conduction of action potentials in the heart. The correlation of an action potential produced in the ventricles to the waves of the ECG is shown in figure 13.22*b*. This figure shows that the spread of depolarization through the ventricles (indicated by the QRS, described shortly) corresponds to the action potential, and thus to contraction of the ventricles.

The spread of depolarization through the atria causes a potential difference that is indicated by an upward deflection of the ECG line. When about half the mass of the atria is depolarized, this upward deflection reaches a maximum value because the potential difference between the depolarized and unstimulated portions of the atria is at a maximum. When the entire mass of the atria is depolarized, the ECG returns to baseline because all regions of the atria have the same polarity. The spread of atrial depolarization thereby creates the **P wave** (fig. 13.23).

Conduction of the impulse into the ventricles similarly creates a potential difference that results in a sharp upward deflection of the ECG line, which then returns to the baseline as the entire mass of the ventricles becomes depolarized. The spread of the depolarization into the ventricles is thereby represented by the **QRS wave.** The plateau phase of the cardiac action potential is related to the *S-T segment* of the ECG (see fig. 13.22*a*). Finally, repolarization of the ventricles produces the **T wave** (fig. 13.23). You might be surprised that ventricular depolarization (the QRS wave) and repolarization (the T wave) point in the same direction, although they are produced by opposite potential changes. This is because depolarization of the ventricles occurs from endocardium to epicardium, whereas repolarization spreads in the opposite direction, from epicardium to endocardium.

There are two types of ECG recording electrodes, or "leads." The *bipolar limb leads* record the voltage between electrodes placed on the wrists and legs (fig. 13.24). These bipolar leads include lead I (right arm to left arm), lead II (right

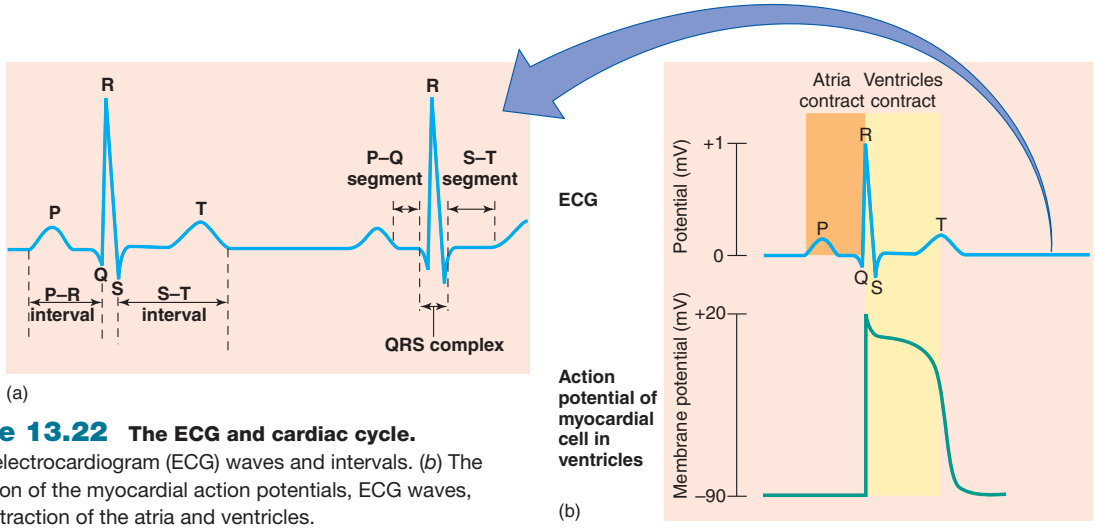


Figure 13.22 The ECG and cardiac cycle.
(*a*) The electrocardiogram (ECG) waves and intervals. (*b*) The correlation of the myocardial action potentials, ECG waves, and contraction of the atria and ventricles.

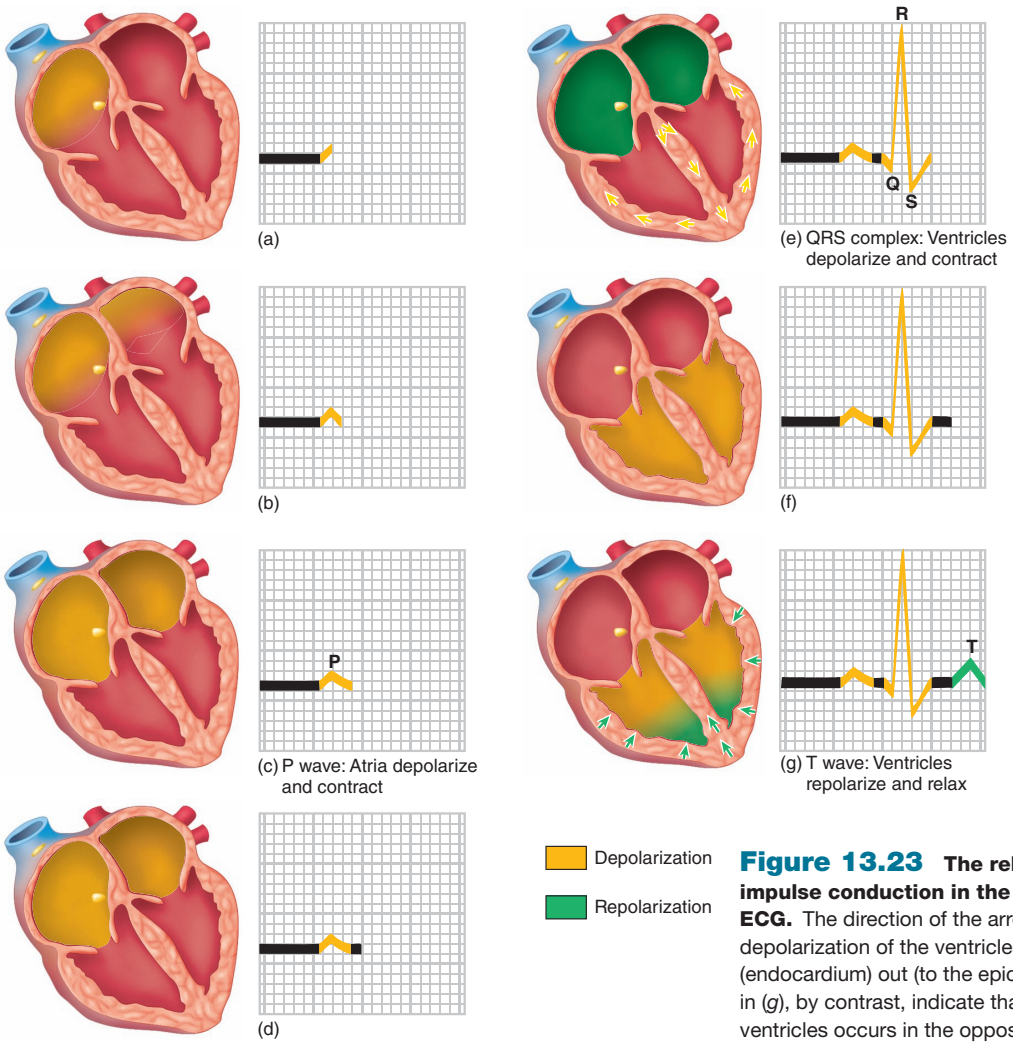


Figure 13.23 The relationship between impulse conduction in the heart and the ECG. The direction of the arrows in (*e*) indicates that depolarization of the ventricles occurs from the inside (endocardium) out (to the epicardium). The arrows in (*g*), by contrast, indicate that repolarization of the ventricles occurs in the opposite direction.

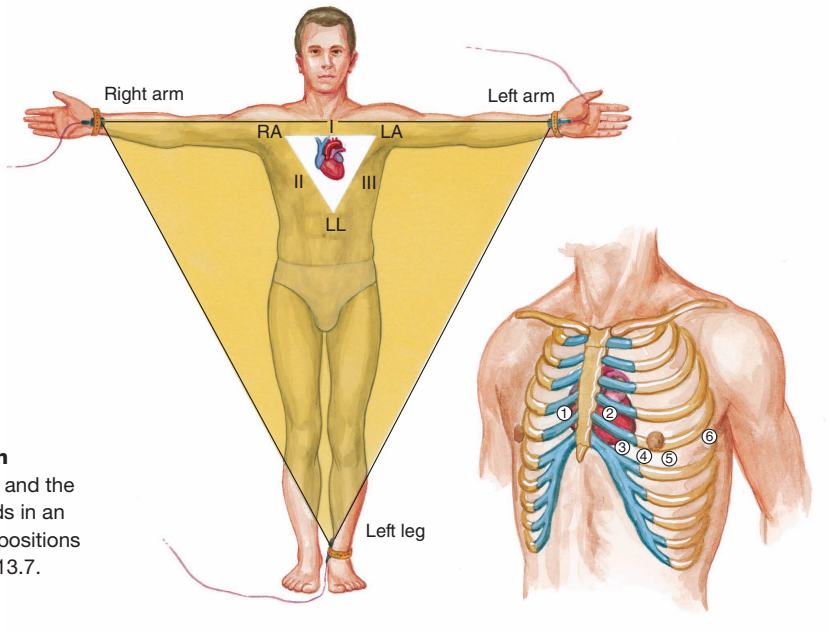


Figure 13.24 The electrocardiograph leads. The placement of the bipolar limb leads and the exploratory electrode for the unipolar chest leads in an electrocardiogram (ECG). The numbered chest positions correspond to V1 through V6, as given in table 13.7. (RA = right arm; LA = left arm; LL = left leg.)

arm to left leg), and lead III (left arm to left leg). The right leg is used as a ground lead. In the *unipolar leads,* voltage is recorded between a single "exploratory electrode" placed on the body and an electrode that is built into the electrocardiograph and maintained at zero potential (ground).

The unipolar limb leads are placed on the right arm, left arm, and left leg, and are abbreviated AVR, AVL, and AVF, respectively. The unipolar chest leads are labeled 1 through 6, starting from the midline position (fig. 13.24). Thus a total of 12 standard ECG leads "view" the changing pattern of the heart's electrical activity from different perspectives (table 13.7). This is important because certain abnormalities are best seen with particular leads and may not be visible at all with other leads.

Correlation of the ECG with Heart Sounds

Depolarization of the ventricles, as indicated by the QRS wave, stimulates contraction by promoting the diffusion of Ca^{2+} into the regions of the sarcomeres. The QRS wave is thus seen at the beginning of systole. The rise in intraventricular pressure that results causes the AV valves to close, so that the first heart sound (S_1, or lub) is produced immediately after the QRS wave (fig. 13.25).

Repolarization of the ventricles, as indicated by the T wave, occurs at the same time that the ventricles relax at the beginning of diastole. The resulting fall in intraventricular pressure causes the aortic and pulmonary semilunar valves to close, so that the second heart sound (S_2, or dub) is produced shortly after the T wave begins in an electrocardiogram.

Table 13.7 | Electrocardiograph (ECG) Leads

Name of Lead	Placement of Electrodes
Bipolar Limb Leads	
I	Right arm and left arm
II	Right arm and left leg
III	Left arm and left leg
Unipolar Limb Leads	
AVR	Right arm
AVL	Left arm
AVF	Left leg
Unipolar Chest Leads	
V_1	4th intercostal space to the right of the sternum
V_2	4th intercostal space to the left of the sternum
V_3	5th intercostal space to the left of the sternum
V_4	5th intercostal space in line with the middle of the clavicle (collarbone)
V_5	5th intercostal space to the left of V_4
V_6	5th intercostal space in line with the middle of the axilla (underarm)

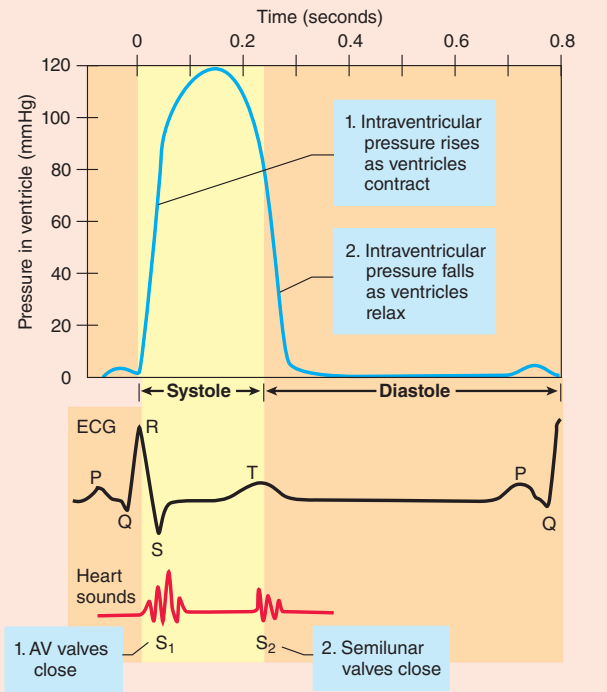


Figure 13.25 The relationship between changes in intraventricular pressure and the ECG. The QRS wave (representing depolarization of the ventricles) occurs at the beginning of systole, whereas the T wave (representing repolarization of the ventricles) occurs at the beginning of diastole. The numbered steps at the bottom of the figure correspond to the numbered steps at the top.

CHECKPOINT

10a. Describe the electrical activity of the cells of the SA node and explain how the SA node functions as the normal pacemaker.

10b. Using a line diagram, illustrate a myocardial action potential and the time course for myocardial contraction. Explain how the relationship between these two events prevents the heart from sustaining a contraction and how it normally prevents abnormal rhythms of electrical activity.

11a. Draw an ECG and label the waves. Indicate the electrical events in the heart that produce these waves.

11b. Draw a figure that shows the relationship between ECG waves and the heart sounds. Explain this relationship.

11c. Describe the pathway of electrical conduction of the heart, starting with the SA node. How does damage to the AV node affect this conduction pathway and the ECG?

13.6 BLOOD VESSELS

The thick muscle layer of the arteries allows them to transport blood ejected from the heart under high pressure. The thinner muscle layer of veins allows them to distend when an increased amount of blood enters them, and their one-way valves ensure that blood flows back to the heart. Capillaries facilitate the rapid exchange of materials between the blood and interstitial fluid.

LEARNING OUTCOMES

After studying this section, you should be able to:

12. Compare the structure and function of arteries and veins, and the significance of the skeletal muscle pumps.

13. Describe the structures and functions of different types of capillaries.

Blood vessels form a tubular network throughout the body that permits blood to flow from the heart to all the living cells of the body and then back to the heart. Blood leaving the heart passes through vessels of progressively smaller diameters, referred to as *arteries, arterioles,* and *capillaries.* Capillaries are microscopic vessels that join the arterial flow to the venous flow. Blood returning to the heart from the capillaries passes through vessels of progressively larger diameters, called *venules* and *veins.*

The walls of arteries and veins are composed of three coats, or "tunics." The outermost layer is the **tunica externa,** the middle layer is the **tunica media,** and the inner layer is the **tunica interna.** The tunica externa is composed of connective tissue, whereas the tunica media is composed primarily of smooth muscle. The tunica interna consists of three parts: (1) an innermost simple squamous epithelium, the *endothelium,* which lines the lumina of all blood vessels; (2) the basement membrane (a layer of glycoproteins) overlying some connective tissue fibers; and (3) a layer of elastic fibers, or *elastin,* forming an *internal elastic lamina.*

Although arteries and veins have the same basic structure (fig. 13.26), there are some significant differences between them. Arteries have more muscle for their diameters than do comparably sized veins. As a result, arteries appear more rounded in cross section, whereas veins are usually partially collapsed. In addition, many veins have valves, which are absent in arteries.

Arteries

In the aorta and other large arteries, there are numerous layers of elastin fibers between the smooth muscle cells of the tunica media. These large **elastic arteries** expand when the pressure of the blood rises as a result of the ventricles' contraction; they recoil like a stretched rubber band when the blood pressure falls during relaxation of the ventricles. This elastic recoil drives the blood during the diastolic phase—the longest phase

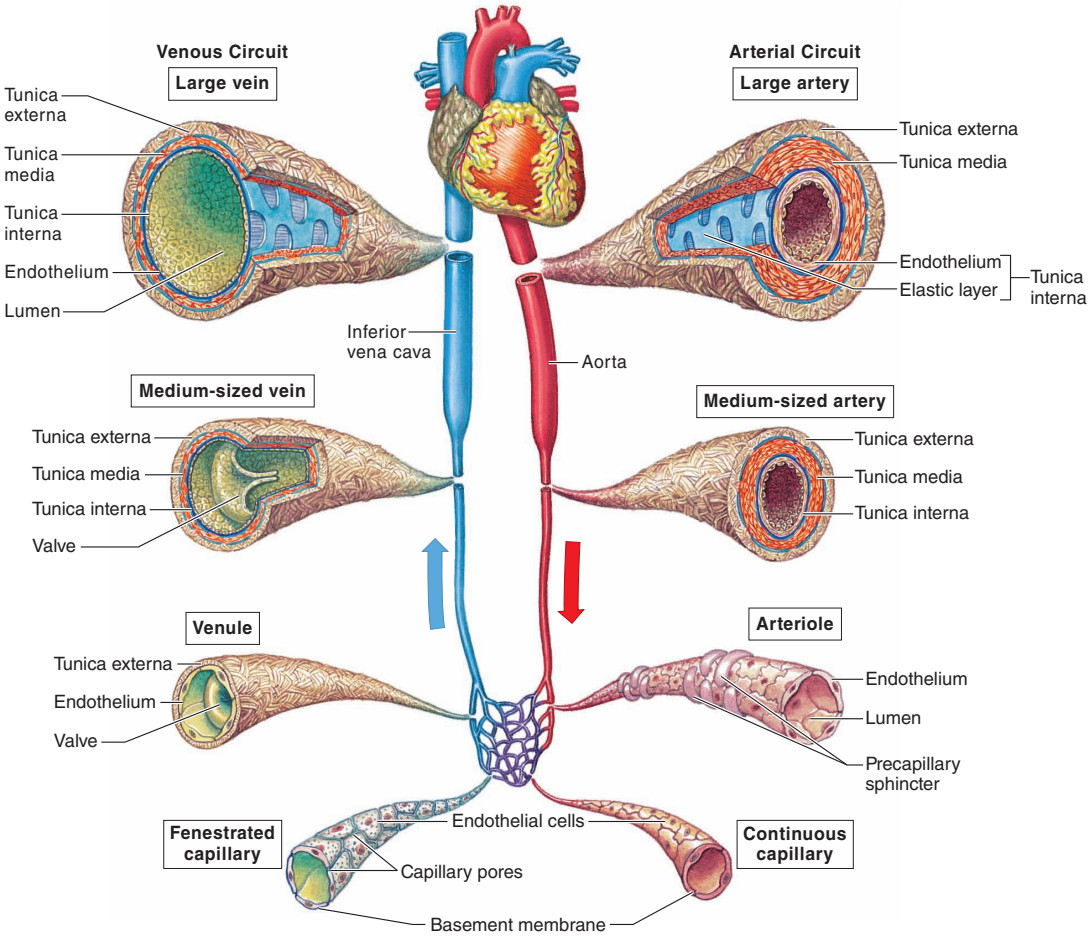


Figure 13.26 **The structure of blood vessels.** Notice the relative thickness and composition of the tunicas (layers) in comparable arteries and veins. AP|R

of the cardiac cycle—when the heart is resting and not providing a driving pressure.

The small arteries and arterioles are less elastic than the larger arteries and have a thicker layer of smooth muscle for their diameters. Unlike the larger elastic arteries, therefore, the diameter of the smaller **muscular arteries** changes only slightly as the pressure of the blood rises and falls during the heart's pumping activity. Because arterioles and small muscular arteries have narrow lumina, they provide the greatest resistance to blood flow through the arterial system.

Small muscular arteries that are 100 μm or less in diameter branch to form smaller **arterioles** (20 to 30 μm in diameter). In some tissues, blood from the arterioles can enter the venules directly through *arteriovenous anastomoses.* In most cases, however, blood from arterioles passes into capillaries (fig. 13.27). Capillaries are the narrowest of blood vessels (7 to 10 μm in diameter). They serve as the "business end" of the circulatory system, where gases and nutrients are exchanged between the blood and the tissues.

Resistance to blood flow is increased by *vasoconstriction* of arterioles (by contraction of their smooth muscle layer), which

CLINICAL APPLICATION

An **aneurism** is a balloon-like swelling in an artery or in a weakened ventricular wall. It most commonly occurs in the aorta—either as a *thoracic aortic aneurism* or an *abdominal aortic aneurism,* but can occur in cerebral and other arteries. A *dissected aorta* is a tear in the wall of the aortic aneurism, which may be detected and corrected before it completely bursts. Aneurisms may result from congenital causes and atherosclerosis (section 13.7), but conditions such as hypertension and diabetes can increase the risk.

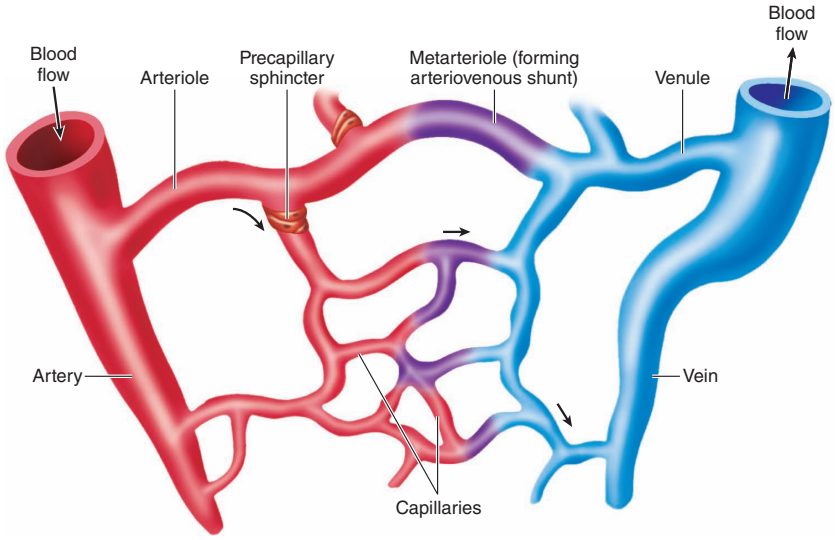


Figure 13.27 **The microcirculation.** Metarterioles (arteriovenous anastomoses) provide a path of least resistance between arterioles and venules. Precapillary sphincter muscles regulate the flow of blood through the capillaries.

decreases the blood flow downstream in the capillaries. Conversely, *vasodilation* of arterioles (by relaxation of the smooth muscle layer) decreases the resistance and thus increases the flow through the arterioles to the capillaries. This topic is discussed in more detail in chapter 14, section 14.3. There is evidence of gap junctions between the cells of the arteriole wall in both the endothelial and smooth muscle layers. The vasoconstrictor effect of norepinephrine and the vasodilator effect of acetylcholine may be propagated for some distance along the arteriole wall by transmissions of depolarization and hyperpolarizations, respectively, through gap junctions in the vascular smooth muscle.

Capillaries

The arterial system branches extensively (table 13.8) to deliver blood to over 40 billion capillaries in the body. The number of capillary branches is so great that scarcely any cell in the body is more than 60 to 80 μm away from a blood capillary. The tiny capillaries provide a total surface area of 1,000 square miles for exchanges between blood and tissue fluid.

The amount of blood flowing through a particular capillary bed depends primarily on the resistance to blood flow in the small arteries and arterioles that supply blood to that capillary bed. Vasoconstriction in these vessels thus decreases blood flow to the capillary bed, whereas vasodilation increases blood flow. The relatively high resistance in the small arteries and arterioles in resting skeletal muscles, for example, reduces capillary blood flow to only about 5% to 10% of its maximum capacity. In some organs (such as the intestine), blood flow may also be regulated by circular muscle bands called *precapillary sphincters* at the origin of the capillaries (fig. 13.27).

Unlike the vessels of the arterial and venous systems, the walls of capillaries are composed of just one cell layer—a simple squamous epithelium, or endothelium (see fig. 13.28). The absence of smooth muscle and connective tissue layers permits a more rapid exchange of materials between the blood and the tissues.

Types of Capillaries

Different organs have different types of capillaries, distinguished by significant differences in structure. In terms of their endothelial lining, these capillary types include those that are *continuous,* those that are *fenestrated,* and those that are *discontinuous.*

Continuous capillaries are those in which adjacent endothelial cells are closely joined together. These are found in muscles, lungs, adipose tissue, and the central nervous system. The lack of intercellular channels in continuous capillaries in the CNS contributes to the blood-brain barrier (chapter 7, section 7.1). Continuous capillaries in other organs have narrow intercellular channels (from 40 to 45 Å in width) that permit the passage of molecules other than protein between the capillary blood and tissue fluid (fig. 13.28).

Examination of endothelial cells with an electron microscope has revealed the presence of pinocytotic vesicles (fig. 13.28), which suggests that the intracellular transport of material may occur across the capillary walls. This type of transport appears to be the only mechanism of capillary exchange available within the central nervous system and may account, in part, for the selective nature of the blood-brain barrier.

Fenestrated capillaries occur in the kidneys, endocrine glands, and intestines. These capillaries are characterized by wide intercellular pores (800 to 1,000 Å) that are covered by a layer of

Table 13.8 | Characteristics of the Vascular Supply to the Mesenteries in a Dog*

Kind of Vessels	Diameter (mm)	Number	Total Cross-Sectional Area (cm^2)	Length (cm)	Total Volume (cm^3)
Aorta	10	1	0.8	40	30
Large arteries	3	40	3.0	20	60
Main artery branches	1	600	5.0	10	50
Terminal branches	.06	1,800	5.0	1	25
Arterioles	0.02	40,000,000	125	0.2	25
Capillaries	0.008	1,200,000,000	600	0.1	60
Venules	0.03	80,000,000	570	0.2	110
Terminal veins	1.5	1,800	30	1	30
Main venous branches	2.4	600	27	10	270
Large veins	6.0	40	11	20	220
Vena cava	12.5	1	1.2	40	50
					930

**Note:* The pattern of vascular supply is similar in dogs and humans.
Source: Animal Physiology, 4th ed. by Gordon et al., © 1982. Adapted by permission of Prentice-Hall, Inc., Upper Saddle River, NJ.

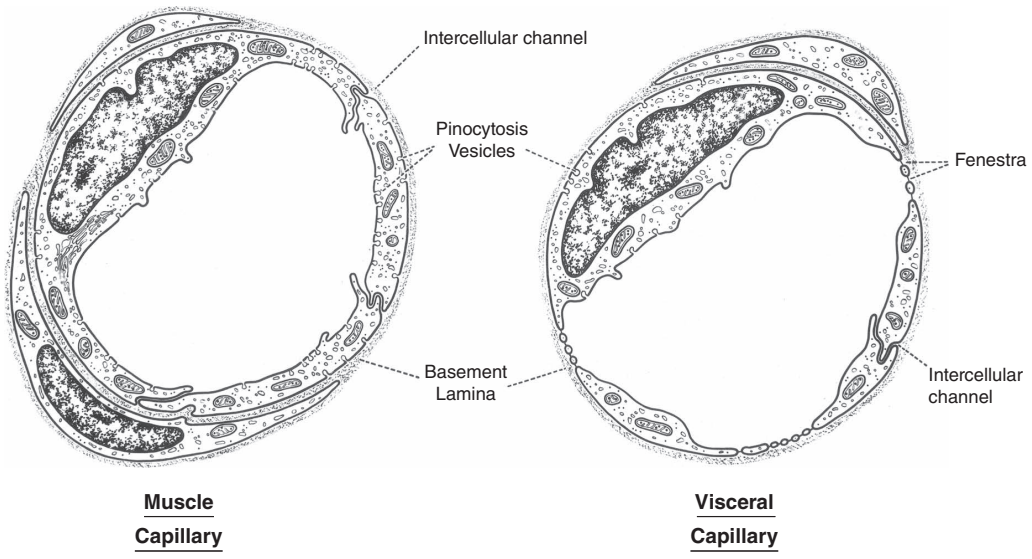


Figure 13.28 Illustration of the structure of a muscle and visceral capillary as seen in electron micrographs. Intercellular channels and fenestrae allow passage of material between capillary endothelial cells, while pinocytotic vesicles transport material through the cell cytoplasm. AP|R

mucoprotein, which serves as a basement membrane over the capillary endothelium. This mucoprotein layer restricts the passage of certain molecules (particularly proteins) that might otherwise be able to pass through the large capillary pores. **Discontinuous capillaries** are found in the bone marrow, liver, and spleen. The distance between endothelial cells is so great that these capillaries look like little cavities (*sinusoids*) in the organ.

In a tissue that is hypoxic (has inadequate oxygen), new capillary networks are stimulated to grow. This growth is promoted by *vascular endothelial growth factor* (*VEGF,* discussed in the

next Clinical Application Box). Capillary growth may additionally be promoted by *adenosine* (derived from AMP), which also stimulates vasodilation of arterioles and thereby increases blood flow to the hypoxic tissue. These changes result in a greater delivery of oxygen-carrying blood to the tissue.

CLINICAL APPLICATION

Angiogenesis refers to the formation of new blood vessels from preexisting vessels, usually venules. This is needed because cells must be within 100 μm of a capillary to survive. Angiogenesis is required for the growth of *neoplasms* (tumors), and is involved in the development of *neovascular age-related macular degeneration,* also known as *wet macular degeneration* (chapter 10, section 10.7). Inhibition of angiogenesis would thus aid the treatment of these conditions.

Two paracrine regulators, **fibroblast growth factor (FGF)** and **vascular endothelial growth factor (VEGF),** bind to tyrosine kinase receptors (chapter 11; see fig. 11.11) to stimulate angiogenesis. The FDA has approved the use of a monoclonal antibody (chapter 15, section 15.4) preparation called *bevacizumab* (*Avastin*), which binds to and inactivates VEGF, for the treatments of cancers of the colon, lung, breast, cervix, ovaries, and kidneys. *Ranibizumab* (*Lucentis*), another monoclonal antibody preparation against VEGF, can be injected into the vitreous humor of the eye to inhibit the angiogenesis of wet macular degeneration.

Veins

Most of the total blood volume is contained in the venous system. Unlike arteries, which provide resistance to the flow of blood from the heart, veins are able to expand as they accumulate additional amounts of blood. The average pressure in the veins is only 2 mmHg, compared to a much higher average arterial pressure of about 100 mmHg. These values, expressed in millimeters of mercury, represent the hydrostatic pressure that the blood exerts on the walls of the vessels.

The low venous pressure is insufficient to return blood to the heart, particularly from the lower limbs. Veins, however, pass between skeletal muscle groups that provide a massaging action as they contract (fig. 13.29). As the veins are squeezed by contracting skeletal muscles, a one-way flow of blood to the heart is ensured by the presence of **venous valves.** The ability of these valves to prevent the flow of blood away from the heart was demonstrated in the seventeenth century by William Harvey (fig. 13.30). After applying a tourniquet to a subject's arm, Harvey found that he could push the blood in a bulging vein toward the heart, but not in the reverse direction.

The effect of the massaging action of skeletal muscles on venous blood flow is often described as the **skeletal muscle pump.** The rate of venous return to the heart is dependent, in large part, on the action of skeletal muscle pumps. When these pumps are less active, as when a person stands still or is bedridden, blood accumulates in the veins and causes them to bulge. When a person is more active, blood returns to the heart at a faster rate and less is left in the venous system.

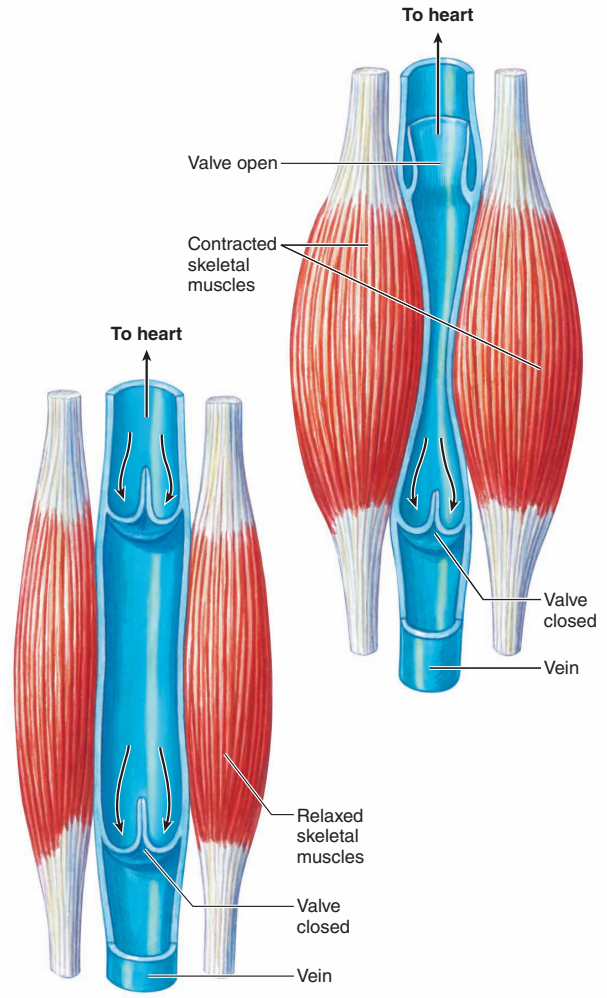


Figure 13.29 **The action of the oneway venous valves.** Contraction of skeletal muscles helps to pump blood toward the heart, but the flow of blood away from the heart is prevented by closure of the venous valves.

Action of the skeletal muscle pumps aids the return of venous blood from the lower limbs to the large abdominal veins. Movement of venous blood from abdominal to thoracic veins, however, is aided by an additional mechanism—breathing. When a person inhales, the diaphragm—a muscular sheet separating the thoracic and abdominal cavities—contracts. Contraction of the dome-shaped diaphragm causes it to flatten and descend inferiorly into the abdomen. This has the dual effect of increasing the pressure in the abdomen, thus squeezing the abdominal veins,

CLINICAL APPLICATION

Varicose veins are enlarged surface veins, generally in the lower limbs, which occur when venous congestion stretches the veins to the point that the venous valves no longer close effectively. Genetic susceptibility, occupations that require long periods of standing, obesity, age, and pregnancy (due to compression of abdominal veins by the fetus) are risk factors. Walking can reduce venous congestion, as can compression stockings and leg elevation; in bedridden patients, flexing and extending the ankle joints activates the soleus muscle pump to help move blood from the legs back to the heart. Surgical treatments of varicose veins include *sclerotherapy* (where chemicals are injected into the veins to scar them), laser therapy (using lasers to destroy the veins), ligation and stripping (tying off and removing the veins), and other techniques.

Inadequate venous flow in a bedridden patient increases the risk of **deep vein thrombosis,** a dangerous condition that can lead to a **venous thromboembolism** (a traveling blood clot). Walking around as soon as possible after a surgery reduces the risk, as do the use of compression stockings and devices that compress the leg. Anticoagulant drugs or thrombolytic agents (discussed in section 13.2) may sometimes be necessary to prevent or treat a thromboembolism so that it doesn't result in a potentially fatal pulmonary embolism.

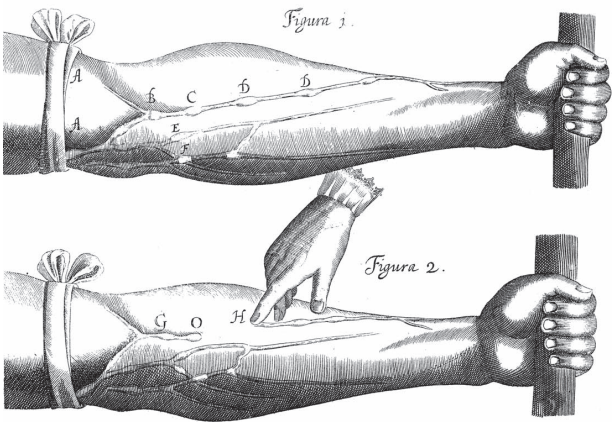


Figure 13.30 **A demonstration of venous valves by William Harvey.** By blocking venous drainage with a tourniquet, Harvey showed that the blood in the bulged vein was not permitted to move away from the heart, thereby demonstrating the action of venous valves. After William Harvey, *On the Motion of the Heart and Blood in Animals,* 1628.

and decreasing the pressure in the thoracic cavity. The pressure difference in the veins created by this inspiratory movement of the diaphragm forces blood into the thoracic veins that return the venous blood to the heart.

CHECKPOINT

12a. Describe the basic structural pattern of arteries and veins. Explain how arteries and veins differ in structure and how these differences contribute to their differences in function.

12b. Describe the functional significance of the skeletal muscle pump and illustrate the action of venous valves.

13. Explain the functions of capillaries and describe the structural differences between capillaries in different organs.

13.7 ATHEROSCLEROSIS AND CARDIAC ARRHYTHMIAS

Atherosclerosis is a disease process that can lead to obstruction of coronary blood flow. As a result, the electrical properties of the heart, and the heart's ability to function as a pump, may be seriously compromised. Abnormal cardiac rhythms, or arrhythmias, can be detected by the abnormal electrocardiogram patterns they produce.

LEARNING OUTCOMES

After studying this section, you should be able to:

14. Explain the causes and dangers of atherosclerosis.

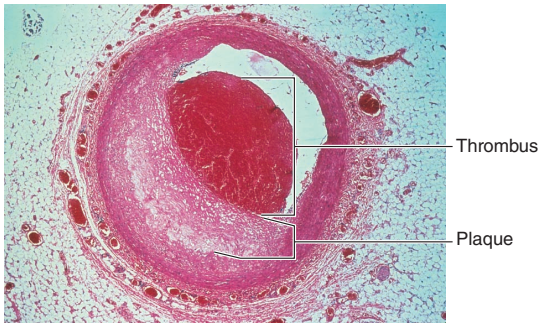
15. Explain the cause and significance of angina pectoris.

16. Describe how different arrhythmias affect the ECG.

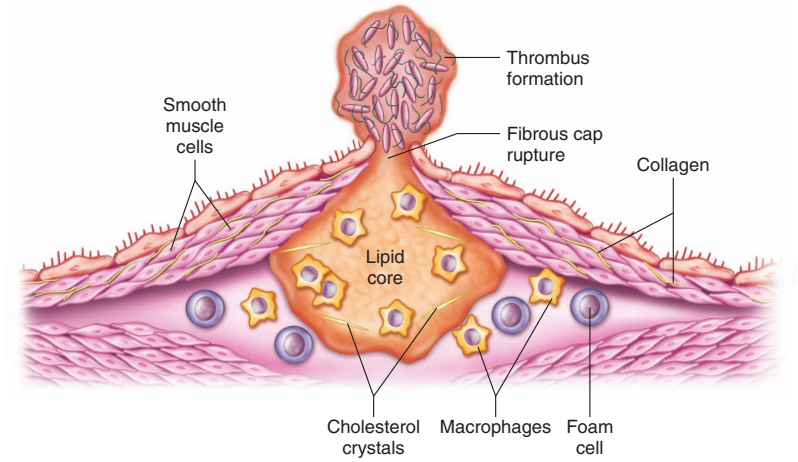
Atherosclerosis

Atherosclerosis is the most common form of arteriosclerosis (hardening of the arteries) and, through its contribution to heart disease and stroke, is responsible for about 50% of the deaths in the United States, Europe, and Japan. In atherosclerosis, localized **plaques,** or *atheromas,* protrude into the lumen of the artery and thus reduce blood flow. The atheromas additionally serve as sites for *thrombus* (blood clot) formation, which can further occlude the blood supply to an organ (fig. 13.31).

It is currently believed that the process of atherosclerosis begins as a result of damage, or "insult," to the endothelium. Such insults are produced by smoking, hypertension (high blood pressure), high blood cholesterol, and diabetes. The first anatomically recognized change is the appearance of *fatty streaks,* which are gray-white areas that protrude into the lumen of arteries, particularly at arterial branch points. These are aggregations of lipid-filled macrophages and lymphocytes within the tunica interna. In the intermediate stage, the area contains layers of macrophages and smooth muscle



(a)



(b)

Figure 13.31 Atherosclerosis. (*a*) A photograph of the lumen (cavity) of a human coronary artery that is partially occluded by an atherosclerotic plaque and a thrombus. (*b*) A diagram of the structure of an atherosclerotic plaque that has ruptured and induced the formation of a thrombus.

cells. The more advanced lesions, called *fibrous plaques,* consist of a cap of connective tissue with smooth muscle cells over accumulated lipid and debris, macrophages that have been derived from monocytes (chapter 15), and lymphocytes. The fibrous cap of an advanced atherosclerotic lesion becomes thin and prone to rupture, promoting the formation of a thrombus.

The disease process may be instigated by damage to the endothelium, but its progression is promoted by inflammation that is stimulated by a wide variety of cytokines and other paracrine regulators secreted by the endothelium and by the other participating cells, including platelets, macrophages, and lymphocytes. Some of these regulators attract monocytes and lymphocytes to the damaged endothelium and cause them to penetrate into the tunica interna. The monocytes then become macrophages, engulf lipids, and take on the appearance of *foam cells.* Smooth muscle cells change from a contractile state to a "synthetic" state, in which they produce and secrete connective tissue matrix proteins. However, cytokines released during inflammation can reduce smooth muscle collagen synthesis and stimulate the production of collagenase enzymes in macrophages, weakening the plaque's collagen cap. When it ruptures and exposes the underlying tissue to the blood, thrombi (clots) form.

Endothelial cells normally prevent the progression just described by presenting a physical barrier to the penetration of monocytes and lymphocytes and by producing paracrine regulators such as nitric oxide. The vasodilator action of nitric oxide helps to counter the vasoconstrictor effects of another paracrine regulator, endothelin-1, which is increased in atherosclerosis. Hypertension, smoking, and high blood cholesterol interfere with the protective function of the endothelium, whereas regular aerobic exercise improves it.

Cholesterol and Plasma Lipoproteins

There is considerable evidence that high blood cholesterol is associated with an increased risk of atherosclerosis. High blood cholesterol can be produced by a diet rich in cholesterol and saturated fat, or it may be the result of an inherited condition known as *familial hypercholesteremia.* This condition is inherited as a single dominant gene; individuals who inherit two of these genes have extremely high cholesterol concentrations (regardless of diet) and usually suffer heart attacks during childhood.

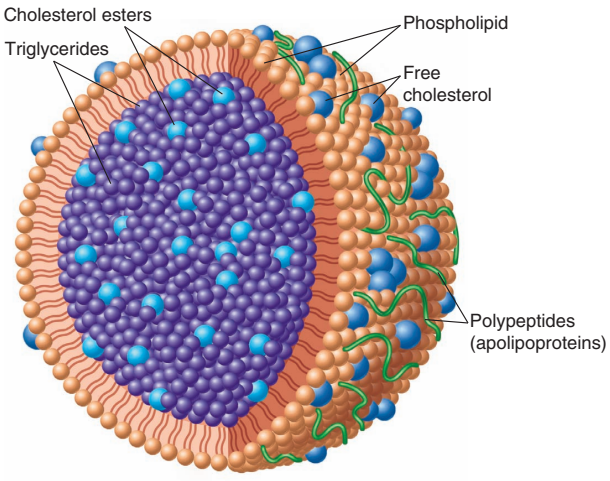


Figure 13.32 **Structure of a lipoprotein.** There is a core of nonpolar triglycerides and cholesterol esters coated by proteins (apolipoproteins), phospholipids, and some free cholesterol.

Lipids, including cholesterol, are carried in the blood attached to protein carriers (fig. 13.32; also see chapter 18, table 18.8). Cholesterol is carried to the arteries by plasma proteins called **low-density lipoproteins (LDLs).** LDLs are derived from *very low-density lipoproteins (VLDLs),* which are small, protein-coated droplets produced by the liver and composed of cholesterol, triglycerides, free fatty acids, and phospolipids. After enzymes in various organs remove most of the triglycerides, the VLDLs become LDLs that transport cholesterol to the organs.

Cells in different organs contain receptors for the proteins (called *apolipoproteins*) in LDLs. When these apolipoproteins bind to their receptors, the cell engulfs the LDL particles by receptor-mediated endocytosis (chapter 3; see fig. 3.4). Most LDL particles are removed in this way by the liver. However, the uptake and accumulation of a particular LDL protein, *apolipoprotein B,* into the subendothelial connective tissue of an artery is believed to initiate the formation of an atherosclerotic plaque. Apolipoprotein B, enhanced by oxidation (discussed shortly), acts on the endothelium to promote the entry of monocytes into the lesion and the conversion of the monocytes into macrophages. Macrophages ingest these lipoproteins and become foam cells, which promote the progression of the disease.

People who eat a diet high in cholesterol and saturated fat, and people with familial hypercholesteremia, have a high blood LDL concentration because their livers have a low number of LDL receptors. With fewer LDL receptors, the liver is less able to remove the LDL from the blood and more LDL is available to enter the endothelial cells of arteries.

High-density lipoprotein (HDL), in contrast, offers protection against atherosclerosis by carrying cholesterol away from the arterial wall. In the development of atherosclerosis, monocytes migrate through the arterial endothelium to the intima, where they become macrophages that are able to engulf oxidized LDLs (discussed shortly). The cholesterol-engorged macrophages are known as foam cells and play an important role in the development of the atherosclerotic lesion. This progress is retarded by HDL, which accepts cholesterol from the foam cells and carries it through the blood to the liver for metabolism. HDL levels are largely determined by genetics, but it is known that HDL levels are higher, and the risk of atherosclerosis is lower, in women (prior to menopause) than in men, and in people who exercise regularly. HDL levels are higher in marathon runners than in joggers, and are higher in joggers than in sedentary people. Drugs that help raise HDL levels include the *statins* (such as Lipitor), the *fibrates,* and high doses of the vitamin *niacin.*

CLINICAL APPLICATION

Statins are drugs that help lower LDL-cholesterol concentrations to reduce the risk of atherosclerosis. Statins are inhibitors of *HMG-coenzyme A reductase,* the enzyme that catalyzes the rate-limiting step in cholesterol synthesis. As a result, the statins reduce the ability of liver cells to produce cholesterol. The lowered intracellular cholesterol then stimulates the production of more LDL receptors in the plasma membrane, allowing the liver cells to engulf more LDL-cholesterol from the blood. This lowers the blood LDL-cholesterol concentration so that less will enter the endothelial cells of the arteries. Statins also have other beneficial effects: they slightly increase the HDL level, and they reduce inflammation, which promotes atherosclerosis as described next.

Inflammation and Atherosclerosis

Notice the important roles played by cells of the immune system—particularly monocytes and lymphocytes—in the development and progression of atherosclerosis. Atherosclerosis is now believed to be an inflammatory disease to a significant degree. This is emphasized by the recent evidence that measurement of blood **C-reactive protein,** a marker of inflammation, is actually a stronger predictor of atherosclerotic heart disease than the blood LDL cholesterol level.

The inflammatory process may be instigated by oxidative damage to the artery wall. When endothelial cells engulf LDL, they oxidize it to a product called *oxidized LDL.* Evidence suggests that oxidized LDL contributes to endothelial cell injury, migration of monocytes and lymphocytes into the tunica interna, conversion of monocytes into macrophages, and other events that occur in the progression of atherosclerosis.

Because oxidized LDL seems to be so important in the progression of atherosclerosis, it would appear that antioxidant compounds could be used to treat this condition or help to prevent it. The antioxidant drug *probucol,* as well as *vitamin C, vitamin E,* and *beta-carotene,* which are antioxidants (chapter 19, section 19.1), have decreased the formation of oxidized LDL *in vitro* but have had only limited success so far in treating atherosclerosis.

FITNESS APPLICATION

Exercise and a proper diet contribute to cardiovascular health. The *American Heart Association* (*AHA*) recommends that people exercise moderately for at least 30 minutes on most days, and even better, engage in 40 minutes of aerobic exercise 3 to 4 times a week. People should eat a diet that encompasses all food groups and contains low amounts of high-calorie/low-nutrient items. To achieve the goal of lowering blood cholesterol, saturated fat and trans fats should be limited to 5% to 6% of total calories. By contrast, 40% to 50% of the calories in many typical fast-food meals are derived from fat. The AHA recommends that people eat fish at least twice a week. One of the benefits of this is that fish—especially oily fish such as trout, salmon, mackerel, herring, and sardines—are rich in omega-3 (or n-3) fatty acids, which appear to provide some protection against cardiovascular disease. Walnuts, soybeans, and rapeseed (canola) oil are also rich in EPA and DHA, the n-3 fatty acids found in fish (chapter 19, section 19.1). However, the singly most effective action that smokers can take to lower their risk of atherosclerosis is to stop smoking.

Ischemic Heart Disease

A tissue is said to be **ischemic** when its oxygen supply is deficient because of inadequate blood flow. The most common cause of myocardial ischemia is atherosclerosis of the coronary arteries. The adequacy of blood flow is relative—it depends on the tissue's metabolic requirements for oxygen. An obstruction in a coronary artery, for example, may allow sufficient coronary blood flow at rest but not when the heart is stressed by exercise or emotional conditions. In these cases, the increased activity of the sympathoadrenal system causes the heart rate and blood pressure to rise, increasing the work of the heart and raising its oxygen requirements. Recent evidence also suggests that mental stress can cause constriction of atherosclerotic coronary arteries, leading to ischemia of the heart muscle. The vasoconstriction is believed to result from abnormal function of a damaged endothelium, which normally prevents constriction (through secretion of paracrine regulators) in response to mental stress. The control of vasoconstriction and vasodilation is discussed more fully in chapter 14, section 14.3.

Myocardial ischemia is associated with increased concentrations of blood lactic acid produced by anaerobic metabolism in the ischemic tissue. This condition often causes substernal pain, which may also be referred to the left shoulder and arm, as well as to other areas. This *referred pain* (chapter 10, section 10.2) is called **angina pectoris.** People with angina frequently take nitroglycerin or related drugs that help to relieve the ischemia and pain. These drugs are effective because they produce vasodilation, which improves circulation to the heart and decreases the work that the ventricles must perform to eject blood into the arteries.

Myocardial cells are adapted for aerobic respiration and cannot metabolize anaerobically for more than a few minutes. If ischemia and anaerobic metabolism are prolonged, *necrosis* (cellular death) may occur in the areas most deprived of oxygen. A sudden, irreversible injury of this kind is called a **myocardial infarction,** or **MI.** Often called "heart attack" (though this imprecise term may also refer to other conditions), myocardial infarction is the leading cause of death in the Western world.

The area of dead cells is not replaced because human myocardial cells have only a very limited capacity to divide. Instead, fibroblasts produce noncontractile scar tissue, which forms the infarct. The area of infarcted tissue is usually relatively small if the person is hospitalized and treated within a few hours after the onset of symptoms. However, after the heart becomes re-perfused with blood (so that it receives sufficient oxygen to resume aerobic respiration), larger numbers of myocardial cells may die. This *reperfusion injury* may be a greater threat than the initial event and is caused by apoptosis (chapter 3, section 3.5) due to the accumulation of Ca^{2+} and the production of superoxide free radicals (chapters 5 and 19) by mitochondria. Apoptosis of myocardial cells surrounding the initial lesion can greatly increase the size of the infarct and weaken the wall of the ventricle.

The infarct may thereby cause the ventricular wall to thin and distend under pressure. In recent years, scientists have investigated a variety of potential stem cell therapies for myocardial infarction. These include the use of stem cells from the bone marrow (which can secrete cytokines that promote healing); the possible differentiation of embryonic stem cells and induced pluripotent stem cells (chapter 20, section 20.6) into myocardial cells; and the transformation of fibroblasts (perhaps within an infarct) into myocardial cells. Another approach has been to stimulate myocardial cell division, which is normally too limited to repair the infarct. This has been achieved in rodent hearts , but more research in these strategies, particularly involving human hearts, is needed before they can become medical therapies.

Acute chest pain caused by myocardial ischemia is a common reason that patients seek emergency medical care. Myocardial ischemia may be detected by changes in the S-T segment of the electrocardiogram (fig. 13.33). Sustained occlusion of a coronary artery that produces a myocardial infarction (MI) is accompanied by an elevation of the S-T segment of the ECG.

Chest pain from myocardial ischemia can indicate the presence of myocardial infarction (MI), and early detection of an MI is very important. Currently, the diagnosis of an MI is based mainly on rising blood troponin levels, primarily troponin I. Troponin is a regulatory protein in muscles (chapter 12, section 12.2) released into the blood from damaged myocardial cells. Tests for enzymes released into the blood from damaged myocardial cells are also useful. These include tests for creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). Once an MI has been detected and the patient is stabilized, the reason for the myocardial ischemia can be addressed. The detection and treatment of coronary thrombosis is discussed with the coronary circulation in chapter 14, section 14.4 (see fig. 14.18).

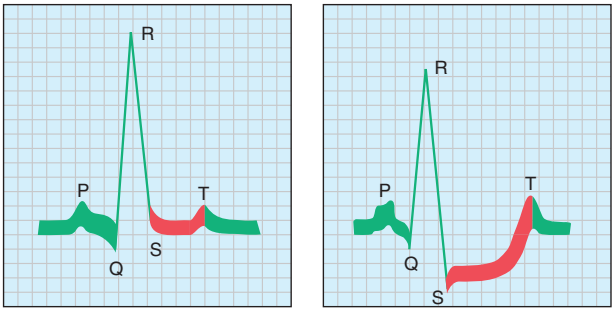


Figure 13.33 **Depression of the ST segment as a result of myocardial ischemia.** This is but one of many ECG changes that alert trained personnel to the existence of heart problems.

CLINICAL APPLICATION

Cerebrovascular accident, also called **stroke,** is the third leading cause of death in the United States and the second worldwide. There are two categories of stroke: *ischemic stroke,* caused by blockage of a cerebral artery by a thrombus and usually the result of atherosclerosis; and *hemorrhagic stroke,* caused by bleeding from a cerebral artery, often because of an aneurism. Hypertension is the major risk factor for stroke; others include atrial fibrillation, high blood cholesterol, and diabetes. Ischemic stroke can be treated with anticoagulant and thrombolytic drugs, but these are most effective if delivered soon after the ischemic injury. This is because of *excitotoxicity* (chapter 7, section 7.7), a process whereby neurons die as a result of the ischemia-induced impairment in the removal of glutamate from the synaptic clefts. This results in excessive inflow of Ca^{2+} through the NMDA receptors, causing neuron death. There is presently no effective way to prevent excitotoxicity and its consequences.

Arrhythmias Detected by the Electrocardiograph

Arrhythmias, or abnormal heart rhythms, can be detected and described by the abnormal ECG tracings they produce. Although proper clinical interpretation of electrocardiograms requires information not covered in this chapter, some knowledge of abnormal rhythms is interesting in itself and is useful in gaining an understanding of normal physiology.

A heartbeat occurs whenever a normal QRS complex is seen, and the ECG chart paper moves at a known speed, so the cardiac rate (beats per minute) can be easily obtained from an ECG recording. A cardiac rate slower than 60 beats per minute indicates **bradycardia;** a rate faster than 100 beats per minute is described as **tachycardia** (fig. 13.34).

Both bradycardia and tachycardia can occur normally. Endurance-trained athletes, for example, often have heart rates ranging from 40 to 60 beats per minute. This *athlete's bradycardia* occurs as a result of higher levels of parasympathetic inhibition of the SA node and is a beneficial adaptation. Activation of the sympathetic division of the ANS during exercise or emergencies ("fight or flight") causes a normal tachycardia.

Abnormal tachycardia occurs if the heart rate increases when the person is at rest. This may be due to abnormally fast pacing by the atria (caused, for example, by drugs), or to the development of abnormally fast *ectopic pacemakers*—cells located outside the SA node that assume a pacemaker function. This abnormal atrial tachycardia thus differs from normal, or *sinus,* (SA node) *tachycardia. Ventricular tachycardia* results when abnormally fast ectopic pacemakers in the ventricles cause them to beat rapidly and independently of the atria. This is very dangerous because it can quickly degenerate into a lethal condition known as *ventricular fibrillation.*

Flutter and Fibrillation

Extremely rapid rates of electrical excitation and contraction of either the atria or the ventricles may produce flutter or

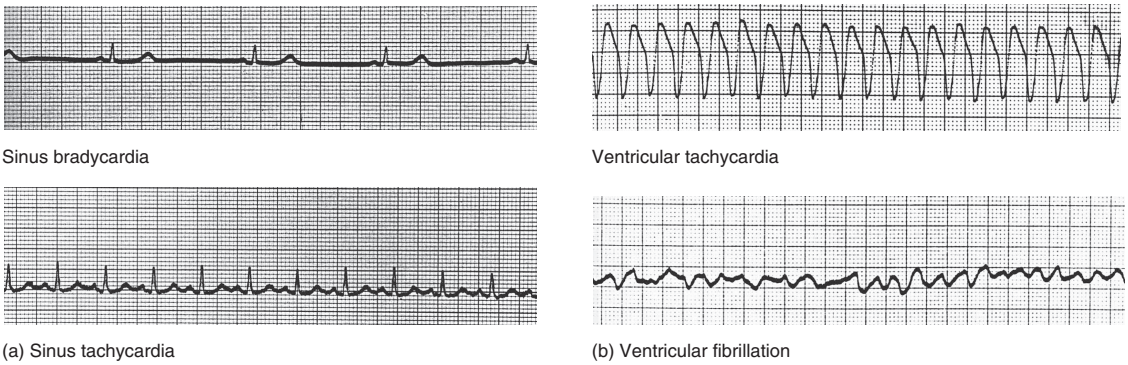


Figure 13.34 **Some arrhythmias detected by the ECG.** In (*a*) the heartbeat is paced by the normal pacemaker—the SA node (hence the name *sinus rhythm*). This can be abnormally slow (bradycardia—42 beats per minute in this example) or fast (tachycardia—125 beats per minute in this example). Compare the pattern of tachycardia in (*a*) with the tachycardia in (*b*). Ventricular tachycardia is produced by an ectopic pacemaker in the ventricles. This dangerous condition can quickly lead to ventricular fibrillation, also shown in (*b*).

fibrillation. In **flutter,** the contractions are very rapid (200 to 300 per minute) but are coordinated. In **fibrillation,** contractions of different groups of myocardial cells occur at different times, so that a coordinated pumping action of the chambers is impossible.

Atrial flutter usually degenerates quickly into *atrial fibrillation,* where the disorganized production of impulses occurs very rapidly (about 600 times per minute) and contraction of the atria is ineffectual. The AV node doesn't respond to all of those impulses, but enough impulses still get through to stimulate the ventricles to beat at a rapid rate (up to 150–180 beats per minute). Since the ventricles fill to about 80% of their end-diastolic volume before even normal atrial contraction, atrial fibrillation only reduces the cardiac output by about 15%. People with atrial fibrillation can live for many years, although this condition is associated with increased mortality due to stroke and heart failure. It has been estimated that 20% to 25% of all strokes may result from thrombi promoted by atrial fibrillation.

Atrial fibrillation is the most common heart arrhythmia, and is usually treated with antithrombotic and antiarrhythmia drugs. Another common treatment is catheter ablation, which destroys atrial tissue (by heating the tissue around the pulmonary veins) that may contribute to the fibrillation.

By contrast, people with *ventricular fibrillation* (fig. 13.34) can live for only a few minutes unless this is extended by cardiopulmonary resuscitation (CPR) techniques or the fibrillation is ended by electrical defibrillation (discussed shortly). Death is caused by the inability of the fibrillating ventricles to pump blood and thus deliver needed oxygen to the heart and brain.

Fibrillation is caused by a continuous recycling of electrical waves, known as **circus rhythms,** through the myocardium. The recycling of action potentials is normally prevented by the entire myocardium entering a refractory period as a single unit, owing to the rapid transmission of the action potential among the myocardial cells by their gap junctions and to the long duration of the action potential provided by its plateau phase (see fig. 13.21). However, if some cells emerge from their refractory periods before others, an action potential can be continuously regenerated and conducted. Recycling of electrical waves along continuously changing pathways produces uncoordinated contraction and an impotent pumping action.

Circus rhythms are thus produced whenever impulses can be conducted without interruption by nonrefractory tissue. This may occur when the conduction pathway is longer than normal, as in a dilated heart. It can also be produced by an electric shock delivered at the middle of the T wave, when different myocardial cells are in different stages of recovery from their refractory period. Finally, circus rhythms and fibrillation may be produced by damage to the myocardium, which slows the normal rate of impulse conduction.

Sudden death from cardiac arrhythmia usually progresses from ventricular tachycardia through ventricular fibrillation, culminating in *asystole* (the cessation of beating, with a straight-line ECG). Sudden death from cardiac arrhythmia is commonly a result of acute myocardial ischemia (insufficient blood flow to the heart muscle), most often due to atherosclerosis of the coronary arteries.

Fibrillation can sometimes be stopped by a strong electric shock delivered to the chest. This procedure is called **electrical defibrillation.** The electric shock depolarizes all of the myocardial cells at the same time, causing them all to enter a refractory state. Conduction of circus rhythms thus stops, and the SA node can begin to stimulate contraction in a normal fashion. This does not correct the initial problem that caused circus rhythms and fibrillation, but it does keep the person alive long enough to take other corrective measures.

A device known as an *implantable converter-defibrillator* is now available for high-risk patients. This device consists of a unit that is implanted into a subcutaneous pocket in the pectoral region, with a lead containing electrodes and a shocking coil that is threaded into the heart (usually the right ventricle). Sensors can detect when ventricular fibrillation occurs, and can distinguish between supraventricular and ventricular tachycardia (fig. 13.34). The coil can deliver defibrillating shocks if ventricular fibrillation is detected.

Clinical Investigation CLUES

The physician told Jessica that she had atrial fibrillation.

- What is atrial fibrillation, and how does it appear on an ECG?
- What is the major danger of atrial fibrillation, and how did Jessica's physician address this?

AV Node Block

The time interval between the beginning of atrial depolarization—indicated by the P wave—and the beginning of ventricular depolarization (as shown by the Q part of the QRS complex) is called the *P-R interval* (see fig. 13.22). In the normal heart, this time interval is 0.12 to 0.20 second in duration. Damage to the AV node causes slowing of impulse conduction and is reflected by changes in the P-R interval. This condition is known as *AV node block* (fig. 13.35).

CLINICAL APPLICATION

An **artificial pacemaker,** about the size of a locket, can be implanted under the skin below the clavicle. This is a battery-powered device with electrodes that are threaded into the heart through a vein using fluoroscopy for guidance, and used to correct for such arrhythmias as a blockage in conduction of the impulse in the AV node or bundle of His. There are many different types of implantable pacemakers; some stimulate just one chamber, and some stimulate both an atrium and a ventricle by delivering a low-voltage shock causing depolarization and contraction. Most sense if a heartbeat is delayed and stimulate the heart on demand to maintain a good cardiac rate, and some can even sense if a person is exercising and adjust the cardiac rate accordingly.

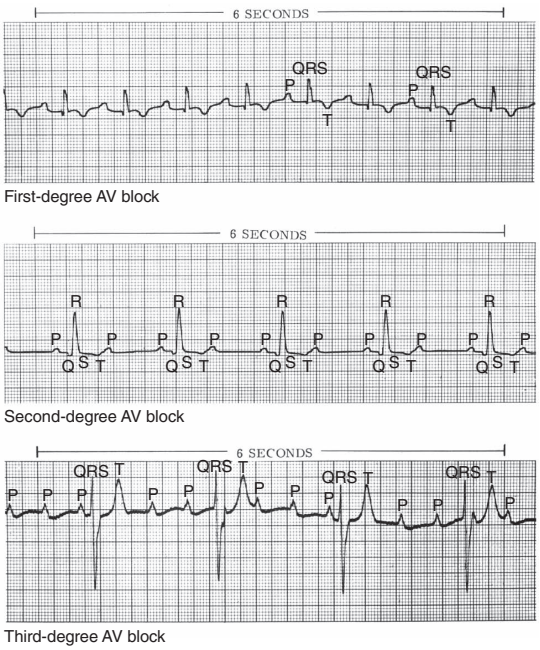


Figure 13.35 **Atrioventricular (AV) node block.** In first-degree block, the P-R interval is greater than 0.20 second (in the example here, the P-R interval is 0.26–0.28 second). In second-degree block, P waves are seen that are not accompanied by QRS waves. In this example, the atria are beating 90 times per minute (as represented by the P waves), while the ventricles are beating 50 times per minute (as represented by the QRS waves). In third-degree block, the ventricles are paced independently of the atria by an ectopic pacemaker. Ventricular depolarization (QRS) and repolarization (T) therefore have a variable position in the electrocardiogram relative to the P waves (atrial depolarization).

First-degree AV node block occurs when the rate of impulse conduction through the AV node (as reflected by the P-R interval) exceeds 0.20 second. **Second-degree AV node block** occurs when the AV node is damaged so severely that only one out of every two, three, or four atrial electrical waves can pass through to the ventricles. This is indicated in an ECG by the presence of P waves without associated QRS waves.

In **third-degree,** or **complete, AV node block,** none of the atrial waves can pass through the AV node to the ventricles. The atria are paced by the SA node (follow a normal "sinus rhythm"), but in complete AV node block a secondary pacemaker in the Purkinje fibers paces the ventricles. The SA node is the normal pacemaker because it has the fastest cycle of spontaneous depolarization, but in complete AV node block the action potentials from the atria cannot reach the Purkinje fibers to suppress their pacemaker activity. The pacemaker rate of the Purkinje fibers (generally about 20 to 40 beats per minute, depending on location) is abnormally slow, and the brady cardia that results is usually corrected by insertion of an artificial pacemaker.

CHECKPOINT

14. Explain how cholesterol is carried in the plasma and how the concentrations of cholesterol carriers are related to the risk for developing atherosclerosis.

15. Explain how angina pectoris is produced and discuss the significance of this symptom.

16a. Identify normal and pathological causes of bradycardia and tachycardia and describe how these affect the ECG. Also, identify flutter and fibrillation and describe how these appear in the ECG.

16b. Explain the effects of first-, second-, and third-degree AV node block on the electrocardiogram.

13.8 LYMPHATIC SYSTEM

Lymphatic vessels absorb excess interstitial fluid and transport this fluid—now called lymph—to ducts that drain into veins. Lymph nodes, and lymphoid tissue in the thymus, spleen, and tonsils, produce lymphocytes, which are white blood cells involved in immunity.

LEARNING OUTCOMES

After studying this section, you should be able to:

17. Explain how the lymph and lymphatic system relate to the blood and cardiovascular system.

18. Describe the function of lymph nodes and lymphatic organs.

The **interstitial space,** or **interstitium,** is the space between blood vessels and the tissue cells of an organ. It contains **interstitial fluid** and the **extracellular matrix.** Interstitial fluid—an aqueous solution containing salts, nutrients, waste products of cell metabolism, and plasma proteins—is formed by filtration out of blood capillaries (chapter 14, section 14.2). The extracellular matrix consists of a fiber scaffolding formed predominantly of collagen proteins and a gel formed of glycosaminoglycans.

The **lymphatic system** has three basic functions: (1) it transports interstitial (tissue) fluid, initially formed as a blood filtrate, back to the blood; (2) it transports absorbed fat from the small intestine to the blood; and (3) its cells—called *lymphocytes*—help provide immunological defenses against disease-causing agents (pathogens).

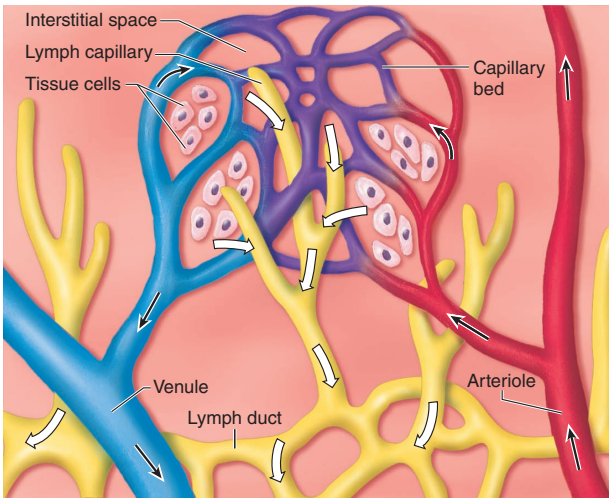


Figure 13.36 **The relationship between blood capillaries and lymphatic capillaries.** Notice that lymphatic capillaries are blind-ended. They are, however, highly permeable, so that excess fluid and protein within the interstitial space can drain into the lymphatic system.

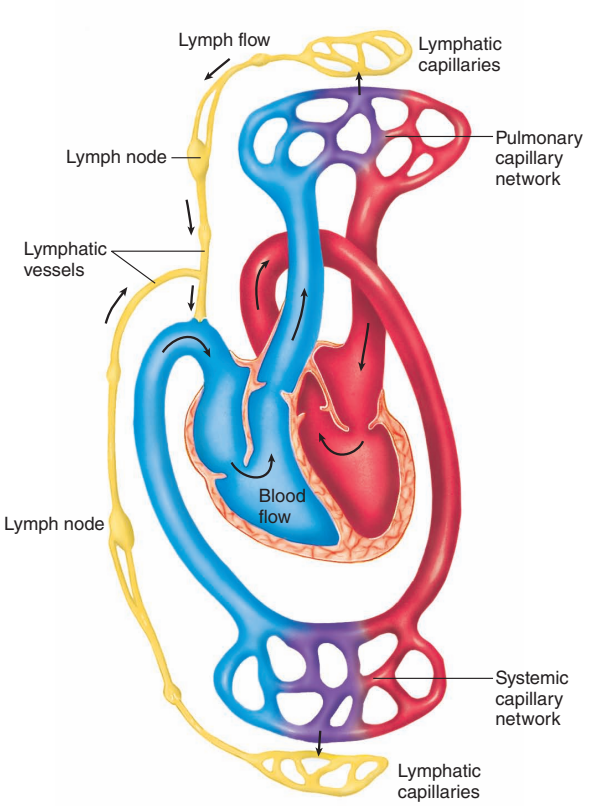


Figure 13.37 **The relationship between the circulatory and lymphatic systems.** This schematic illustrates that the lymphatic system transports fluid from the interstitial space back to the blood through a system of lymphatic vessels. Lymph is eventually returned to the vascular system at the subclavian veins.

The smallest vessels of the lymphatic system are the **lymphatic capillaries** (fig. 13.36). Lymphatic capillaries are microscopic closed-ended tubes that form vast networks in the intercellular spaces within most organs. Because the walls of lymphatic capillaries are composed of endothelial cells with porous junctions, interstitial fluid, proteins, extravasated white blood cells, microorganisms, and absorbed fat (in the intestine) can easily enter. Once fluid enters the lymphatic capillaries, it is referred to as **lymph.**

From merging lymphatic capillaries, the lymph is carried into larger lymphatic vessels called **lymph ducts.** The walls of lymph ducts are similar to those of veins. They have the same three layers and also contain valves to prevent backflow. Fluid movement within these vessels occurs as a result of peristaltic waves of contraction (chapter 12, section 12.6). The smooth muscle within the lymph ducts contains a pacemaker that initiates action potentials associated with the entry of Ca^{2+}, which stimulates contraction. The activity of the pacemaker, and hence the peristaltic waves of contraction, are increased in response to stretch of the vessel. The lymph ducts eventually empty into one of two principal vessels: the *thoracic duct* or the *right lymphatic duct.* These ducts drain the lymph into the left and right subclavian veins, respectively. Thus interstitial fluid, which is formed by filtration of plasma out of blood capillaries (chapter 14, section 14.2), is ultimately returned to the cardiovascular system (fig. 13.37).

Before the lymph is returned to the cardiovascular system, it is filtered through **lymph nodes** (fig. 13.38). Lymph nodes

CLINICAL APPLICATION

Lymphedema is a swelling of an arm or leg caused by excessive amounts of fluid and protein in the interstitial fluid. This results from blockage or destruction of the lymphatic drainage, usually because of surgery or radiation treatments for breast and other cancers. There are presently no cures for lymphedema, and the protein-rich interstitial fluid can trigger inflammation that leads to degenerative changes in the surrounding tissues. Lymphedema can also occur in the tropical equatorial regions because of infection with a species of nematode worm, which can block lymphatic vessels and cause enormous swelling of a leg or scrotum in the disease *elephantiasis* (chapter 14; see fig. 14.10).

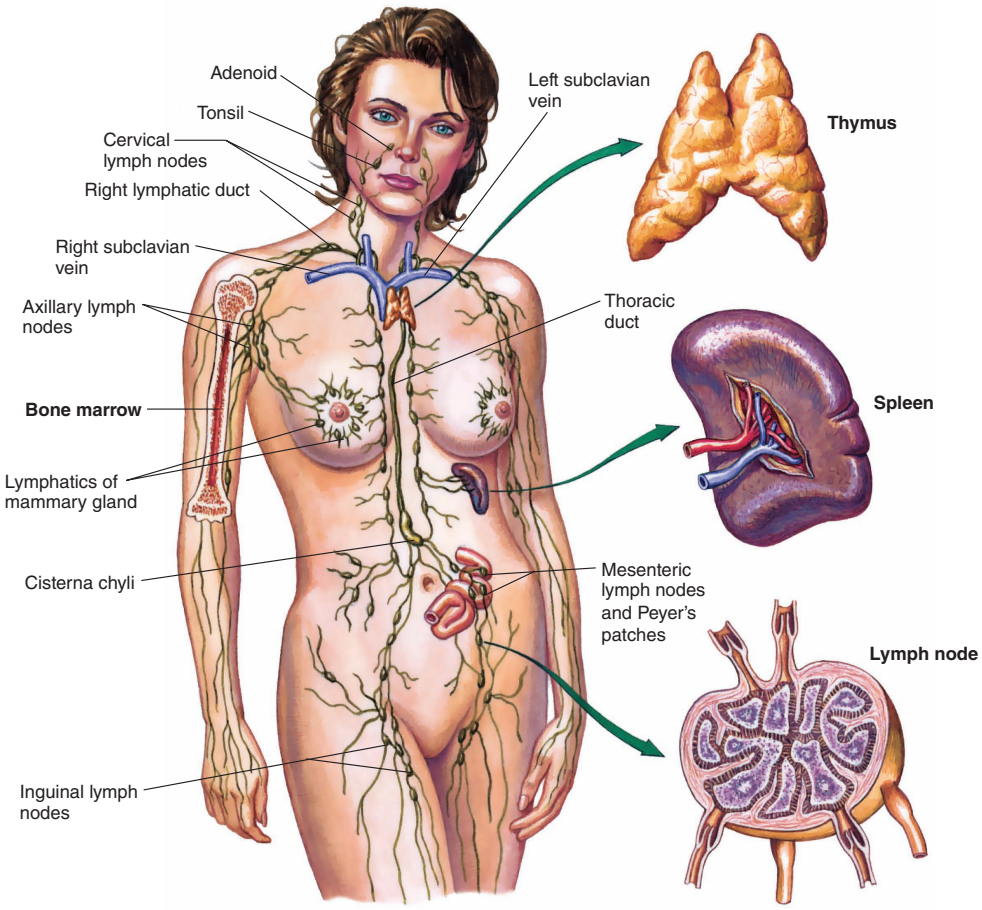


Figure 13.38 **The location of lymph nodes along the lymphatic pathways.** Lymph nodes are small bean-shaped bodies, enclosed within dense connective tissue capsules. AP|R

contain phagocytic cells, which help remove pathogens, and *germinal centers,* which are sites of lymphocyte production. The tonsils, thymus, and spleen—together called **lymphoid organs**—likewise contain germinal centers and are sites of lymphocyte production. Lymphocytes are the cells of the immune system that respond in a specific fashion to antigens, and their functions are described as part of the immune system in chapter 15.

Although the lymphatic system transports lymphocytes and antigen-presenting cells for immune protection, it may also transport cancer cells that can enter and later leave the porous lymphatic capillaries, thereby seeding distant organs. The lymphatic system can help cancer to spread, or *metastasize.* Metastasis to regional lymph nodes is the first step in the dissemination of tumors for cancers of the breast, colon, prostate, and others.

CHECKPOINT

17a. Compare the composition of lymph and blood, and describe the relationship between blood capillaries and lymphatic capillaries.

17b. Explain how the lymphatic system and the cardiovascular system are related. How do these systems differ?

18. Describe the functions of lymph nodes and lymphoid organs.

Clinical Investigation SUMMARY

Jessica experienced heavy menstruation. This could cause sufficient loss of iron to produce iron-deficiency anemia, which would be revealed by a low red blood cell count. Her mitral valve prolapse is a common condition involving blood leaking past the mitral valve and producing a murmur, which is best heard by a stethoscope place at the apex position of the heart. However, this usually does not cause symptoms unless the leakage is great enough to significantly reduce the output of the left ventricle. Her atrial fibrillation was revealed by the lack of a P wave in the ECG. This may not have obvious symptoms, but it may cause fatigue if the cardiac output cannot increase sufficiently when she is active. The major danger is the tendency to form blood clots in the heart. This can cause an ischemic stroke, which damages neurons because of the ischemia-induced lack of oxygen and nutrients and excitotoxicity. The physician prescribed a drug that inactivates factor X, thereby inhibiting the formation of thrombin by both clotting pathways. Smoking is a major risk factor for atherosclerosis, which promotes coronary heart disease and the formation of a thrombus.

See the additional chapter 13 Clinical Investigations on Mitral Valve Prolapse and AV Node Block in the Connect site for this text.

SUMMARY

13.1 Functions and Components of the Circulatory System 405

A. The blood transports oxygen and nutrients to all the cells of the body and removes waste products from the tissues. It also serves a regulatory function through its transport of hormones.
1. Oxygen is carried by red blood cells, or erythrocytes.
2. White blood cells, or leukocytes, serve to protect the body from disease.

B. The circulatory system consists of the cardiovascular system (heart and blood vessels) and the lymphatic system.

13.2 Composition of the Blood 406

A. Plasma is the fluid part of the blood, containing dissolved ions and various organic molecules.
1. Hormones are found in the plasma portion of the blood.
2. The plasma proteins are albumins, globulins (alpha, beta, and gamma), and fibrinogen.

B. The formed elements of the blood are erythrocytes, leukocytes, and platelets.
1. Erythrocytes, or red blood cells, contain hemoglobin and transport oxygen.
2. Leukocytes may be granular (also called polymorpho-nuclear) or agranular. They function in immunity.
3. Platelets, or thrombocytes, are required for blood clotting.

C. The production of red blood cells is stimulated by the hormone erythropoietin, and the development of different kinds of white blood cells is controlled by chemicals called cytokines.

D. The major blood-typing groups are the ABO system and the Rh system.
1. Blood type refers to the kind of antigens found on the surface of red blood cells.
2. When different types of blood are mixed, antibodies against the red blood cell antigens cause the red blood cells to agglutinate.

E. When a blood vessel is damaged, platelets adhere to the exposed subendothelial collagen proteins.
1. Platelets that stick to collagen undergo a release reaction in which they secrete ADP, serotonin, and thromboxane A_2.
2. Serotonin and thromboxane A_2 cause vasoconstriction. ADP and thromboxane A_2 attract other platelets and cause them to stick to the growing mass of platelets that are stuck to the collagen in the broken vessel.

F. In the formation of a blood clot, a soluble protein called fibrinogen is converted into insoluble threads of fibrin.

1. This reaction is catalyzed by the enzyme thrombin.
2. Thrombin is derived from prothrombin, its inactive precursor, by either an intrinsic or an extrinsic pathway.
   a. The intrinsic pathway, the longer of the two, requires the activation of more clotting factors.
   b. The shorter extrinsic pathway is initiated by the secretion of tissue thromboplastin.
3. The clotting sequence requires Ca^{2+} as a cofactor and phospholipids present in the platelet cell membranes.

G. Dissolution of the clot eventually occurs by the action of plasmin, which cleaves fibrin into split products.

13.3 Structure of the Heart 418

A. The right and left sides of the heart pump blood through the pulmonary and systemic circulations, respectively.
1. The right ventricle pumps blood to the lungs. This blood then returns to the left atrium.
2. The left ventricle pumps blood into the aorta and systemic arteries. This blood then returns to the right atrium.

B. The heart contains two pairs of one-way valves.
1. The atrioventricular valves allow blood to flow from the atria to the ventricles, but not in the reverse direction.
2. The semilunar valves allow blood to leave the ventricles and enter the pulmonary and systemic circulations, but they prevent blood from returning from the arteries to the ventricles.

C. Closing of the AV valves produces the first heart sound, or "lub," at systole. Closing of the semilunar valves produces the second heart sound, or "dub," at diastole. Abnormal valves can cause abnormal sounds called murmurs.

13.4 Cardiac Cycle 422

A. The heart is a two-step pump. The atria contract first, and then the ventricles.
1. During diastole, first the atria and then the ventricles fill with blood.
2. The ventricles are about 80% filled before the atria contract and add the final 20% to the end-diastolic volume.
3. Contraction of the ventricles ejects about two-thirds of their blood, leaving about one-third as the end-systolic volume.

B. When the ventricles contract at systole, the pressure within them first rises sufficiently to close the AV valves and then rises sufficiently to open the semilunar valves.
1. Blood is ejected from the ventricles until the pressure within them falls below the pressure in the arteries. At this point, the semilunar valves close and the ventricles begin relaxation.
2. When the pressure in the ventricles falls below the pressure in the atria, a phase of rapid filling of the ventricles occurs, followed by the final filling caused by contraction of the atria.

13.5 Electrical Activity of the Heart and the Electrocardiogram 425

A. In the normal heart, action potentials originate in the SA node as a result of spontaneous depolarization called the pacemaker potential.
1. When this spontaneous depolarization reaches a threshold value, opening of the voltage-regulated Na^+ gates and fast Ca^{2+} channels produces an action potential.
2. Repolarization is produced by the outward diffusion of K^+, but a stable resting membrane potential is not attained because spontaneous depolarization once again occurs.
3. Other myocardial cells are capable of spontaneous activity, but the SA node is the normal pacemaker because its rate of spontaneous depolarization is the fastest.
4. When the action potential produced by the SA node reaches other myocardial cells, they produce action potentials with a long plateau phase because of the slow inward diffusion of Ca^{2+}.
5. The long action potential and long refractory period of myocardial cells allows the entire mass of cells to be in a refractory period while it contracts. This prevents the myocardium from being stimulated again until after it relaxes.

B. The electrical impulse begins in the sinoatrial node and spreads through both atria by electrical conduction from one myocardial cell to another.
1. The impulse then excites the atrioventricular node, from which it is conducted by the bundle of His into the ventricles.
2. The Purkinje fibers transmit the impulse into the ventricular muscle and cause it to contract.

C. The regular pattern of conduction in the heart produces a changing pattern of potential differences between two points on the body surface.
1. The recording of this changing pattern caused by the heart's electrical activity is called an electrocardiogram (ECG).
2. The P wave is caused by depolarization of the atria; the QRS wave is caused by depolarization of the ventricles; and the T wave is produced by repolarization of the ventricles.

13.6 Blood Vessels 431

A. Arteries contain three layers, or tunics: the interna, media, and externa.
1. The tunica interna consists of a layer of endothelium, which is separated from the tunica media by a band of elastin fibers.
2. The tunica media consists of smooth muscle.
3. The tunica externa is the outermost layer.
4. Large arteries, containing many layers of elastin, can expand and recoil with rising and falling blood pressure. Medium and small arteries and arterioles are less distensible, and thus provide greater resistance to blood flow.

B. Capillaries are the narrowest but the most numerous of the blood vessels.
1. Capillary walls consist of just one layer of endothelial cells. They provide for the exchange of molecules between the blood and the surrounding tissues.

2. The flow of blood from arterioles to capillaries is regulated by precapillary sphincter muscles.
3. The capillary wall may be continuous, fenestrated, or discontinuous.

C. Veins have the same three tunics as arteries, but they generally have a thinner muscular layer than comparably sized arteries.
1. Veins are more distensible than arteries and can expand to hold a larger quantity of blood.
2. Many veins have venous valves that ensure a one-way flow of blood to the heart.
3. The flow of blood back to the heart is aided by contraction of the skeletal muscles that surround veins. The effect of this action is called the skeletal muscle pump.

13.7 Atherosclerosis and Cardiac Arrhythmias 436

A. Atherosclerosis of arteries can occlude blood flow to the heart and brain and is a causative factor in about 50% of all deaths in the United States, Europe, and Japan.
1. Atherosclerosis begins with injury to the endothelium, the movement of monocytes and lymphocytes into the tunica interna, and the conversion of monocytes into macrophages that engulf lipids. Smooth muscle cells then proliferate and secrete extracellular matrix.
2. Atherosclerosis is promoted by such risk factors as smoking, hypertension, and high plasma cholesterol concentration. Low-density lipoproteins (LDLs), which carry cholesterol into the artery wall, are oxidized by the endothelium and are a major contributor to atherosclerosis.

B. Occlusion of blood flow in the coronary arteries by atherosclerosis may produce ischemia of the heart muscle and angina pectoris, which may lead to myocardial infarction.

C. The ECG can be used to detect abnormal cardiac rates, abnormal conduction between the atria and ventricles, and other abnormal patterns of electrical conduction in the heart.

13.8 Lymphatic System 442

A. Lymphatic capillaries are blind-ended but highly permeable. They drain excess tissue fluid into lymph ducts.

B. Lymph passes through lymph nodes and is returned by way of the lymph ducts to the venous blood.

REVIEW ACTIVITIES

Test Your Knowledge

1. Which of these statements is *false?*
   a. Most of the total blood volume is contained in veins.
   b. Capillaries have a greater total surface area than any other type of vessel.
   c. Exchanges between blood and tissue fluid occur across the walls of venules.
   d. Small arteries and arterioles present great resistance to blood flow.
2. All arteries in the body contain oxygen-rich blood with the exception of
   a. the aorta.
   b. the pulmonary artery.
   c. the renal artery.
   d. the coronary arteries.
3. The "lub," or first heart sound, is produced by closing of
   a. the aortic semilunar valve.
   b. the pulmonary semilunar valve.
   c. the tricuspid valve.
   d. the bicuspid valve.
   e. both AV valves.
4. The first heart sound is produced at
   a. the beginning of systole.
   b. the end of systole.
   c. the beginning of diastole.
   d. the end of diastole.
5. Changes in the cardiac rate primarily reflect changes in the duration of
   a. systole.
   b. diastole.
6. The QRS wave of an ECG is produced by
   a. depolarization of the atria.
   b. repolarization of the atria.
   c. depolarization of the ventricles.
   d. repolarization of the ventricles.
7. The second heart sound immediately follows the occurrence of
   a. the P wave.
   b. the QRS wave.
   c. the T wave.
8. The cells that normally have the fastest rate of spontaneous diastolic depolarization are located in
   a. the SA node.
   b. the AV node.
   c. the bundle of His.
   d. the Purkinje fibers.
9. Which of these statements is *true?*
   a. The heart can produce a graded contraction.
   b. The heart can produce a sustained contraction.
   c. The action potentials produced at each cardiac cycle normally travel around the heart in circus rhythms.
   d. All of the myocardial cells in the ventricles are normally in a refractory period at the same time.
10. An ischemic injury to the heart that destroys myocardial cells is
    a. angina pectoris.
    b. a myocardial infarction.
    c. fibrillation.
    d. heart block.

11. The activation of factor X occurs in
    a. the intrinsic pathway only.
    b. the extrinsic pathway only.
    c. both the intrinsic and extrinsic pathways.
    d. neither the intrinsic nor extrinsic pathway.
12. Platelets
    a. form a plug by sticking to each other.
    b. release chemicals that stimulate vasoconstriction.
    c. provide phospholipids needed for the intrinsic pathway.
    d. serve all of these functions.
13. Antibodies against both type A and type B antigens are found in the plasma of a person who is
    a. type A.
    b. type B.
    c. type AB.
    d. type O.
    e. any of these types.
14. Production of which of the following blood cells is stimulated by a hormone secreted by the kidneys?
    a. Lymphocytes
    b. Monocytes
    c. Erythrocytes
    d. Neutrophils
    e. Thrombocytes
15. Which of these statements about plasmin is *true?*
    a. It is involved in the intrinsic clotting system.
    b. It is involved in the extrinsic clotting system.
    c. It functions in fibrinolysis.
    d. It promotes the formation of emboli.
16. During the phase of isovolumetric relaxation of the ventricles, the pressure in the ventricles is
    a. rising.
    b. falling.
    c. first rising, then falling.
    d. constant.
17. Peristaltic waves of contraction move fluid within which of these vessels?
    a. Arteries
    b. Veins
    c. Capillaries
    d. Lymphatic vessels
    e. All of these

Test Your Understanding

18. Describe how the pacemaker cells produce a spontaneous diastolic depolarization, and how this leads to the production of action potentials.
19. What characteristic of the SA node distinguishes it from other possible pacemaker regions and allows it to function as the normal pacemaker? How do action potentials from the SA node reach the atria and the ventricles?
20. Compare the duration of the heart's contraction with the myocardial action potential and refractory period. Explain the significance of these relationships.
21. Step by step, describe the pressure changes that occur in the ventricles during the cardiac cycle. Explain how these pressure changes relate to the occurrence of the heart sounds.
22. Can a defective valve be detected by an ECG? Can a partially damaged AV node be detected by auscultation (listening) with a stethoscope? Explain.
23. Describe the causes of the P, QRS, and T waves of an ECG, and indicate at which point in the cardiac cycle each of these waves occurs. Explain why the first heart sound occurs immediately after the QRS wave and why the second sound occurs at the time of the T wave.
24. The lungs are the only organs that receive the entire output of a ventricle. Explain this statement, and describe how this relates to the differences in structure and function between the right and left ventricles.
25. Explain the process of Ca^{2+}-induced Ca^{2+} release in the myocardium. How does this process differ from excitation-contraction coupling in skeletal muscles?
26. Explain how a cut in the skin initiates both the intrinsic and the extrinsic clotting pathways. Which pathway is shorter? Why?
27. Explain how aspirin, coumarin drugs, EDTA, and heparin function as anticoagulants. Which of these are effective when added to a test tube? Which are not? Why?
28. Explain how blood moves through arteries, capillaries, and veins. How does exercise affect this movement?
29. Explain the processes involved in the development of atherosclerosis. How might antioxidants help retard the progression of this disease? How might exercise help? What other changes in lifestyle might help prevent or reduce atherosclerotic plaques?

Test Your Analytical Ability

30. Hematopoietic stem cells account for less than 1% of the cells in the bone marrow. These cells can be separated from the others prior to bone marrow transplantation, but it is better to first inject the donor with recombinant cytokines. Identify the cytokines that might be used and describe their effects.
31. A patient has a low red blood cell count, and microscopic examination of his blood reveals an abnormally high proportion of circulating reticulocytes. Upon subsequent examination, the patient is diagnosed with a bleeding ulcer. This is surgically corrected, and in due course his blood measurements return to normal. What was the reason for the low red blood cell count and high proportion of reticulocytes?
32. A chemical called EDTA, like citrate, binds to (or "chelates") Ca^{2+}. Suppose a person had EDTA infused into their blood. What effect would this have on the intrinsic and extrinsic clotting pathways? How would these effects differ from the effects of aspirin on blood clotting?
33. During the course of a physiology laboratory, a student finds that her PR interval is 0.24 second. Concerned, she takes her own ECG again an hour later and sees an area of the ECG strip where the PR interval becomes longer and longer.

Performing an ECG measurement on herself for a third time, she sees an area of the strip where a P wave is not followed by a QRS or T; farther along in the strip, however, a normal pattern reappears. What do you think these recordings indicate?

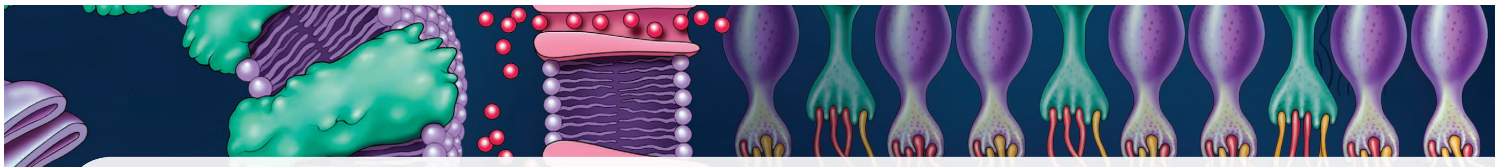
34. A newborn baby with a patent foramen ovale or a ventricular septal defect might be cyanotic (blue). Will a two-year-old with these defects also be cyanotic? Explain your answer.
35. People with paroxysmal atrial tachycardia (commonly called "palpitations") are sometimes given drugs that block voltage-gated Ca^{2+} channels in the plasma membrane of myocardial cells in order to slow the beat. By what mechanism could these drugs help?
36. The mechanism of excitation-contraction coupling in cardiac muscle differs from that in skeletal muscle. How might these differences relate to the differences in the action potentials in cardiac muscle compared to skeletal muscle?
37. Explain how homeostasis of the circulating blood platelet count is maintained. By what mechanism would blood loss increase the platelet count?

Test Your Quantitative Ability

Refer to figure 13.17 to answer the following questions:

38. At which pressure value did blood just start to leave the left ventricle and enter the aorta?
39. How much blood was ejected by the left ventricle by the time the second heart sound was produced?
40. How much blood was in the left ventricle just before the atrial contraction?
41. How much blood was added to the left ventricle by contraction of the left atrium?
42. What is the change in intraventricular pressure between the time the first heart sound begins and the time it ends?

ONLINE STUDY TOOLS



CHAPTER

14

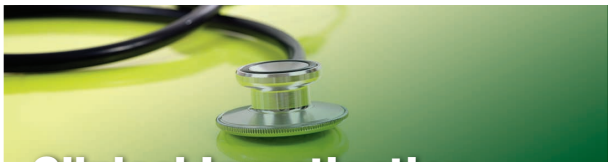
Cardiac Output, Blood Flow, and Blood Pressure

Refresh Your Memory

Before you begin this chapter, you may want to review these concepts from previous chapters:

- **Pulmonary and Systemic Circulations 418**
- **Pressure Changes During the Cardiac Cycle 423**
- **Excitation-Contraction Coupling in Heart Muscle 427**
- **Blood Vessels 431**

CHAPTER OUTLINE



Clinical Investigation

Mark complained of abdominal pain and swelling in his legs, and his physician said that he had edema and hypoproteinemia. After a colonoscopy with biopsies, he was diagnosed with Crohn's disease, an autoimmune intestinal disorder that caused plasma proteins to leak through his intestinal lining. He later began an intense exercise program, lifting heavy weights and training to run marathons. The day after a long run on a hot day, he noticed that he got very dizzy when he stood up and was told that he should drink more and switch to sports drinks during such training. A couple of years later, Mark was diagnosed with essential hypertension and was prescribed an ACE inhibitor. The physician advised him not to hold his breath when he lifted heavy weights.

Some of the new terms and concepts you will encounter include:

- Oncotic pressure and interstitial fluid formation
- Cardiac output, blood volume, and peripheral resistance.
- Baroreceptor reflex and Valsalva maneuver

14.1 CARDIAC OUTPUT

The pumping ability of the heart is a function of the beats per minute (cardiac rate) and the volume of blood ejected per beat (stroke volume). The cardiac rate and stroke volume are regulated by autonomic nerves and by mechanisms intrinsic to the cardiovascular system.

LEARNING OUTCOMES

After studying this section, you should be able to:

1. Describe the extrinsic regulation of cardiac rate and contractility.
2. Explain the relationship between stroke volume and venous return.
3. Explain the Frank-Starling law of the heart.

The **cardiac output** is the volume of blood pumped per minute by each ventricle. The average resting **cardiac rate** in an adult is 70 beats per minute; the average **stroke volume** (volume of blood pumped per beat by each ventricle) is 70 to 80 ml per beat. The product of these two variables gives an average cardiac output of 5,500 ml (5.5 L) per minute:

$$\underset{(ml/min)}{\text{Cardiac output}} = \underset{(ml/beat)}{\text{Stroke volume}} \times \underset{(beats/min)}{\text{cardiac rate}}$$

Because the cardiac output of the right ventricle is normally the same as that of the left ventricle, the lungs receive the entire cardiac output while other organs share the output of the left ventricle. In order for this to be true, the pulmonary circulation must have a low resistance, low pressure, and high blood flow compared to the systemic circulation. For comparison, the mean arterial pressure (discussed in section 14.3) of the pulmonary circulation is 10–20 mmHg compared to 70–105 mmHg in the systemic circulation.

The **total blood volume** also averages about 5.5 L. This means that each ventricle pumps the equivalent of the total blood volume each minute under resting conditions. Put another way, it takes about a minute for a drop of blood to complete the systemic and pulmonary circuits. An increase in cardiac output, as occurs during exercise, must thus be accompanied by an increased rate of blood flow through the circulation. This is accomplished by factors that regulate the cardiac rate and stroke volume.

Regulation of Cardiac Rate

In the complete absence of neural influences, the heart will continue to beat as long as the myocardial cells are alive. This automatic rhythm is a result of a spontaneous, diastolic depolarization of the pacemaker cells in the SA node. This pacemaker potential is produced by mechanisms discussed in chapter 13, section 13.5, and serves as the depolarization stimulus for the production of action potentials (fig. 14.1).

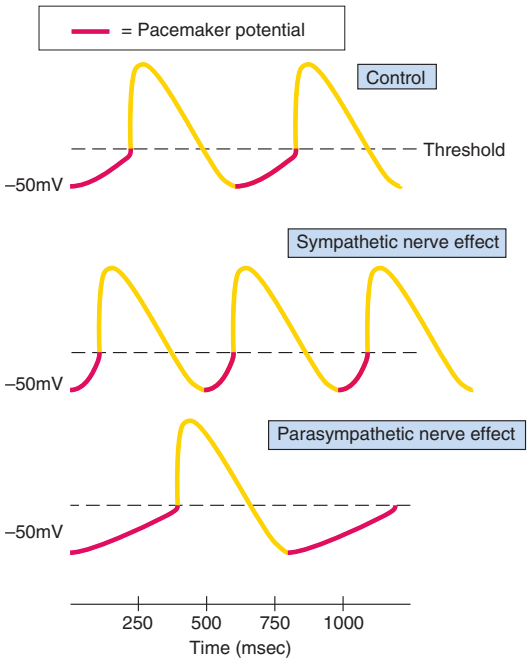


Figure 14.1 The effect of autonomic nerves on the pacemaker potentials in the SA node. The heart's rhythm is set by the rate of spontaneous depolarization in the SA node. This spontaneous depolarization is known as the pacemaker potential, and its rate is increased by sympathetic nerve stimulation and decreased by parasympathetic nerve inhibition. AP|R

Each action potential is accompanied by contraction of the myocardium.

Both sympathetic and parasympathetic innervations to the heart are active to a greater or lesser degree. Norepinephrine from sympathetic axons and epinephrine from the adrenal medulla bind to β_1-adrenergic receptors in the heart to stimulate the production of cyclic AMP (chapter 7; see fig. 7.31). Cyclic AMP acts on the HCN and Ca^{2+} channels of the pacemaker cells that produce the pacemaker potential to increase the rate of diastolic depolarization. This stimulates a faster production of action potentials and thus a faster cardiac rate (fig. 14.1).

Acetylcholine, released by vagus nerve endings, binds to muscarinic ACh receptors and causes the opening of separate K^+ channels in the membrane (see chapter 7, fig. 7.27; also see chapter 9, fig. 9.11). The outward diffusion of K^+ partially counters the depolarizing mechanisms that produce the pacemaker potential. This results in a slower rate of diastolic depolarization and action potential production, and thus in a slower cardiac rate. The vagus nerve is tonically active to some degree, and the ACh effects generally keep the resting cardiac rate slower that the 90–100 beats per minute that it would be in the absence of this inhibition (fig. 14.1).

The actual pace set by the SA node at any time depends on the net effect of these antagonistic influences (see fig. 14.5). Mechanisms that affect the cardiac rate are said to have a **chronotropic effect** (*chrono* = time). Those that increase cardiac rate have a *positive chronotropic effect;* those that decrease the rate have a *negative chronotropic effect.*

Autonomic innervation of the SA node is the major means by which cardiac rate is regulated. However, other autonomic control mechanisms also affect cardiac rate to a lesser degree. Sympathetic endings in the musculature of the atria and ventricles increase the strength of contraction and cause a slight decrease in the time spent in systole when the cardiac rate is high (table 14.1).

The resting bradycardia (slow heart rate) of endurance-trained athletes is largely due to high vagus nerve activity. During exercise, the cardiac rate increases as a result of decreased vagus nerve inhibition of the SA node. Further increases in cardiac rate are achieved by increased sympathetic nerve stimulation.

Table 14.1 | Effects of Autonomic Nerve Activity on the Heart

Region Affected	Sympathetic Nerve Effects	Parasympathetic Nerve Effects
SA node	Increased rate of diastolic depolarization; increased cardiac rate	Decreased rate of diastolic depolarization; decreased cardiac rate
AV node	Increased conduction rate	Decreased conduction rate
Atrial muscle	Increased strength of contraction	No significant effect
Ventricular muscle	Increased strength of contraction	No significant effect

The activity of the autonomic innervation of the heart is coordinated by the **cardiac control center** in the medulla oblongata of the brain stem. The cardiac control center, in turn, is affected by higher brain areas and by sensory feedback from pressure receptors, or *baroreceptors,* in the aorta and carotid arteries. In this way, a fall in blood pressure can produce a reflex increase in the heart rate (chapter 1; see fig. 1.6). This baroreceptor reflex is discussed in more detail in relation to blood pressure regulation in section 14.6.

Regulation of Stroke Volume

The stroke volume is regulated by three variables:

1. the **end-diastolic volume (EDV),** which is the volume of blood in the ventricles at the end of diastole;
2. the **total peripheral resistance,** which is the frictional resistance, or impedance to blood flow, in the arteries; and
3. the **contractility,** or strength, of ventricular contraction.

The end-diastolic volume is the amount of blood in the ventricles immediately before they begin to contract. This is a workload imposed on the ventricles prior to contraction, and thus is sometimes called a **preload.** The stroke volume is directly proportional to the preload; an increase in EDV results in an increase in stroke volume. (This relationship is known as the *Frank-Starling law of the heart,* discussed shortly.) The stroke volume is also directly proportional to contractility; when the ventricles contract more forcefully, they pump more blood.

In order to eject blood, the pressure generated in a ventricle when it contracts must be greater than the pressure in the arteries (because blood flows only from higher pressure to lower pressure). The pressure in the arterial system before the ventricle contracts is, in turn, a function of the total peripheral resistance—the higher the peripheral resistance, the higher the pressure. As blood begins to be ejected from the ventricle, the added volume of blood in the arteries causes a rise in mean arterial pressure against the "bottleneck" presented by the peripheral resistance. Ejection of blood stops shortly after the aortic pressure becomes equal to the intraventricular pressure. The total peripheral resistance thus presents an impedance to the ejection of blood from the ventricle, or an **afterload** imposed on the ventricle after contraction has begun. This can be medically significant; a person with a high total peripheral resistance has a high arterial blood pressure, and thus a high afterload imposed on the ventricular muscle.

In summary, the stroke volume is inversely proportional to the total peripheral resistance; the greater the peripheral resistance, the lower the stroke volume. It should be noted that this lowering of stroke volume in response to a raised peripheral resistance occurs for only a few beats. Thereafter, a healthy heart is able to compensate for the increased peripheral resistance by beating more strongly. This compensation occurs by means of a mechanism described in the next section (Frank-Starling law of the heart). An inability of the heart to compensate can lead to congestive heart failure.

The proportion of the end-diastolic volume that is ejected against a given afterload depends on the strength of ventricular contraction. Normally, contraction strength is sufficient to eject 70 to 80 ml of blood out of a total end-diastolic volume of 110 to 130 ml. The **ejection fraction** is thus about 60%. The ejection fraction remains relatively constant over a range of end-diastolic volumes, so that the amount ejected per beat (stroke volume) increases as the end-diastolic volume increases. In order for this to be true, the strength of ventricular contraction must increase as the end-diastolic volume increases.

Frank-Starling Law of the Heart

Two physiologists, Otto Frank and Ernest Starling, demonstrated that the strength of ventricular contraction varies directly with the end-diastolic volume (fig. 14.2). Even in experiments where the heart is removed from the body (and is thus not subject to neural or hormonal regulation) and where the still-beating heart is filled with blood flowing from a reservoir, an increase in EDV within the physiological range results in increased contraction strength and, therefore, in increased stroke volume. This relationship between EDV, contraction strength, and stroke volume is thus a built-in, or *intrinsic,* property of heart muscle, and is known as the **Frank-Starling law of the heart.**

Intrinsic Control of Contraction Strength

The intrinsic control of contraction strength and stroke volume is due to variations in the degree to which the myocardium is stretched by the end-diastolic volume. As the EDV rises within the physiological range, the myocardium is increasingly stretched and, as a result, contracts more forcefully.

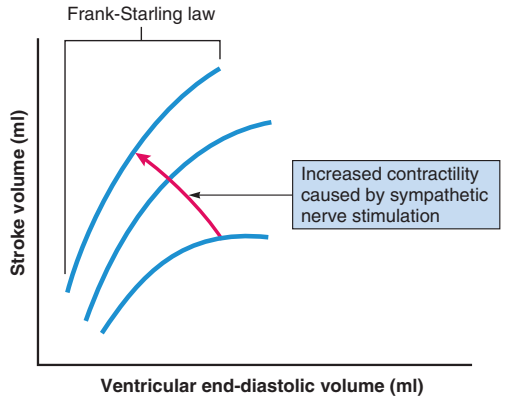


Figure 14.2 The frank-starling law and sympathetic nerve effects. The graphs demonstrate the Frank-Starling law: As the end-diastolic volume is increased, the stroke volume is increased. The graphs also demonstrate, by comparing the three curves, that the stroke volume is higher at any given end-diastolic volume when the ventricle is stimulated by sympathetic nerves. This is shown by the steeper curves to the left (see the red arrow).

As discussed in chapter 12, stretch can also increase the contraction strength of skeletal muscles (see fig. 12.21). The resting length of skeletal muscles, however, is close to ideal, so that significant stretching decreases contraction strength. This is not true of the heart. Prior to filling with blood during diastole, the sarcomere lengths of myocardial cells are only about 1.5 μm. At this length, the actin filaments from each side overlap in the middle of the sarcomeres, and the cells can contract only weakly (fig. 14.3).

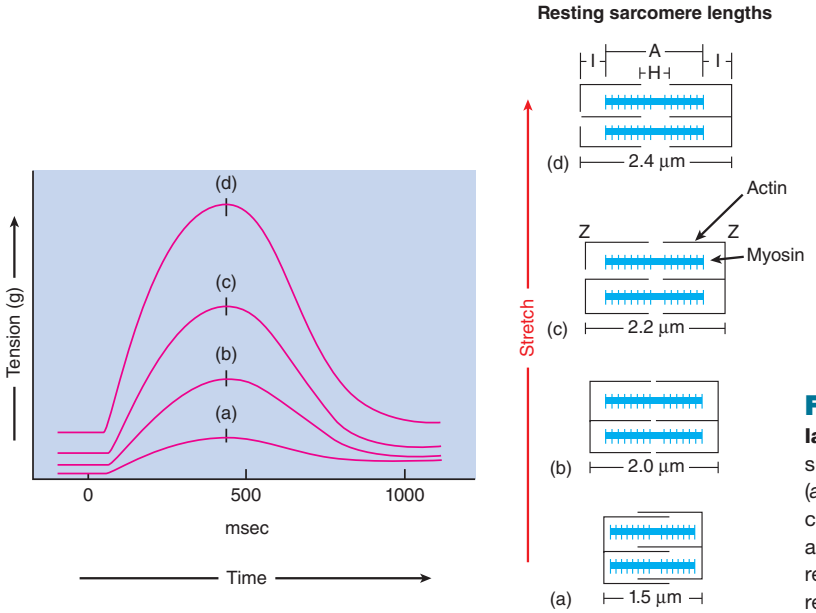


Figure 14.3 The Frank-Starling law of the heart. When the heart muscle is subjected to an increasing degree of stretch (*a* through *d*), it contracts more forcefully. The contraction strength is indicated on the *y*-axis as the tension. Notice that the time required to reach maximum contraction remains constant, regardless of the degree of stretch.

As the ventricles fill with blood, the myocardium stretches so that the actin filaments overlap with myosin only at the edges of the A bands (fig. 14.3). This increases the number of interactions between actin and myosin, allowing more force to be developed during contraction. Also, stretching of myocardial cells during diastole increases the sensitivity of the Ca^{2+}-release channels in the sarcoplasmic reticulum (SR), promoting their release of Ca^{2+} in response to stimulation (chapter 12; see fig. 12.34). This greater release of Ca^{2+} results in a stronger contraction.

The Frank-Starling mechanism results in the initial rapid increase in contractility when the ventricles are stretched. However, the force of myocardial contraction then gradually increases over the next 10–15 minutes following stretching of the ventricles. This is known as the **Anrep effect,** and appears to be due to increased Ca^{2+} entering the cytoplasm through the Na^+/Ca^{2+} exchanger (chapter 12, section 12.5). Because the degree of myocardial stretching depends on the end-diastolic volume, these mechanisms ensure that an increase in end-diastolic volume intrinsically produces an increase in contraction strength and stroke volume.

As shown in figure 14.4, muscle length has a more pronounced effect on contraction strength in cardiac muscle than in skeletal muscle. That is, a particular increase in sarcomere length will stimulate contraction strength more in cardiac muscle than in skeletal muscle. This is believed to be due to an increased sensitivity of stretched cardiac muscle to the stimulatory effects of Ca^{2+}.

The Frank-Starling law explains how the heart can adjust to a rise in total peripheral resistance: (1) a rise in peripheral resistance causes a decrease in the stroke volume of the ventricle, so that (2) more blood remains in the ventricle and the end-diastolic volume is greater for the next cycle; as a result, (3) the ventricle is stretched to a greater degree in the next cycle and contracts more strongly to eject more blood. This allows a healthy ventricle to sustain a normal cardiac output when there are changes in the total peripheral resistance.

A very important consequence of these events is that the cardiac output of the left ventricle, which pumps blood into the systemic circulation with its ever-changing resistances, can be adjusted to match the output of the right ventricle (which pumps blood into the pulmonary circulation). The rate of blood flow through the pulmonary and systemic circulations must be equal to prevent fluid accumulation in the lungs and to deliver fully oxygenated blood to the body.

Extrinsic Control of Contractility

Contractility is the strength of contraction at any given fiber length. At any given degree of stretch, the strength of ventricular contraction depends on the activity of the sympathoadrenal system. Norepinephrine from sympathetic nerve endings and epinephrine from the adrenal medulla produce an increase in contraction strength (see figs. 14.2 and 14.4). This **positive inotropic effect** results from an increase in the amount of Ca^{2+} available to the sarcomeres.

The cardiac output is thus affected in two ways by the activity of the sympathoadrenal system: (1) through a positive inotropic effect on contractility and (2) through a positive chronotropic effect on cardiac rate (fig. 14.5). Stimulation through parasympathetic nerve endings to the SA node and conducting tissue has a negative chronotropic effect but does not directly affect the contraction strength of the ventricles. However, the increased EDV that results from a slower cardiac rate can increase contraction strength through the mechanism described by the Frank-Starling law of the heart. This increases stroke volume, but not enough to completely compensate for the slower cardiac rate. Thus, the cardiac output is decreased when the heart beats slower, a fact used by people who treat their hypertension with beta-adrenergic blocking drugs that slow the cardiac rate.

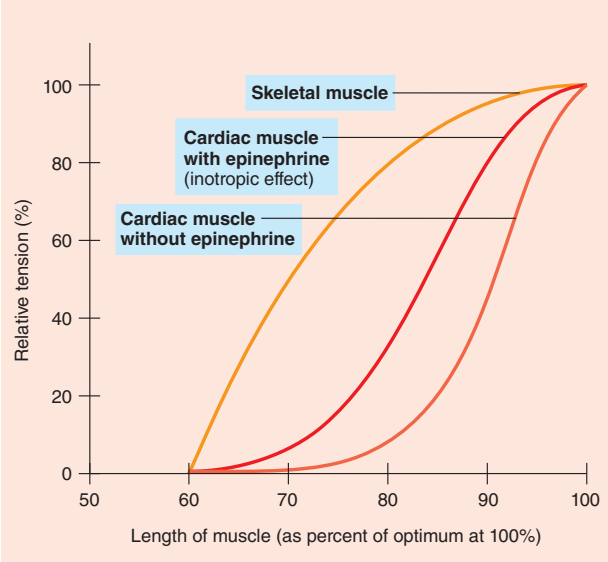


Figure 14.4 The effect of muscle length and epinephrine on contraction strength. In this schematic comparison, all three curves demonstrate that each muscle contracts with its maximum force (100% relative tension) at its own optimum length (100% optimum length). As the length is decreased from optimum, each curve demonstrates a decreased contraction strength. Notice that the decline is steeper for cardiac muscle than for skeletal muscle, demonstrating the importance of the Frank-Starling relationship in heart physiology. At any length, however, epinephrine increases the strength of myocardial contraction, demonstrating a positive inotropic effect.

Venous Return

The end-diastolic volume—and thus the stroke volume and cardiac output—is controlled by factors that affect the **venous return,** which is the return of blood to the heart via veins. The rate at which the atria and ventricles are filled with venous blood depends on the total blood volume and the venous pressure (pressure in the veins). It is the venous pressure that serves as the driving force for the return of blood to the heart.

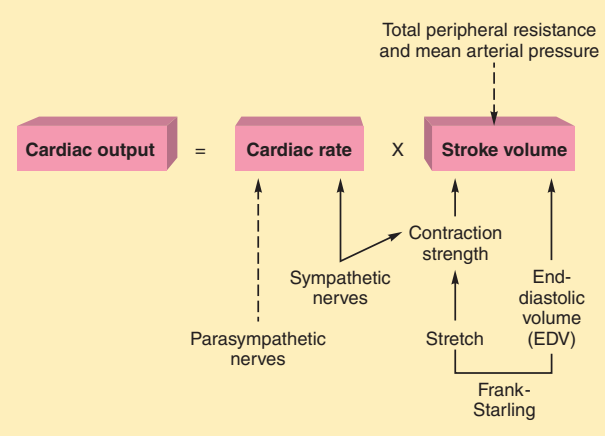


Figure 14.5 **The regulation of cardiac output.** Factors that stimulate cardiac output are shown as solid arrows; factors that inhibit cardiac output are shown as dashed arrows. AP|R

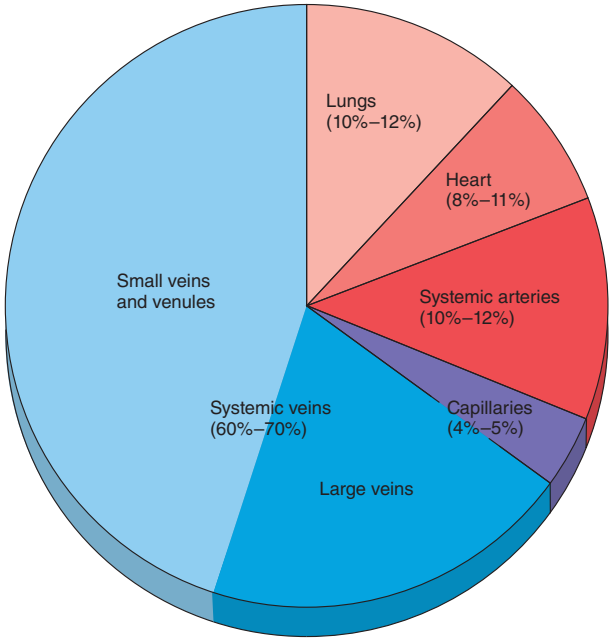


Figure 14.6 **The distribution of blood within the circulatory system at rest.** Notice that the venous system contains most of the blood; it functions as a reservoir from which more blood can be added to the circulation under appropriate conditions (such as exercise). AP|R

Veins have thinner, less muscular walls than do arteries; thus, they have a higher **compliance.** This means that a given amount of pressure will cause more distension (expansion) in veins than in arteries, so that the veins can hold more blood. Approximately two-thirds of the total blood volume is located in the veins (fig. 14.6). Veins are therefore called **capacitance vessels,** after electronic devices called capacitors that store electrical charges. Muscular arteries and arterioles expand less under pressure (are less compliant), and thus are called *resistance vessels.*

Although veins contain almost 70% of the total blood volume, the mean venous pressure is only 2 mmHg, compared to a mean arterial pressure of 90 to 100 mmHg. The lower venous pressure is due in part to a pressure drop between arteries and capillaries and in part to the high venous compliance.

The venous pressure is highest in the venules (10 mmHg) and lowest at the junction of the venae cavae with the right atrium (0 mmHg). This produces a pressure difference that promotes the return of blood to the heart. In addition, the venous return is aided by (1) sympathetic nerve activity, which stimulates smooth muscle contraction in the venous walls and thereby reduces compliance; (2) the skeletal muscle pump, which squeezes veins during muscle contraction; and (3) the pressure difference between the thoracic and abdominal cavities, which promotes the flow of venous blood back to the heart.

Contraction of the skeletal muscles functions as a "pump" by virtue of its squeezing action on veins (chapter 13; see fig. 13.29). Contraction of the diaphragm during inhalation also improves venous return. The diaphragm lowers as it contracts, increasing the thoracic volume and decreasing the abdominal volume. This creates a partial vacuum in the thoracic cavity and a higher pressure in the abdominal cavity. The pressure difference thus produced favors blood flow from abdominal to thoracic veins (fig. 14.7).

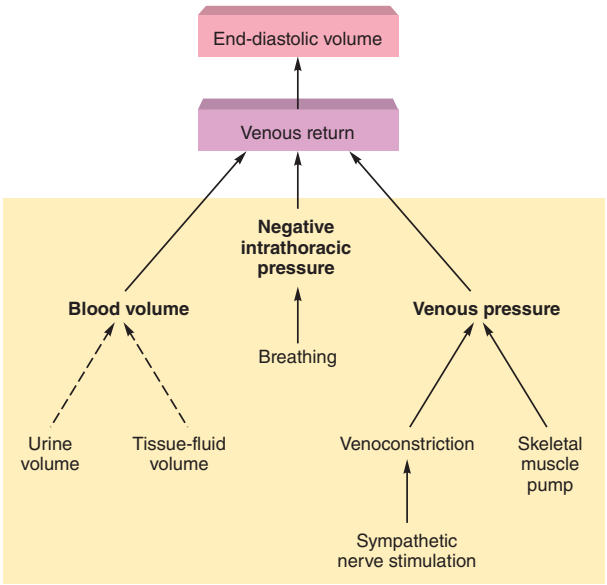


Figure 14.7 **Variables that affect venous return and thus end-diastolic volume.** Direct relationships are indicated by solid arrows; inverse relationships are shown with dashed arrows. AP|R

CHECKPOINT

1. Describe the effects of sympathoadrenal and parasympathetic nerve activity on the cardiac rate and stroke volume.

2a. Describe the factors that regulate the venous return, and explain how the venous return is related to the end-diastolic volume and the stroke volume.

2b. Describe how the stroke volume is intrinsically regulated by the end-diastolic volume and explain the significance of this relationship.

2c. Define the terms *preload* and *afterload* and explain how they affect the cardiac output.

3. Use the Frank-Starling law of the heart to explain how an increase in venous return can result in an increase in stroke volume and cardiac output.

14.2 BLOOD VOLUME

Fluid in the extracellular environment of the body is distributed between the blood and the interstitial fluid compartments by forces acting across the walls of capillaries. The kidneys influence blood volume because urine is derived from blood plasma, and the hormones ADH and aldosterone act on the kidneys to help regulate the blood volume.

LEARNING OUTCOMES

After studying this section, you should be able to:

4. Explain the forces that act in capillaries and how edema can be produced.
5. Explain how the kidneys regulate blood volume, and the hormonal regulation of this process.

Blood volume represents one part, or compartment, of the total body water. Approximately two-thirds of the total body water is contained within cells—in the intracellular compartment. The remaining one-third is in the **extracellular compartment.** This extracellular fluid is normally distributed so that about 80% is contained in the tissues—as *tissue,* or *interstitial, fluid*—with the blood plasma accounting for the remaining 20% (fig. 14.8).

The distribution of water between the interstitial fluid and the blood plasma is determined by a balance between opposing forces acting at the capillaries. Blood pressure, for example, promotes the formation of interstitial fluid from plasma, whereas osmotic forces draw water from the tissues into the vascular system. The total volume of intracellular and extracellular fluid is normally maintained constant by a balance between water loss and water gain. Mechanisms that affect drinking, urine volume, and the distribution of water between plasma and interstitial fluid thus help to regulate blood volume and, by this means, help to regulate cardiac output and blood flow.

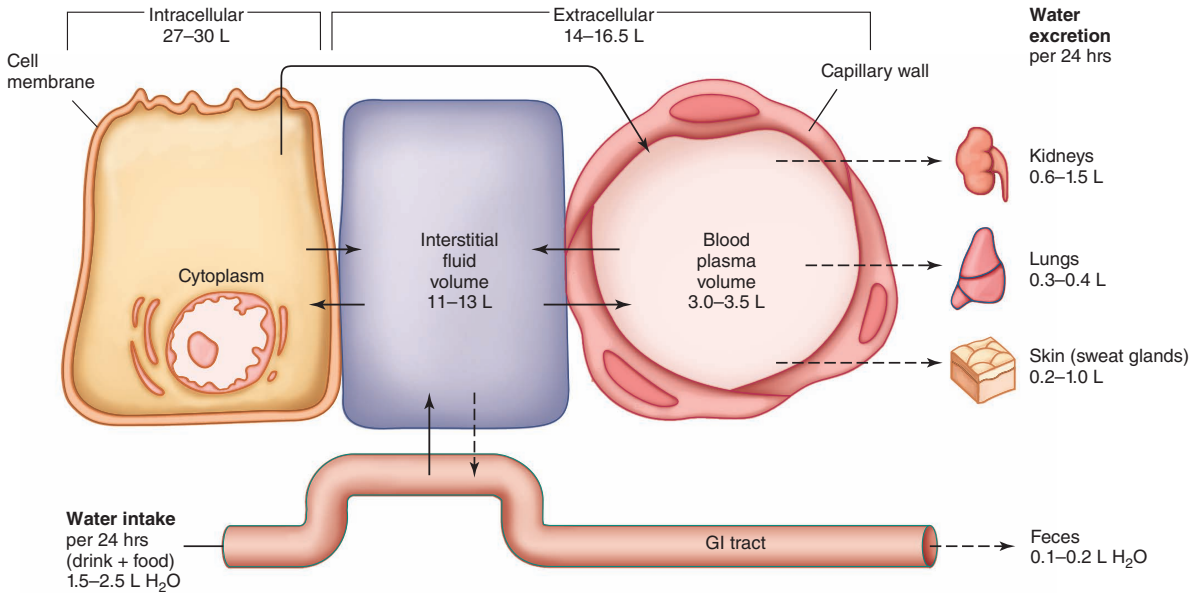


Figure 14.8 The distribution of body water between the intracellular and extracellular compartments. The extracellular compartment includes the blood plasma and the interstitial (tissue) fluid.

Exchange of Fluid Between Capillaries and Tissues

The distribution of extracellular fluid between the plasma and interstitial compartments is in a state of dynamic equilibrium. Tissue fluid is not normally a "stagnant pond;" rather, it is a continuously circulating medium, formed from and returning to the vascular system. In this way, the tissue cells receive a continuously fresh supply of glucose and other plasma solutes that are filtered through tiny endothelial channels in the capillary walls.

Filtration results from blood pressure within the capillaries. This hydrostatic pressure, which is exerted against the inner capillary wall, is equal to about 37 mmHg at the arteriolar end of systemic capillaries and drops to about 17 mmHg at the venular end of the capillaries. The **net filtration pressure** is equal to the hydrostatic pressure of the blood in the capillaries minus the hydrostatic pressure of tissue fluid outside the capillaries, which opposes filtration. If, as an extreme example, these two values were equal, there would be no filtration. However, the hydrostatic pressure of interstitial fluid is normally kept low by the removal of fluid through drainage into lymphatic vessels (chapter 13; see fig. 13.36).

The magnitude of the tissue hydrostatic pressure varies from organ to organ. With a hydrostatic pressure in the interstitial fluid of 1 mmHg, as it is outside the capillaries of skeletal muscles, the net filtration pressure would be 37 − 1 = 36 mmHg at the arteriolar end of the capillary and 17 − 1 = 16 mmHg at the venular end.

Glucose, comparably sized organic molecules, inorganic salts, and ions are filtered along with water through the capillary pores. The concentrations of these substances in interstitial (tissue) fluid are thus the same as in plasma. The protein concentration of interstitial fluid (2 g/100 ml), however, is less than the protein concentration of plasma (6 to 8 g/100 ml). This difference is due to the restricted filtration of proteins through the capillary pores. The osmotic pressure exerted by plasma proteins—called the **colloid osmotic pressure** of the plasma (because proteins are present as a colloidal suspension)—is therefore much greater than the colloid osmotic pressure of interstitial fluid. The difference between these two osmotic pressures is called the **oncotic pressure.** The colloid osmotic pressure of the interstitial fluid is sufficiently low to be neglected, so the oncotic pressure is essentially equal to the colloid osmotic pressure of the plasma. This value has been estimated to be 25 mmHg. Because water will move by osmosis from the solution of lower to the solution of higher osmotic pressure (chapter 6), this oncotic pressure favors the movement of water into the capillaries.

Whether fluid will move out of or into the capillary depends on the magnitude of the net filtration pressure, which varies from the arteriolar to the venular end of the capillary, and on the oncotic pressure. These opposing forces that affect the distribution of fluid across the capillary are known as **Starling forces,** and their effects can be calculated according to this relationship:

Fluid movement is proportional to:

$$\underbrace{(p_c + \pi_i)}_{\text{(Fluid out)}} - \underbrace{(p_i + \pi_p)}_{\text{(Fluid in)}}$$

where

P_c = hydrostatic pressure in the capillary
π_i = colloid osmotic pressure of the interstitial (tissue) fluid
P_i = hydrostatic pressure of interstitial fluid
π_p = colloid osmotic pressure of the blood plasma

The expression to the left of the minus sign represents the sum of forces acting to move fluid out of the capillary. The expression to the right represents the sum of forces acting to move fluid into the capillary. Figure 14.9 provides typical values for blood capillaries in skeletal muscles. Notice that the sum of the forces acting on the capillary is a positive number at the arteriolar end and a negative number at the venular end of the capillary. Examination of figure 14.9 reveals that this change is caused by the decrease in hydrostatic pressure (blood pressure) within the capillary as blood travels from the arteriolar to the venular end. The positive value at the arteriolar end indicates that the Starling forces that favor the filtration of fluid out of the capillary predominate. The negative value at the venular end indicates that the net Starling forces favor the return of fluid to the capillary. Fluid thus leaves the capillaries at the arteriolar end and returns to the capillaries at the venular end (fig. 14.9, *top*).

This "classic" view of capillary dynamics has been modified in recent years by the realization that the balance of filtration and reabsorption varies in different tissues and under different conditions in a particular capillary. For example, a capillary may be open or closed off by precapillary muscles that function as sphincters. When the capillary is open, blood flow is high and the net filtration force exceeds the force for the osmotic return of water throughout the length of the capillary. The opposite is true if the precapillary sphincter closes and the blood flow through the capillary is reduced.

Through the action of the Starling forces, plasma and interstitial fluid are continuously interchanged. The return of fluid to the vascular system at the venular ends of the capillaries, however, does not exactly equal the amount filtered at the arteriolar ends. Approximately 85% to 90% of the filtrate is returned directly to the blood capillaries; the remaining 10% to 15% is returned to the blood by way of the lymphatic system. This amounts to about 1–2 L of interstitial fluid per day, containing 20–30 g of protein per liter that enters lymphatic capillaries. As may be recalled from chapter 13 (see fig. 13.36), lymphatic capillaries are blind-ended, highly permeable vessels that drain their contents (now called lymph) into lymphatic vessels, which ultimately return this fluid to the venous system.

Causes of Edema

Excessive accumulation of interstitial fluid is known as **edema.** This condition is normally prevented by a proper balance between capillary filtration and osmotic uptake of water and by proper lymphatic drainage. Edema may thus result from

1. *high arterial blood pressure,* which increases capillary pressure and causes excessive filtration;
2. *venous obstruction*—as in phlebitis (where a thrombus forms in a vein) or mechanical compression of veins

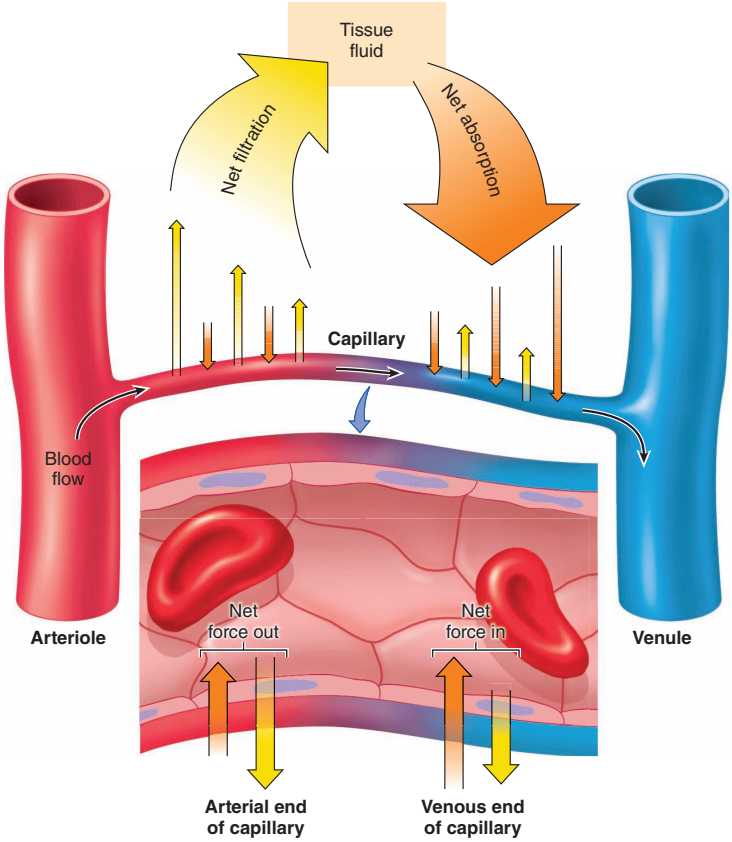


Figure 14.9 **The distribution of fluid across the walls of a capillary.** Tissue, or interstitial, fluid is formed by filtration (*yellow arrows*) as a result of blood pressures at the arteriolar ends of capillaries; it is returned to the venular ends of capillaries by the colloid osmotic pressure of plasma proteins (*orange arrows*). AP|R

See the *Test Your Quantitative Ability* section of the Review Activities at the end of this chapter.

(during pregnancy, for example)—which produces a congestive increase in capillary pressure;

3. *leakage of plasma proteins into interstitial fluid,* which causes reduced osmotic flow of water into the capillaries (this occurs during inflammation and allergic reactions as a result of increased capillary permeability);
4. *myxedema*—the excessive production of particular glycoproteins (mucin) in the extracellular matrix caused by hypothyroidism;
5. *decreased plasma protein concentration,* as a result of liver disease (the liver makes most of the plasma proteins) or kidney disease where plasma proteins are excreted in the urine;
6. *obstruction of the lymphatic drainage* due to parasitic larvae in elephantiasis (fig. 14.10 and table 14.2) or to surgery (breast surgery is a leading cause of lymphedema).

Clinical Investigation CLUES

Mark had hypoproteinemia (low plasma protein concentration) as a result of protein leakage through his intestine, and he had edema.

- How does his hypoproteinemia relate to his edema?
- Once his hypoproteinemia is corrected, how will his edema be resolved?

CLINICAL APPLICATION

Filariasis is a tropical disease in which bloodsucking insects such as mosquitos spread a parasitic nematode worm. In **elephantiasis** (fig. 14.10), species of these worms take up residence in the lymphatic system, where their larvae block the lymphatic drainage. The edema that results can greatly swell tissues and produce a thickening and cracking of the skin. This disease is found in about 72 tropical countries, where over a billion people live and are threatened by infection. However, there are effective drugs available against the filariasis parasite, and the Global Program to Eliminate Filariasis, begun in 2000, has successfully treated millions of people in an effort to eradicate this disease.

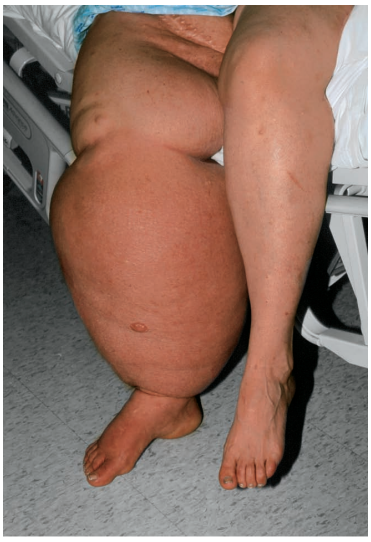


Figure 14.10 **The severe edema of elephantiasis.** Parasitic larvae that block lymphatic drainage produce tissue edema and the tremendous enlargement of the limbs and scrotum in elephantiasis.

Regulation of Blood Volume by the Kidneys

The formation of urine by the kidneys begins in the same manner as the formation of interstitial fluid—by filtration of plasma through capillary pores. These capillaries are known as *glomeruli,* and the filtrate they produce enters a system of tubules that transports and modifies the filtrate (by mechanisms discussed in chapter 17). The total blood volume is only about 5.5 L, yet the kidneys produce about 180 L/day of blood filtrate; thus, most of this filtrate must be returned to the vascular system and recycled. Only about 1.5 L of urine is excreted daily; 98% to 99% of the amount filtered is **reabsorbed** back into the vascular system.

The volume of urine excreted can be varied by changes in the reabsorption of filtrate. If 99% of the filtrate is reabsorbed, for example, 1% must be excreted. Decreasing the reabsorption by only 1%—from 99% to 98%—would double the volume of urine excreted (an increase to 2% of the amount filtered). Carrying the logic further, a doubling of urine volume from, for example, 1 to 2 liters, would result in the loss of an additional liter of blood volume. The percentage of the glomerular filtrate reabsorbed—and thus the urine volume and blood volume—is adjusted according to the needs of the body by the action of

Table 14.2 | Causes of Edema

Cause	Comments
Increased blood pressure or venous obstruction	Increases capillary filtration pressure so that more tissue fluid is formed at the arteriolar ends of capillaries.
Increased tissue protein concentration	Decreases osmosis of water into the venular ends of capillaries. Usually a localized tissue edema due to leakage of plasma proteins through capillaries during inflammation and allergic reactions. Myxedema due to hypothyroidism is also in this category.
Decreased plasma protein concentration	Decreases osmosis of water into the venular ends of capillaries. May be caused by liver disease (which can be associated with insufficient plasma protein production), kidney disease (due to leakage of plasma protein into urine), or protein malnutrition.
Obstruction of lymphatic vessels	Infections by filaria roundworms (nematodes) transmitted by a certain species of mosquito block lymphatic drainage, causing edema and tremendous swelling of the affected areas.

specific hormones on the kidneys. Through their effects on the kidneys and the resulting changes in blood volume, these hormones serve important functions in the regulation of the cardiovascular system.

The sympathetic nervous system is also involved in the homeostasis of blood volume. An increase in blood volume is detected by stretch receptors in the atria of the heart, which selectively regulate sympathetic nerve activity. The activity of sympathetic fibers to the heart is increased, while the sympathetic nerve activity to the kidneys is reduced (there is little change in sympathetic nerve activity to other organs). Reduced sympathetic nerve stimulation of renal arteries produces vasodilation and increased blood flow, thereby promoting increased urine production to lower the blood volume and complete the negative feedback loop.

Regulation by Antidiuretic Hormone (ADH)

One of the major hormones involved in the regulation of blood volume is **antidiuretic hormone (ADH),** also known as *vasopressin.* This hormone is produced by neurons in the hypothalamus, transported by axons into the posterior pituitary, and released from this storage gland in response to hypothalamic stimulation (chapter 11, section 11.3). The release of ADH from the posterior pituitary occurs when neurons in the hypothalamus called **osmoreceptors** detect an increase in plasma osmolality (fig. 14.11).

An increase in plasma osmolality occurs when the plasma becomes more concentrated. This can be produced either by *dehydration* or by excessive *salt intake.* Stimulation of osmoreceptors produces sensations of thirst, leading to increased water intake and an increase in the amount of ADH released from the posterior pituitary. Through mechanisms that will be discussed in conjunction with kidney physiology (chapter 17, section 17.3), ADH stimulates water reabsorption from the filtrate. A smaller volume of urine is thus excreted as a result of the action of ADH (fig. 14.11).

A person who is dehydrated or who consumes excessive amounts of salt thus drinks more and urinates less. This raises the blood volume and, in the process, dilutes the plasma to lower its previously elevated osmolality. The rise in blood volume that results from these mechanisms is extremely important in stabilizing the condition of a dehydrated person with low blood volume and pressure.

Drinking excessive amounts of water without excessive amounts of salt does not result in a prolonged increase in blood volume and pressure. The water does enter the blood from the intestine and momentarily raises the blood volume; at the same time, however, it dilutes the blood. Dilution of the blood decreases the plasma osmolality and thus inhibits the release of ADH. With less ADH there is less reabsorption of water in the kidneys—a larger volume of more-dilute urine is excreted. Water is therefore a *diuretic*—a substance that promotes urine formation—because it inhibits the release of antidiuretic hormone.

Dilution of the blood (decreased blood osmolality) lowers ADH secretion, but a rise in blood volume itself (even in the absence of dilution) can reduce ADH secretion. This is because an increased blood volume mechanically stimulates stretch receptors in the left atrium, aortic arch, and carotid sinus, which in turn cause increased firing of sensory neurons (in cranial nerves IX and X). ADH secretion is inhibited by this sensory input, so that more water is eliminated from the blood by the kidneys.

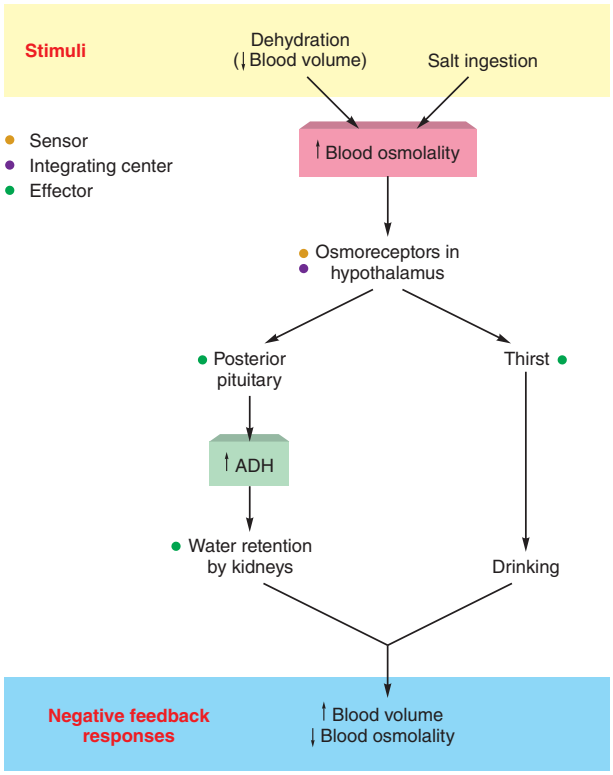


Figure 14.11 The negative feedback control of blood volume and blood osmolality. Thirst and ADH secretion are triggered by a rise in plasma osmolality. Homeostasis is maintained by countermeasures, including drinking and conservation of water by the kidneys.

Conversely, a lowering of blood volume by about 10% reduces stimulation of these stretch receptors, reducing the firing of their associated sensory neurons. This produces an increase in ADH secretion, which stimulates the kidneys to retain more water in the blood. These negative feedback loops thereby help to maintain homeostasis of blood volume.

When blood volume rises, the stimulation of stretch receptors in the atria of the heart has an additional effect: it stimulates the atria to secrete a hormone known as *atrial natriuretic peptide.* This hormone increases the excretion of salt and water in the urine, thereby working, like a decrease in ADH secretion, to lower blood volume. Atrial natriuretic peptide is discussed in a separate section.

FITNESS APPLICATION

Hydration during exercise becomes increasingly important as the exercise is prolonged, because sweating can cause the loss of a substantial amount of water (up to 900 mL per hour). Lowered blood volume can lower the cardiac output and blood flow. Among other effects, this reduces the ability of the body to dissipate heat and limits the extent of the exercise. Drinking appropriate amounts of water can alleviate this, but only if the exercise is not too long and strenuous. If it is, then electrolytes—primarily Na^+, K^+, and Cl^-—that are also lost in sweat must be replenished. When that happens, drinking water may quench thirst (because the water restores a normal plasma osmolality, satisfying the osmoreceptors) but not maintain the blood volume. **Sports drinks** that contain the proper amount of electrolytes and carbohydrates (to help maintain blood glucose when glycogen reserves are depleted), taken not just when thirsty but at predetermined intervals, may be better for long, endurance exercises.

Clinical Investigation CLUES

Mark trained for marathons and experienced dizziness upon standing. He was told to drink more and to switch to sports drinks for such prolonged exercise.

- What might have caused Mark's dizziness?
- How might sports drinks under these circumstances be better for him than water?

Regulation by Aldosterone

From the preceding discussion, it is clear that a certain amount of dietary salt is required to maintain blood volume and pressure. Since Na^+ and Cl^- are easily filtered in the kidneys, a mechanism must exist to promote the reabsorption and retention of salt when the dietary salt intake is too low. **Aldosterone,** a steroid hormone secreted by the adrenal cortex, stimulates the reabsorption of salt by the kidneys. Aldosterone is thus a "salt-retaining hormone." Retention of salt indirectly promotes retention of water (in part, by the action of ADH, as previously discussed). The action of aldosterone produces an increase in blood volume, but, unlike ADH, it does not produce a change in plasma osmolality. This is because aldosterone promotes the reabsorption of salt and water in proportionate amounts, whereas ADH promotes only the reabsorption of water. Thus, unlike ADH, aldosterone does not act to dilute the blood.

The secretion of aldosterone is stimulated during salt deprivation, when the blood volume and pressure are reduced. The adrenal cortex, however, is not directly stimulated to secrete aldosterone by these conditions. Instead, a decrease in blood volume and pressure activates an intermediate mechanism, described next.

FITNESS APPLICATION

Salt has been highly valued throughout human history because it is often in short supply, is needed to maintain blood volume and pressure, and is used for food preservation. For example, salt cakes were used as money in Abyssinia, and Roman soldiers were often paid with salt—a practice from which the word *salary* (sal = *salt*) derives, as does the phrase "worth his salt." Salt has also played roles in many national events; for example, Mahatma Gandhi led Indians, in their bid for independence, to make their own salt in defiance of a British monopoly.

Renin-Angiotensin-Aldosterone System

Salt deprivation results in low blood volume and pressure, as described in the previous section on ADH. This lowers the blood pressure in the renal artery and reduces the amount of NaCl and water in the renal filtrate. The *juxtaglomerular apparatus* in the kidneys (chapter 17; see fig. 17.26) senses these changes and, in response, secretes the enzyme **renin** into the blood (chapter 17, section 17.5). This enzyme cleaves a ten-amino-acid polypeptide called *angiotensin I* from a plasma protein called *angiotensinogen.* As angiotensin I passes through the capillaries of the lungs, an *angiotensin-converting enzyme (ACE)* removes two amino acids. This leaves an eight-amino-acid polypeptide called **angiotensin II** (fig. 14.12). Conditions of salt deprivation, low blood volume, and low blood pressure, in summary, cause increased production of angiotensin II in the blood. (High blood pressure, by contrast, suppresses renin secretion and thereby results in reduced production of angiotensin II.)

Angiotensin II exerts numerous effects that cause blood pressure to rise. Its most direct effect is to stimulate contraction of the smooth muscle layers of the small arteries and arterioles. By this means, angiotensin II is a powerful vasoconstrictor, increasing the total peripheral resistance and thus the arterial blood pressure. Angiotensin II also promotes a rise in blood volume (thereby increasing the blood pressure) by stimulating (1) the thirst center in the hypothalamus, and (2) the adrenal cortex to secrete aldosterone.

When the thirst center in the hypothalamus is stimulated, more water is taken into the intestine and then the blood. When the adrenal cortex is stimulated by angiotensin II to secrete more aldosterone, the increased aldosterone stimulates the kidneys to retain more salt and water. The relationship between the kidneys, angiotensin II, and aldosterone is described as the **renin-angiotensin-aldosterone system.** As a result of thirst and the activation of the renin-angiotensin-aldosterone system, we drink more, retain more NaCl, and urinate less (thereby increasing the blood volume) when conditions of low blood volume and pressure cause an increased secretion of renin from the juxtaglomerular apparatus of the kidneys.

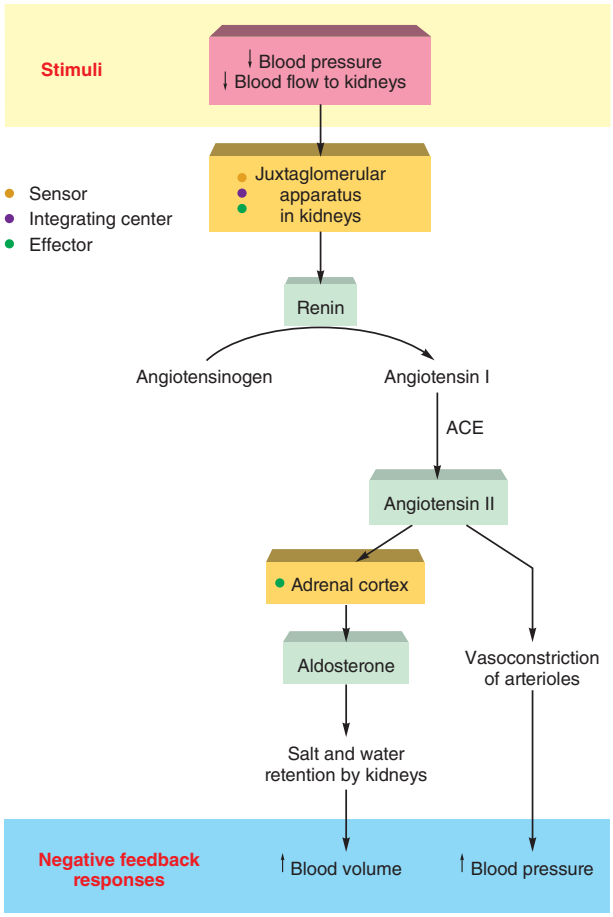


Figure 14.12 The renin-angiotensin-aldosterone system. This system helps to maintain homeostasis through the negative feedback control of blood volume and pressure. (ACE = angiotensin-converting enzyme.)

The renin-angiotensin-aldosterone system can also work in the opposite direction: high salt intake, leading to high blood volume and pressure, normally inhibits renin secretion. With less angiotensin II formation and less aldosterone secretion, less salt is retained by the kidneys and more is excreted in the urine. Unfortunately, many people with chronically high blood pressure may have normal or even elevated levels of renin secretion. In these cases, the intake of salt must be lowered to match the impaired ability to excrete salt in the urine.

Atrial Natriuretic Peptide

Scientists have long known that a rise in blood volume, or an increased venous return for any other reason, leads to increased urine production (*diuresis*). In fact, it is a common observation that immersion in water (which increases venous return) causes increased diuresis. But how is this accomplished? Experiments suggest that the increased water excretion under conditions of high blood volume or venous return is at least partly due to an increase in the excretion of Na^+ in the urine, or *natriuresis* (*natrium* = sodium; *uresis* = making water).

Increased Na^+ excretion (natriuresis) may be produced by a decline in aldosterone secretion, but there is evidence that there is a separate hormone that stimulates natriuresis. This *natriuretic hormone* would thus be antagonistic to aldosterone and would promote Na^+ and water excretion in the urine in response to a rise in blood volume. A polypeptide hormone with these properties, identified as **atrial natriuretic peptide (ANP),** is produced by the atria of the heart.

When a person floats in water, there is an increase in venous return to the heart. This (like an increase in blood volume) stretches the atria, thereby stimulating the release of ANP. In addition, ADH secretion from the posterior pituitary is inhibited, due to sensory information traveling to the hypothalamus in the vagus nerves from stretch receptors in the left atrium. Increased ANP, together with decreased ADH, leads to a greater excretion of salt and water in the urine. This works as a negative feedback correction to lower the blood volume and thus maintain homeostasis (fig. 14.13).

CLINICAL APPLICATION

Angiotensin converting enzyme inhibitors (ACE inhibitors) are drugs that prevent the conversion of angiotensin I to angiotensin II, reducing the ability of angiotensin II to stimulate vasoconstriction. This action promotes vasodilation and a lowering of the total peripheral resistance, thereby lowering blood pressure. ACE inhibitors—including *captopril, enalapril,* and *lisinopril*—help to treat hypertension, heart failure, stroke, and potential kidney failure, and aid the survival of people who have had myocardial infarctions. **Angiotensin receptor blockers (ARBs)**—including *telmisartan, losartan,* and *valsartan*—inhibit the binding of angiotensin II to its receptors on vascular smooth muscles, thereby reducing vasoconstriction. This promotes vasodilation and a lowering of the blood pressure, much like the actions of the ACE inhibitors, and so ARBs have similar medical uses.

Clinical Investigation CLUES

Mark was diagnosed with essential hypertension, for which the physician prescribed an ACE inhibitor.

- What is ACE, and what does it do?
- How does an ACE inhibitor help to lower the blood pressure?

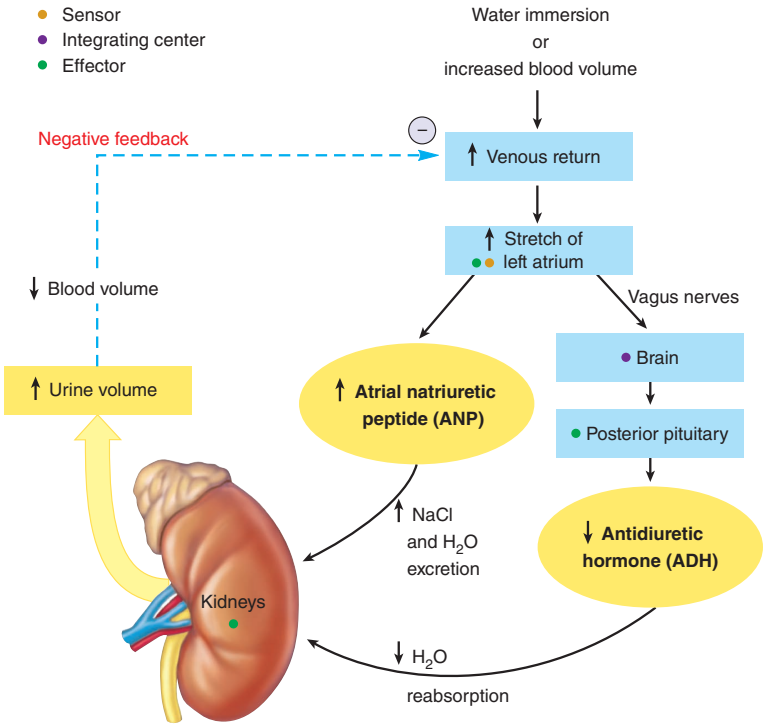


Figure 14.13 **Negative feedback correction of increased venous return.** Stimulation of stretch receptors in the left atrium causes secretion of atrial natriuretic peptide (ANP), which increases urinary excretion of salt and water. At the same time, stimulation of these stretch receptors leads to decreased antidiuretic hormone (ADH) secretion. Because ADH stimulates the kidneys to reabsorb (retain) water, a fall in ADH works together with the increased ANP to increase urine volume. This maintains homeostasis by lowering blood volume and venous return.

CHECKPOINT

4a. Describe the composition of interstitial fluid. Using a flow diagram, explain how interstitial fluid is formed and how it is returned to the vascular system.

4b. Define the term *edema* and describe four different mechanisms that can produce this condition.

5a. Describe the effects of dehydration on blood and urine volumes. What cause-and-effect mechanism is involved?

5b. Explain why salt deprivation causes increased salt and water retention by the kidneys.

5c. Describe the actions of atrial natriuretic peptide and explain their significance.

14.3 VASCULAR RESISTANCE TO BLOOD FLOW

The rate of blood flow to an organ is related to the resistance to flow in the small arteries and arterioles. Vasodilation decreases resistance and increases flow, whereas vasoconstriction increases resistance and decreases flow. These changes occur in response to various regulatory mechanisms.

LEARNING OUTCOMES

After studying this section, you should be able to:

6. Describe the factors that affect blood flow through vessels.

7. Describe the intrinsic and extrinsic regulation of peripheral resistance.

The amount of blood that the heart pumps per minute is equal to the rate of venous return, and thus is equal to the rate of blood flow through the entire circulation. The cardiac output is about 5 to 6 L per minute, depending upon body size and other factors. This total cardiac output is distributed unequally to the different organs because of unequal resistances to blood flow through the organs. The distribution of the cardiac output to various organs at rest, in terms of percentages and rates of blood flow, is provided in table 14.3.

Table 14.3 | Estimated Distribution of the Cardiac Output at Rest

Organs	Blood Flow	
	Milliliters per Minute	Percent Total
Gastrointestinal tract and liver	1,400	24
Kidneys	1,100	19
Brain	750	13
Heart	250	4
Skeletal muscles	1,200	21
Skin	500	9
Other organs	600	10
Total organs	5,800	100

Source: From O. L. Wade and J. M. Bishop, *Cardiac Output and Regional Blood Flow.* Copyright © 1962 Blackwell Science, Ltd. Used with permission.

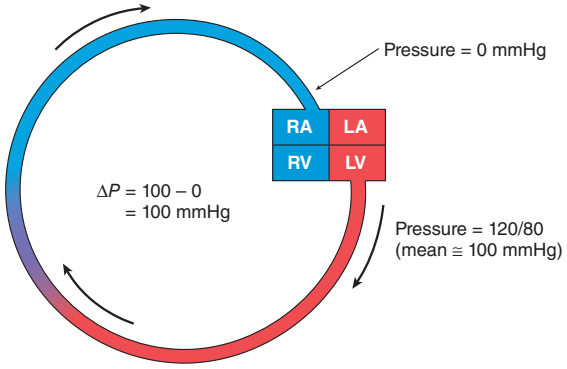


Figure 14.14 Blood flow is produced by a pressure difference. The flow of blood in the systemic circulation is ultimately dependent on the pressure difference (Δ *P*) between the mean pressure of about 100 mmHg at the origin of flow in the aorta and the pressure at the end of the circuit—0 mmHg in the vena cava, where it joins the right atrium (RA). (LA = left atrium; RV = right ventricle; LV = left ventricle.)

Physical Laws Describing Blood Flow

The flow of blood through the vascular system, like the flow of any fluid through a tube, depends in part on the difference in pressure at the two ends of the tube. If the pressure at both ends of the tube is the same, there will be no flow. If the pressure at one end is greater than at the other, blood will flow from the region of higher to the region of lower pressure. The rate of blood flow is proportional to the pressure difference ($P_1 - P_2$) between the two ends of the tube. The term **pressure difference** is abbreviated ΔP, in which the Greek letter Δ (*delta*) means "change in."

If the systemic circulation is pictured as a single tube leading from and back to the heart (fig. 14.14), blood flow through this system would occur as a result of the pressure difference between the beginning of the tube (the aorta) and the end of the tube (the junction of the venae cavae with the right atrium). The average pressure, or **mean arterial pressure (MAP),** is about 100 mmHg; the pressure at the right atrium is 0 mmHg. The "pressure head," or driving force (Δ *P*), is therefore about 100 − 0 = 100 mmHg.

Blood flow is directly proportional to the pressure difference between the two ends of the tube (ΔP) but is *inversely proportional* to the frictional resistance to blood flow through the vessels. Inverse proportionality is expressed by showing one of the factors in the denominator of a fraction, since a fraction decreases when the denominator increases:

$$\text{Blood flow} \propto \frac{\Delta P}{\text{resistance}}$$

The **resistance** to blood flow through a vessel is directly proportional to the length of the vessel and to the viscosity of the blood (the "thickness," or ability of molecules to "slip over" each other; for example, honey is quite viscous). Of particular physiological importance, the resistance is inversely proportional to the fourth power of the radius of the vessel:

$$\text{Resistance} \propto \frac{L\eta}{r^4}$$

where

L = length of vessel
η = viscosity of blood
r = radius of vessel

For example, if one vessel has half the radius of another and if all other factors are the same, the smaller vessel will have 16 times (2^4) the resistance of the larger vessel. Blood flow through the larger vessel, as a result, will be 16 times greater than in the smaller vessel (fig. 14.15).

When physical constants are added to this relationship, the rate of blood flow can be calculated according to **Poiseuille's** (*pwˇa-zuh'yez*) **law:**

$$\text{Blood flow} \propto \frac{\Delta P r^4 (\pi)}{\eta L (8)}$$

Vessel length (L) and blood viscosity (the Greek letter *eta,* written η) do not vary significantly in normal physiology, although blood viscosity is increased in severe dehydration and in the polycythemia (high red blood cell count) that occurs as an adaptation to life at high altitudes. The major physiological regulators of blood flow through an organ are the mean arterial pressure (P, driving the flow) and the vascular resistance to flow. At a given mean arterial pressure, blood can be diverted from one organ to another by variations in the degree of vasoconstriction and vasodilation of small arteries and arterioles (that is, by variations in vessel radius, r). Vasoconstriction in

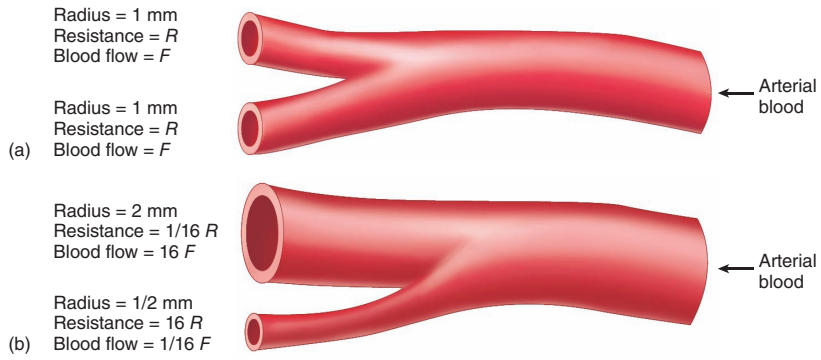


Figure 14.15 **The relationships between blood flow, vessel radius, and resistance.** (*a*) The resistance and blood flow are equally divided between two branches of a vessel. (*b*) A doubling of the radius of one branch and halving of the radius of the other produces a sixteenfold increase in blood flow in the former and a sixteenfold decrease of blood flow in the latter.

See the *Test Your Quantitative Ability* section of the Review Activities at the end of this chapter.

one organ and vasodilation in another result in a diversion, or *shunting,* of blood to the second organ. Because arterioles are the smallest arteries and can become narrower by vasoconstriction, they provide the greatest resistance to blood flow (fig. 14.16). Blood flow to an organ is thus largely determined by the degree of vasoconstriction or vasodilation of its arterioles. The rate of blood flow to an organ can be increased by dilation of its arterioles and can be decreased by constriction of its arterioles.

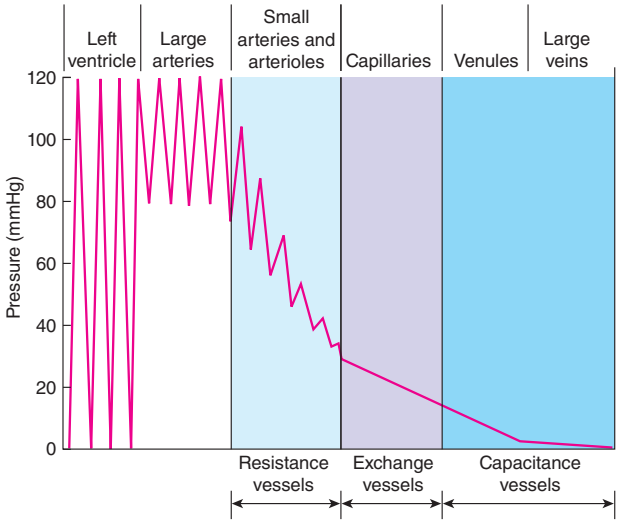


Figure 14.16 **Blood pressure in different vessels of the systemic circulation.** Notice that the pressure generated by the beating of the ventricles is largely dissipated by the time the blood gets into the venous system, and that this pressure drop occurs primarily as blood goes through the arterioles and capillaries.

Total Peripheral Resistance

The sum of all the vascular resistances within the systemic circulation is called the **total peripheral resistance.** The arteries that supply blood to the organs are generally in parallel rather than in series with each other. That is, arterial blood passes through only one set of resistance vessels (arterioles) before returning to the heart (fig. 14.17). Because one organ is not "downstream" from another in terms of its arterial supply, changes in resistance within one organ directly affect blood flow in that organ only.

Vasodilation in a large organ might, however, significantly decrease the total peripheral resistance and, by this means, might decrease the mean arterial pressure. In the absence of compensatory mechanisms, the driving force for blood flow through all organs might be reduced. This situation is normally prevented by an increase in the cardiac output and by vasoconstriction in other areas. During exercise of the large muscles, for example, the arterioles in the exercising muscles are dilated. This would cause a great fall in mean arterial pressure if there were no compensations. But the blood pressure actually rises during exercise, primarily because of increased cardiac output and vasoconstriction in the viscera. Also, sympathetic nerves produce cutaneous vasoconstriction at the beginning of exercise, raising blood pressure. However, when exercise is prolonged, increased metabolic heat production overrides this effect to increase the flow of warm blood to the skin for improved heat loss (see table 14.7).

Extrinsic Regulation of Blood Flow

The term *extrinsic regulation* refers to control by the autonomic nervous system and endocrine system. Angiotensin II, for example, directly stimulates vascular smooth muscle to produce vasoconstriction. Antidiuretic hormone (ADH) also has a vasoconstrictor effect at high concentrations; this is why it is also called *vasopressin.* However, this vasopressor effect

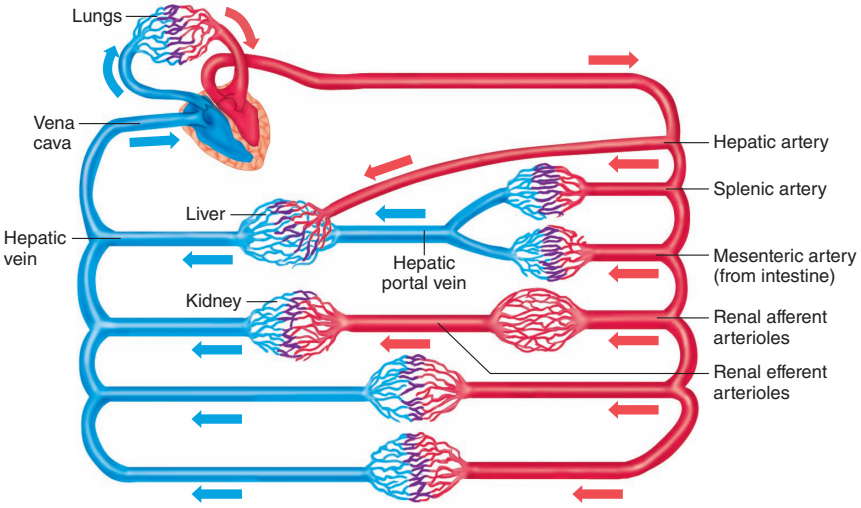


Figure 14.17 A diagram of the systemic and pulmonary circulations. Notice that with few exceptions (such as blood flow in the renal circulation) the flow of arterial blood is in parallel rather than in series (arterial blood does not usually flow from one organ to another). AP|R

of ADH is not believed to be significant under physiological conditions in humans.

Regulation by Sympathetic Nerves

Stimulation of the sympathoadrenal system produces an increase in the cardiac output (as previously discussed) and an increase in total peripheral resistance. The latter effect is due to alpha-adrenergic stimulation (chapter 9; see fig. 9.10) of vascular smooth muscle by norepinephrine and, to a lesser degree, by epinephrine. This produces vasoconstriction of the arterioles in the viscera and skin.

Even when a person is calm, the sympathoadrenal system is active to a certain degree and helps set the "tone" of vascular smooth muscles. In this case, **adrenergic sympathetic fibers** (those that release norepinephrine) activate alpha-adrenergic receptors to cause a basal level of vasoconstriction throughout the body. During the fight-or-flight reaction, an increase in the activity of adrenergic fibers produces vasoconstriction in the digestive tract, kidneys, and skin.

Arterioles in skeletal muscles receive **cholinergic sympathetic fibers,** which release acetylcholine as a neurotransmitter. During the fight-or-flight reaction, the activity of these cholinergic fibers increases. This causes vasodilation. Vasodilation in skeletal muscles is also produced by epinephrine secreted by the adrenal medulla, which stimulates beta-adrenergic receptors. During the fight-or-flight reaction, therefore, blood flow is decreased to the viscera and skin because of the alpha-adrenergic effects of vasoconstriction in these organs, whereas blood flow to the skeletal muscles is increased. This diversion of blood flow to the skeletal muscles during emergency conditions may give these muscles an "extra edge" in responding to the emergency. Once exercise begins, however, the blood flow to skeletal muscles increases far more due to other mechanisms (described shortly under Intrinsic Regulation of Blood Flow).

Parasympathetic Control of Blood Flow

Parasympathetic endings in arterioles are always cholinergic and always promote vasodilation. Parasympathetic innervation of blood vessels, however, is limited to the digestive tract, external genitalia, and salivary glands. Because of this limited distribution, the parasympathetic system is less important than the sympathetic system in the control of total peripheral resistance.

The extrinsic control of blood flow is summarized in table 14.4.

Paracrine Regulation of Blood Flow

Paracrine regulators are molecules produced by one tissue that help to regulate another tissue of the same organ (chapter 11, section 11.7). Blood vessels are particularly subject to paracrine regulation. Specifically, the endothelium of the tunica interna produces a number of paracrine regulators that cause the smooth muscle of the tunica media to either relax or contract.

Smooth muscle relaxation results from the local effects of a number of molecules produced by the vessel endothelium, including **bradykinin, nitric oxide,** and several prostaglandins, particularly **prostaglandin I_2 (prostacyclin).** The relaxation of vascular smooth muscle produces vasodilation, which is an effect that can be medically useful. For example, the vasodilation induced by nitric oxide explains why *nitroglycerin* and related drugs (which can be converted to nitric oxide) are beneficial for the treatment of angina pectoris. As another example, people with pulmonary hypertension—a disease in which increased vascular resistance in the pulmonary circulation can lead to failure of the right ventricle—are sometimes treated by intravenous administration of prostacyclin (prostaglandin I_2).

The endothelium of arterioles contains an enzyme, *endothelial nitric oxide synthase (eNOS),* which produces nitric

Table 14.4 | Extrinsic Control of Vascular Resistance and Blood Flow

Extrinsic Agent	Effect	Comments
Sympathetic nerves		
Alpha-adrenergic	Vasoconstriction	Vasoconstriction is the dominant effect of sympathetic nerve stimulation on the vascular system, and it occurs throughout the body.
Beta-adrenergic	Vasodilation	There is some activity in arterioles in skeletal muscles and in coronary vessels, but effects are masked by dominant alpha-receptor-mediated constriction.
Cholinergic	Vasodilation	Effects are localized to arterioles in skeletal muscles and are produced only during defense (fight-or-flight) reactions.
Parasympathetic nerves	Vasodilation	Effects are restricted primarily to the gastrointestinal tract, external genitalia, and salivary glands and have little effect on total peripheral resistance.
Angiotensin II	Vasoconstriction	A powerful vasoconstrictor produced as a result of secretion of renin from the kidneys; it may function to help maintain adequate filtration pressure in the kidneys when systemic blood flow and pressure are reduced.
ADH (vasopressin)	Vasoconstriction	Although the effects of this hormone on vascular resistance and blood pressure in anesthetized animals are well documented, the importance of these effects in conscious humans is controversial.
Histamine	Vasodilation	Histamine promotes localized vasodilation during inflammation and allergic reactions.
Bradykinins	Vasodilation	Bradykinins are polypeptides secreted by sweat glands and by the endothelium of blood vessels; they promote local vasodilation.
Prostaglandins	Vasodilation or vasoconstriction	Prostaglandins are cyclic fatty acids that can be produced by most tissues, including blood vessel walls. Prostaglandin I_2 is a vasodilator, whereas thromboxane A_2 is a vasoconstrictor. The physiological significance of these effects is presently controversial.

oxide (NO) from L-arginine. The NO diffuses into the smooth muscle cells of the tunica media of arterioles and activates the enzyme guanylate cyclase, which converts GTP into cyclic GMP (cGMP) and pyrophosphate (PP_i). The cGMP serves as a second messenger that, through a variety of mechanisms, lowers the cytoplasmic Ca^{2+} concentration. This leads to smooth muscle relaxation and thus to vasodilation (see chapter 20, fig. 20.21).

Many scientists believe that nitric oxide, in addition to functioning as a paracrine regulator within the vessel wall where it is produced, also functions as a hormone carried by the blood to distant vessels. Nitric oxide can bind to the sulfur atoms of cysteine amino acids within hemoglobin (forming *S-nitrosohemoglobin,* abbreviated *SNO*), which may then transport the nitric oxide in the blood downstream to vessels of other organs. The binding of nitric oxide to the cysteines in hemoglobin is favored by high oxygen concentrations, and the release of nitric oxide—producing vasodilation and thus increased blood flow—is favored by low oxygen concentrations. However, the physiological significance of this effect is not yet firmly established.

The endothelium also produces paracrine regulators that promote vasoconstriction. Notable among these is the polypeptide **endothelin-1.** This paracrine regulator stimulates vasoconstriction of arterioles, thus raising the total peripheral resistance. Endothelin-1 receptor antagonists are now medically available to block the vasoconstrictor effect of endothelin-1, and thus promote vasodilation. For example, endothelin-1 receptor antagonists may be used to help treat pulmonary hypertension. In normal physiology, the effects of endothelin-1 may be balanced by nitric oxide to help regulate blood flow and blood pressure.

Intrinsic Regulation of Blood Flow

Intrinsic, or "built-in," mechanisms within individual organs provide a localized regulation of vascular resistance and blood flow. **Autoregulation** refers to the ability of some organs—particularly the brain and kidneys—to utilize intrinsic control mechanisms to maintain a relatively constant blood flow despite wide fluctuations in blood pressure. Intrinsic mechanisms are classified as *myogenic* or *metabolic.*

Myogenic Control Mechanisms

If the arterial blood pressure and flow through an organ are inadequate—if the organ is inadequately *perfused* with blood—the metabolism of the organ cannot be maintained beyond a limited time period. However, excessively high blood pressure can also be dangerous, particularly in the brain, because this may result in the rupture of fine blood vessels (causing a cerebrovascular accident—CVA, or stroke).

Autoregulation of blood flow helps to mitigate these possibilities. Changes in systemic arterial pressure are compensated for

in the brain and some other organs by the appropriate responses of vascular smooth muscle. A decrease in arterial pressure causes cerebral vessels to dilate, so that adequate blood flow can be maintained despite the decreased pressure. High blood pressure, by contrast, causes cerebral vessels to constrict, so that finer vessels downstream are protected from the elevated pressure. These responses are myogenic; they are direct responses by the vascular smooth muscle to changes in pressure.

Metabolic Control Mechanisms

Local vasodilation within an organ can occur as a result of the chemical environment created by the organ's metabolism. The localized chemical conditions that promote vasodilation include (1) *decreased oxygen concentrations* that result from increased metabolic rate; (2) *increased carbon dioxide concentrations;* (3) *decreased tissue pH* (due to CO_2, lactic acid, and other metabolic products); and (4) *release of* K^+ *and paracrine regulators* (such as adenosine, nitric oxide, and others) from tissue cells. Through these chemical changes, the organ signals its blood vessels that it needs increased oxygen delivery.

The vasodilation that occurs in response to tissue metabolism can be demonstrated by constricting the blood supply to an area for a short time and then removing the constriction. The constriction allows metabolic products to accumulate by preventing venous drainage of the area. When the constriction is removed and blood flow resumes, the metabolic products that have accumulated cause vasodilation. The tissue thus appears red. This response is called **reactive hyperemia.** A similar increase in blood flow occurs in skeletal muscles and other organs as a result of increased metabolism. This is called **active hyperemia.** The increased blood flow can wash out the vasodilator metabolites, so that blood flow can fall to pre-exercise levels a few minutes after exercise ends.

CHECKPOINT

6a. Describe the relationship between blood flow, arterial blood pressure, and vascular resistance.

6b. Describe the relationship between vascular resistance and the radius of a vessel. Explain how blood flow can be diverted from one organ to another.

7a. Explain how vascular resistance and blood flow are regulated by (a) sympathetic adrenergic fibers, (b) sympathetic cholinergic fibers, and (c) parasympathetic fibers.

7b. Describe the formation and action of nitric oxide. Why is this molecule considered a paracrine regulator?

7c. Define *autoregulation* and explain how this process occurs through myogenic and metabolic mechanisms.

14.4 BLOOD FLOW TO THE HEART AND SKELETAL MUSCLES

Blood flow to the heart and skeletal muscles is regulated by both extrinsic and intrinsic mechanisms. These mechanisms provide increased blood flow when the metabolic requirements of these tissues are raised during exercise.

LEARNING OUTCOMES

After studying this section, you should be able to:

8. Explain the mechanisms that regulate blood flow to the heart and skeletal muscles.

9. Describe the circulatory changes that occur during exercise.

Survival requires that the heart and brain receive an adequate supply of blood at all times. The ability of skeletal muscles to respond quickly in emergencies and to maintain continued high levels of activity also may be critically important for survival. During such times, high rates of blood flow to the skeletal muscles must be maintained without compromising blood flow to the heart and brain. This is accomplished by mechanisms that increase the cardiac output and divert the blood away from the viscera and skin so that the heart, skeletal muscles, and brain receive a greater proportion of the total blood flow.

Aerobic Requirements of the Heart

The coronary arteries supply an enormous number of capillaries, which are packed within the myocardium at a density ranging from 2,500 to 4,000 per cubic millimeter of tissue. For comparison, fast-twitch skeletal muscles have a capillary density of 300 to 400 per cubic millimeter of tissue. As a consequence of its greater density of capillaries, each myocardial cell is within only 10 μm of a capillary, compared to an average distance of 70 μm in other organs. The exchange of gases by diffusion between myocardial cells and capillary blood thus occurs very quickly.

Contraction of the myocardium squeezes the coronary arteries. For this reason, unlike other organs, the blood flow in the coronary vessels is less during systole than diastole. For example, only 15% to 20% of the blood flow through the left ventricle occurs during systole when a person is not exercising. However, the myocardium contains large amounts of *myoglobin,* a pigment related to hemoglobin (the molecules in red blood cells that carry oxygen). Myoglobin in the myocardium stores oxygen during diastole and releases its oxygen during systole. In this way, the myocardial cells can receive a continuous supply of oxygen even though coronary blood flow is temporarily reduced during systole.

In addition to containing large amounts of myoglobin, heart muscle contains numerous mitochondria and aerobic respiratory enzymes. This indicates that—even more than slow-twitch skeletal muscles—the heart is extremely specialized for

aerobic respiration. Almost all of the ATP produced in the heart is a result of aerobic respiration and oxidative phosphorylation within mitochondria (chapter 5, section 5.2). This is so effective that scientists estimate that the ATP within myocardial cells is completely turned over (broken down and resynthesized) every 10 seconds. The resting heart obtains 50% to 70% of this ATP from acetyl CoA produced by the β-oxidation of fatty acids (chapter 5, figure 5.14). The balance of ATP is derived almost equally from the aerobic respiration of glucose and lactate.

The normal heart always respires aerobically, even during heavy exercise when the metabolic demand for oxygen can rise to six times resting levels (largely due to increased cardiac rate). This increased oxygen requirement is met primarily by a corresponding increase in coronary blood flow, from about 80 ml at rest to about 400 ml per minute per 100 g tissue during heavy exercise.

Regulation of Coronary Blood Flow

The coronary arterioles contain both alpha- and beta-adrenergic receptors, which promote vasoconstriction and vasodilation, respectively. Norepinephrine released by sympathetic nerve fibers stimulates alpha-adrenergic receptors to raise vascular

CLINICAL APPLICATION

An **angiogram** of the coronary arteries might reveal narrowing caused by atherosclerotic plaque (chapter 13, section 13.7), a thrombus, or a spasm (fig. 14.18). An angiogram is an X-ray picture taken after a catheter is inserted into a brachial or femoral artery, threaded under guidance by a fluoroscope to the desired site at the coronary arteries, and iodine contrast (dye) is injected. A coronary angiogram is the standard method for assessing **coronary artery disease.**

Coronary angioplasty is the technique of inserting a catheter with a balloon into the occluded site of a coronary artery and then inflating the balloon to push the artery open. However, *restenosis* (recurrence of narrowing) often occurs after this *balloon angioplasty,* and for that reason, a **stent**—a metallic mesh tube—is often inserted to support the opened section of the coronary artery. If required, a **coronary bypass grafting** (**CABG**) surgery may be performed. This is the most common open-heart surgery, involving the grafting of a vessel taken from the patient onto the aorta so that it bypasses the narrowed coronary artery (fig. 14.19).

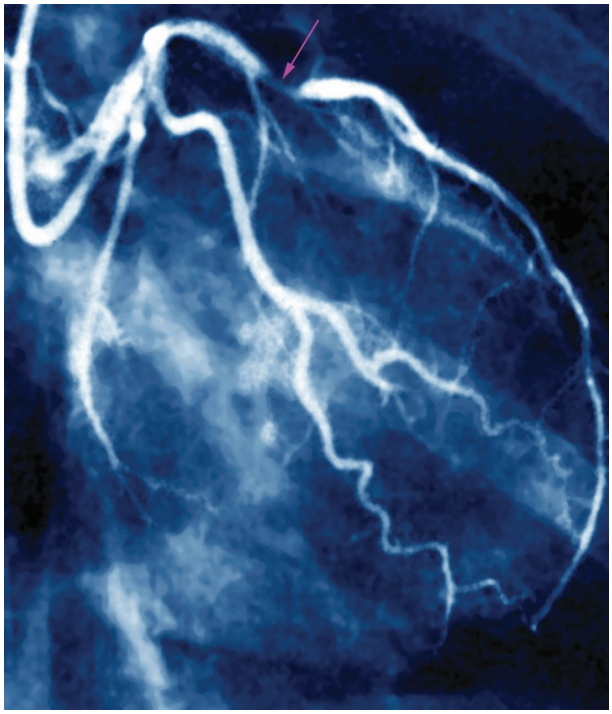


Figure 14.18 An angiogram of the coronary arteries. The red arrow points to an area where the contrast material of the angiogram is occluded by an obstruction, likely due to atherosclerosis. This can cause myocardial ischemia and lead to a myocardial infarction. AP|R

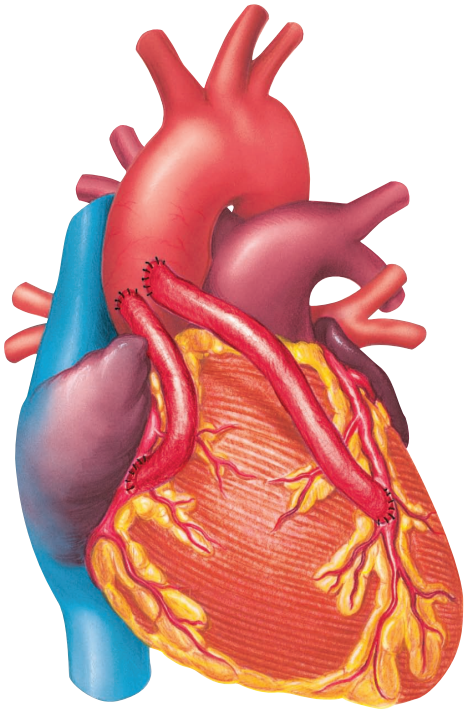


Figure 14.19 A diagram of coronary artery bypass surgery. Segments of the saphenous vein of the patient are commonly used as coronary bypass vessels.

resistance at rest. Epinephrine released by the adrenal medulla can stimulate the beta-adrenergic receptors to produce vasodilation when the sympathoadrenal system is activated during the fight-or-flight reaction.

During heavy exercise, the oxygen consumption of the myocardium can increse from four to six times resting values. This involves an increased β-oxidation of fatty acids and an even greater increase in the oxidation of glucose, requiring a four- to sixfold increase in coronary blood flow due to vasodilation. The vasodilation and decreased resistance of the coronary circulation during exercise is produced partly by sympathoadrenal system changes, but mostly by intrinsic metabolic changes. As the metabolism of the myocardium increases, there are increased local tissue concentrations of carbon dioxide, K^+, and released paracrine regulators that include nitric oxide, adenosine, and prostaglandins. These act directly on the vascular smooth muscle to cause vasodilation. Exercise training (1) increases the density of coronary arterioles and capillaries, (2) increases the production of nitric oxide for promoting vasodilation, and (3) decreases the compression of the coronary vessels in systole, due to the lower cardiac rate (and thus frequency of systoles) in trained athletes.

Regulation of Blood Flow Through Skeletal Muscles

The arterioles in skeletal muscles, like those of the coronary circulation, have a high vascular resistance at rest as a result of alpha-adrenergic sympathetic stimulation. This produces a relatively low blood flow. Because muscles have such a large mass, however, they still receive from 20% to 25% of the total blood flow in the body at rest. Also, as in the heart, blood flow in a skeletal muscle decreases when the muscle contracts and squeezes its arterioles, and in fact blood flow stops entirely when the muscle contracts beyond about 70% of its maximum. Pain and fatigue thus occur much more quickly when an isometric contraction is sustained (in *static exercise*) than when rhythmic isotonic contractions are performed (in *dynamic exercise*).

In addition to adrenergic fibers, which promote vasoconstriction by stimulation of alpha-adrenergic receptors, there are also cholinergic sympathetic fibers in skeletal muscles. These cholinergic fibers, together with the stimulation of beta-adrenergic receptors by the hormone epinephrine, stimulate vasodilation as part of the fight-or-flight response to any stressful state, including that existing just prior to exercise (table 14.5). These extrinsic controls have been previously discussed and function to regulate blood flow through muscles at rest and upon the anticipation of exercise.

As dynamic exercise progresses, the vasodilation and increased skeletal muscle blood flow that occur are almost entirely due to intrinsic metabolic control. The high metabolic rate of skeletal muscles during exercise causes local changes, such as increased carbon dioxide concentrations, decreased pH (due to carbonic acid and lactic acid), decreased oxygen, increased extracellular K^+, and the secretion of adenosine. As in the intrinsic control of the coronary circulation, these changes cause vasodilation of arterioles in skeletal muscles. This decreases the vascular resistance and increases the blood flow. As a result of these changes, skeletal muscles can receive as much as 85% of the total blood flow in the body during maximal exercise (fig. 14.20).

Circulatory Changes During Exercise

Both breathing and pulse rate increase within one second of exercise, suggesting that the motor cortex responsible for originating the exercise also influences the cardiovascular adjustments to exercise. However, cardiovascular changes during exercise are also affected by sensory feedback from the contracting muscles and by the baroreceptor reflex (discussed shortly in conjunction with blood pressure regulation). These mechanisms increase the activity of the sympathoadrenal system and reduce parasympathetic nerve activity during exercise. As a result, there is an increase in cardiac rate, stroke volume, and cardiac output.

The vascular resistance through muscles decreases during dynamic exercise but increases during static (isometric exercise), while the resistance to flow through the visceral organs and skin increases in both static and dynamic exercise. The increased resistance through the viscera and skin is produced by vasoconstriction due to increased activity of adrenergic sympathetic fibers. In summary, the blood flow through dynamically exercising muscles increases due to: (1) increased total

Table 14.5 | Changes in Skeletal Muscle Blood Flow Under Conditions of Rest and Exercise

Condition	Blood Flow (ml/min)	Mechanism
Rest	1,000	High adrenergic sympathetic stimulation of vascular alpha receptors, causing vasoconstriction
Beginning exercise	Increased	Dilation of arterioles in skeletal muscles due to cholinergic sympathetic nerve activity and stimulation of beta-adrenergic receptors by the hormone epinephrine
Heavy exercise	20,000	Fall in alpha-adrenergic activity Increased cholinergic sympathetic activity Increased metabolic rate of exercising muscles, producing intrinsic vasodilation

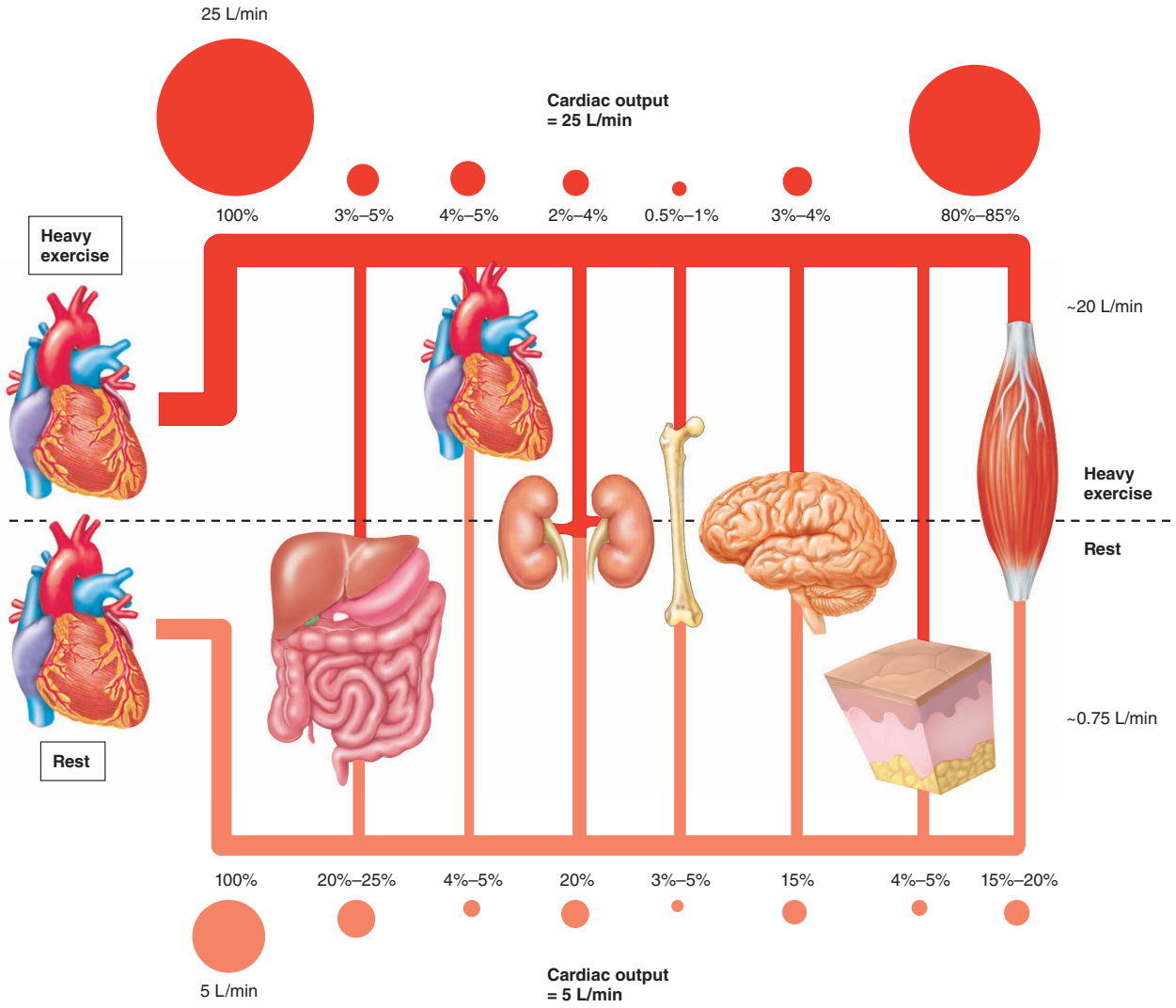


Figure 14.20 **The distribution of blood flow (cardiac output) during rest and heavy exercise.** At rest, the cardiac output is 5 L per minute (*bottom of figure*); during heavy exercise the cardiac output increases to 25 L per minute (*top of figure*). At rest, for example, the brain receives 15% of 5 L per minute (= 750 ml/min), whereas during exercise it receives 3% to 4% of 25 L per minute (0.03 × 25 L/min = 750 ml/min; at 4%, the brain receives 1000 ml/min). Flow to the skeletal muscles increases more than twentyfold because the total cardiac output increases (from 5 L/min to 25 L/min) and because the percentage of the total received by the muscles increases from 15% to 80%. Note that the percentage of blood flow to the skin during heavy exercise was immeasurably low, so no percentage is indicated. Also, the percentages for the blood flow to different organs at rest only add up to 95% because these percentages are estimated averages.

blood flow (cardiac output); (2) metabolic vasodilation in the exercising muscles; and (3) the diversion of blood away from the viscera and skin. For similar reasons, coronary blood flow to cardiac muscle also increases significantly during exercise.

The total blood flow to the brain is relatively constant (fig. 14.20), but recent studies suggest that cerebral blood flow increases somewhat during light to moderate exercise. This is believed to result from vasodilation induced by increased metabolism of the brain regions responsible for motor control and somatosensory information. By contrast, during heavier exercise (at greater than 60% of the maximal oxygen uptake) the cerebral blood flow decreases somewhat. This is because the person hyperventilates, which lowers the blood CO_2 and thereby produces cerebral vasoconstriction. This cerebral vasoconstriction during heavy exercise may contribute to central fatigue (chapter 12, section 12.4).

Table 14.6 | Relationship Between Age and Average Maximum Cardiac Rate*

Age	Maximum Cardiac Rate
20–29	190 beats/min
30–39	160 beats/min
40–49	150 beats/min
50–59	140 beats/min
60+	130 beats/min

*Maximum cardiac rate can be estimated by subtracting your age from 220.

During exercise, the cardiac output can increase fivefold—from about 5 L per minute to about 25 L per minute. This is primarily due to an increase in cardiac rate. The cardiac rate, however, can increase only up to a maximum value (table 14.6), which is determined mainly by a person's age. In well-trained athletes, the stroke volume can also increase significantly, allowing these individuals to achieve cardiac outputs during strenuous exercise up to six or seven times greater than their resting values. This high cardiac output results in increased oxygen delivery to the exercising muscles; this is the major reason for the much higher than average maximal oxygen uptake (max) of elite athletes (chapter 12).

In most people, the increase in stroke volume that occurs during exercise will not exceed 35%. The fact that the stroke volume can increase at all during exercise may at first be surprising, given that the heart has less time to fill with blood between beats when it is pumping faster. Despite the faster beat, however, the end-diastolic volume during exercise is not decreased. This is because the venous return is aided by the improved action of the skeletal muscle pumps and by increased respiratory movements of the diaphragm during exercise (fig. 14.21). The end-diastolic volume is not significantly changed during exercise, so any increase in stroke volume that occurs must be due to an increase in the proportion of blood ejected per stroke.

The proportion of the end-diastolic volume ejected per stroke can increase from 60% at rest to as much as 90% during heavy exercise. This increased *ejection fraction* is produced by the increased contractility that results from sympathoadrenal stimulation. There also may be a decrease in total peripheral resistance as a result of vasodilation in the exercising skeletal muscles, which decreases the afterload and thus further augments the increase in stroke volume. The cardiovascular changes that occur during exercise are summarized in table 14.7.

Endurance training often results in a lowering of the resting cardiac rate and an increase in the resting stroke volume. The lowering of the resting cardiac rate results from a greater inhibition of the SA node by the vagus nerve. The increased resting stroke volume is believed to be due to an increase in blood volume; indeed, studies have shown that the blood volume can increase by about 500 ml after only eight days of training. These adaptations enable the trained athlete to produce a larger proportionate increase in cardiac output and achieve a higher absolute cardiac output during exercise. This large cardiac output is the major reason for the improved oxygen delivery to skeletal muscles that occurs as a result of endurance training.

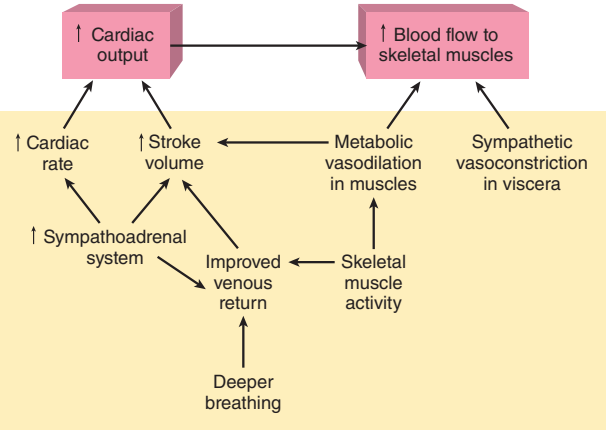


Figure 14.21 Cardiovascular adaptations to exercise. These adaptations (1) increase the cardiac output, and thus the total blood flow; and (2) cause vasodilation in the exercising muscles, thereby diverting a higher proportion of the blood flow to those muscles.

Clinical Investigation CLUES

Mark trained to run marathons.

- What happened to his cardiac output and blood flow through his brain, heart, and skeletal muscles during these sessions?
- How might such endurance training affect his resting cardiac rate and stroke volume?

CHECKPOINT

8. Describe blood flow and oxygen delivery to the myocardium during systole and diastole.

9a. State how blood flow to the heart is affected by exercise. Explain how blood flow to the heart is regulated at rest and during exercise.

9b. Describe the mechanisms that produce vasodilation in exercising muscles, and list the cardiovascular changes that contribute to increased blood flow to exercising muscles.

9c. Explain how the stroke volume can increase during exercise despite a shorter time available for the heart chambers to fill with blood.

Table 14.7 | Cardiovascular Changes During Moderate Exercise

Variable	Change	Mechanisms
Cardiac output	Increased	Increased cardiac rate and stroke volume
Cardiac rate	Increased	Increased sympathetic nerve activity; decreased activity of the vagus nerve
Stroke volume	Increased	Increased myocardial contractility due to stimulation by sympathoadrenal system; decreased total peripheral resistance
Total peripheral resistance	Decreased	Vasodilation of arterioles in skeletal muscles (and in skin when thermoregulatory adjustments are needed)
Arterial blood pressure	Increased	Increased systolic and pulse pressure due primarily to increased cardiac output; diastolic pressure rises less due to decreased total peripheral resistance
End-diastolic volume	Unchanged	Decreased filling time at high cardiac rates is compensated for by increased venous pressure, increased activity of the skeletal muscle pump, and decreased intrathoracic pressure aiding the venous return
Blood flow to heart and muscles	Increased	Increased muscle metabolism produces intrinsic vasodilation; aided by increased cardiac output and increased vascular resistance in visceral organs
Blood flow to visceral organs	Decreased	Vasoconstriction in digestive tract, liver, and kidneys due to sympathetic nerve stimulation
Blood flow to skin	Increased	Metabolic heat produced by exercising muscles produces reflex (involving hypothalamus) that reduces sympathetic constriction of arteriovenous shunts and arterioles
Blood flow to brain	Unchanged*	Autoregulation of cerebral vessels, which maintains constant cerebral blood flow despite increased arterial blood pressure

**There can be slight changes in cerebral blood flow (see text), but the extent of these changes is buffered by autoregulation due to myogenic control mechanisms.*

14.5 BLOOD FLOW TO THE BRAIN AND SKIN

Intrinsic control mechanisms help maintain a relatively constant blood flow to the brain. Blood flow to the skin, by contrast, can vary tremendously in response to regulation by sympathetic nerve stimulation.

LEARNING OUTCOMES

After studying this section, you should be able to:

10. Explain how blood flow to the brain is regulated.
11. Explain how blood flow to the skin is regulated.

The examination of cerebral and cutaneous blood flow is a study in contrasts. Cerebral blood flow is regulated primarily by intrinsic mechanisms; cutaneous blood flow is regulated by extrinsic mechanisms. Cerebral blood flow is relatively constant; cutaneous blood flow exhibits more variation than blood flow in any other organ. The brain is the organ that can least tolerate low rates of blood flow, whereas the skin can tolerate low rates of blood flow better than any other organ.

Cerebral Circulation

When the brain is deprived of oxygen for just a few seconds, a person loses consciousness; irreversible brain injury may occur after a few minutes. For these reasons, the cerebral blood flow is held remarkably constant at about 750 ml per minute. This amounts to about 15% of the total cardiac output at rest.

Unlike the coronary and skeletal muscle blood flow, cerebral blood flow is not much influenced by sympathetic nerve activity under normal conditions. Only when the mean arterial pressure rises to about 200 mmHg do sympathetic nerves cause a significant degree of vasoconstriction in the cerebral circulation. This vasoconstriction helps to protect small, thin-walled arterioles from bursting under the pressure, and thus helps to prevent cerebrovascular accident (stroke).

In the normal range of arterial pressures, cerebral blood flow is regulated almost exclusively by local intrinsic mechanisms—a process called *autoregulation,* as previously mentioned. These mechanisms help to ensure a relatively constant blood flow despite changes in systemic arterial pressure. The autoregulation of cerebral blood flow is achieved by both myogenic and metabolic mechanisms.

Myogenic Regulation

Myogenic regulation occurs when there is variation in systemic arterial pressure. When the blood pressure falls, the cerebral arteries automatically dilate; when the pressure rises, they constrict. This helps to maintain a constant flow rate during the normal pressure variations that occur during rest, exercise, and emotional states.

The cerebral vessels are also sensitive to the carbon dioxide concentration of arterial blood. When the carbon

dioxide concentration rises as a result of inadequate ventilation (hypoventilation), the cerebral arterioles dilate. This is believed to be due to decreases in the pH of cerebrospinal fluid rather than to a direct effect of CO_2 on the cerebral vessels. Conversely, when the arterial CO_2 falls below normal during hyperventilation, the cerebral vessels constrict. The resulting decrease in cerebral blood flow is responsible for the dizziness that occurs during hyperventilation.

Metabolic Regulation

Although the mechanisms just described maintain a relatively constant total cerebral blood flow, the particular brain regions that are most active receive an increased blood flow. Indeed, active brain regions are *hyperemic*—their blood flow actually exceeds the aerobic requirements of the active neurons.

This shunting of blood between different brain regions occurs because the cerebral arterioles are exquisitely sensitive to local changes in metabolic activity, so that those brain regions with the highest metabolic activity receive the most blood. Indeed, areas of the brain that control specific processes have been mapped by the changing patterns of blood flow that result when these areas are activated. Visual and auditory stimuli, for example, increase blood flow to the appropriate sensory areas of the cerebral cortex (fig. 14.22), whereas motor activities, such as movements of the eyes, arms, and organs of speech, result in different patterns of blood flow.

The mechanisms by which increased activity within a brain region causes increased blood flow to that region are complex and not completely understood. Active neurons release many substances that stimulate vasodilation, including K^+, adenosine, nitric oxide (NO), and others. The close association of astrocytes with both neurons and cerebral vessels (chapter 7; see fig. 7.10) suggests that they may also play a role. Indeed, astrocytes have been shown to secrete vasodilator chemicals (including prostaglandin E_2 and carbon monoxide) when stimulated by the neurotransmitter glutamate, released into the synapse by neurons. Molecules released by astrocytes and active neurons could also stimulate the endothelial cells of the arterioles to produce vasodilators, including nitric oxide.

In this way, neurons, astrocytes, and arterioles function together—a process termed *neurovascular coupling*—so that increased neuronal activity in a local brain region is accompanied by an increased cerebral blood flow to that region. Because of this *functional hyperemia* (increased blood flow in response to activity), the active neurons receive more oxygen and glucose for their increased needs.

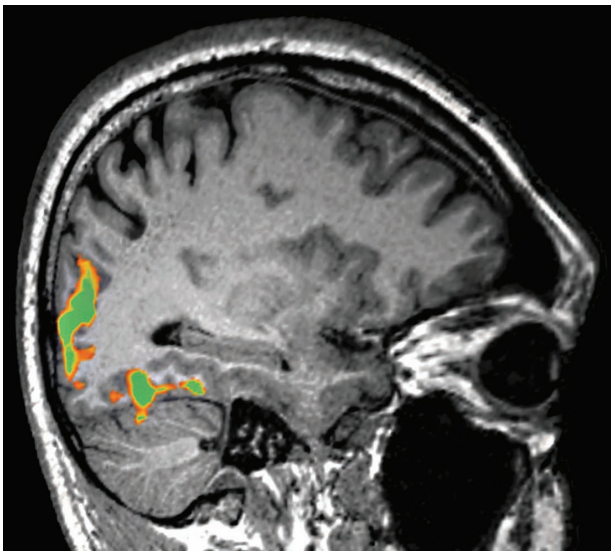


Figure 14.22 A functional MRI with a BOLD (blood oxygenation level dependent) image of the brain. The colors indicate increased blood flow to the brain areas stimulated when the subject views a screen displaying images that change at 30 second intervals. AP|R

Cutaneous Blood Flow

The skin is the outer covering of the body and as such serves as the first line of defense against invasion by disease-causing organisms. The skin, as the interface between the internal and external environments, also helps to maintain a constant deep-body temperature despite changes in the ambient (external) temperature—a process called *thermoregulation.* The thinness and large area of the skin (1.0 to 1.5 mm thick; 1.7 to 1.8 square meters in surface area) make it an effective radiator of heat when the body temperature rises above the ambient temperature. The transfer of heat from the body to the external environment is aided by the flow of warm blood through capillary loops near the surface of the skin.

Blood flow through the skin is adjusted to maintain deep-body temperature at about 37°C (98.6°F). These adjustments are made by variations in the degree of constriction or dilation of ordinary arterioles and of unique **arteriovenous anastomoses** (fig. 14.23). These latter vessels, found predominantly in the fingertips, palms of the hands, toes, soles of the feet, ears, nose, and lips, shunt (divert) blood directly from arterioles to deep venules, thus bypassing superficial capillary loops. Both the ordinary arterioles and the arteriovenous anastomoses are innervated by sympathetic nerve fibers. When the ambient temperature is low, sympathetic nerves stimulate cutaneous vasoconstriction. Cutaneous blood flow is thus decreased, so that less heat will be lost from the body. Because the arteriovenous anastomoses also constrict, the skin may appear rosy because the blood is diverted to the superficial capillary loops. In spite of this rosy appearance, however, the total cutaneous blood flow and rate of heat loss is lower than under usual conditions.

Skin can tolerate an extremely low blood flow in cold weather because its metabolic rate decreases when the ambient temperature decreases. In cold weather, therefore, the skin

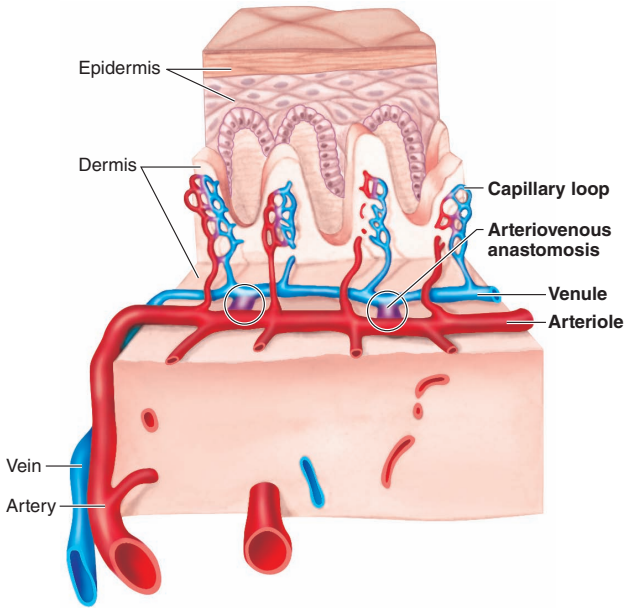


Figure 14.23 Circulation in the skin showing arteriovenous anastomoses. These vessels function as shunts, allowing blood to be diverted directly from the arteriole to the venule, and thus to bypass superficial capillary loops. AP|R

requires less blood. As a result of exposure to extreme cold, however, blood flow to the skin can be so severely restricted that the tissue dies—a condition known as *frostbite.* Blood flow to the skin can vary from less than 20 ml per minute at maximal vasoconstriction to as much as 3 to 4 L per minute at maximal vasodilation.

As the temperature warms, cutaneous arterioles in the hands and feet dilate as a result of decreased sympathetic nerve activity. Continued warming causes dilation of arterioles in other areas of the skin. If the resulting increase in cutaneous blood flow is not sufficient to cool the body, sweat gland secretion may be stimulated. Perspiration helps cool the body as it evaporates from the surface of the skin. The sweat glands also secrete **bradykinin,** a polypeptide that stimulates vasodilation.

In usual ambient temperatures, the cutaneous vascular resistance is high and the blood flow is low when a person is not exercising. In the pre-exercise state of fight or flight, sympathetic nerve activity reduces cutaneous blood flow still further. During exercise, however, the need to maintain a deep-body temperature takes precedence over the need to maintain an adequate systemic blood pressure. As the body temperature rises during exercise, vasodilation in cutaneous vessels occurs together with vasodilation in the exercising muscles.

This can cause an even greater lowering of total peripheral resistance during exercise. However, the mean arterial pressure is still high during exercise because of the increased cardiac output. If a person exercises in hot and humid weather, especially if restrictive clothing prevents adequate evaporative cooling of the skin (from perspiration), the increased skin temperature and resulting vasodilation can persist after exercise has ceased. If the total peripheral resistance remains very low as the cardiac output declines toward resting values, the blood pressure may fall precipitously; people have lost consciousness and even died as a result.

Changes in cutaneous blood flow occur as a result of changes in sympathetic nerve activity. Because the activity of the sympathetic nervous system is controlled by the brain, emotional states, acting through control centers in the medulla oblongata, can affect sympathetic activity and cutaneous blood flow. During fear reactions, for example, vasoconstriction in the skin, along with activation of the sweat glands, can produce a pallor and a "cold sweat." Other emotions may cause vasodilation and blushing.

CHECKPOINT

10a. Define the term *autoregulation* and describe how this process is accomplished in the cerebral circulation.

10b. Explain how hyperventilation can cause dizziness.

11. Explain how cutaneous blood flow is adjusted to maintain a constant deep-body temperature.

14.6 BLOOD PRESSURE

The pressure of the arterial blood is affected by the blood volume, total peripheral resistance, and the cardiac rate. These variables are regulated by a variety of negative feedback control mechanisms to maintain homeostasis. Arterial pressure rises and falls as the heart goes through systole and diastole.

LEARNING OUTCOMES

After studying this section, you should be able to:

12. Explain how blood pressure is regulated.

13. Describe how blood pressure is measured.

Resistance to flow in the arterial system is greatest in the arterioles because these vessels have the smallest diameters. Although the total blood flow through a system of arterioles must be equal to the flow in the larger vessel that gave rise to those arterioles, the narrow diameter of each arteriole reduces the flow in each according to Poiseuille's law. Blood flow and pressure are thus reduced in the capillaries, which are located downstream of the high resistance imposed by the arterioles. (The slow velocity of blood flow through capillaries enhances diffusion across the

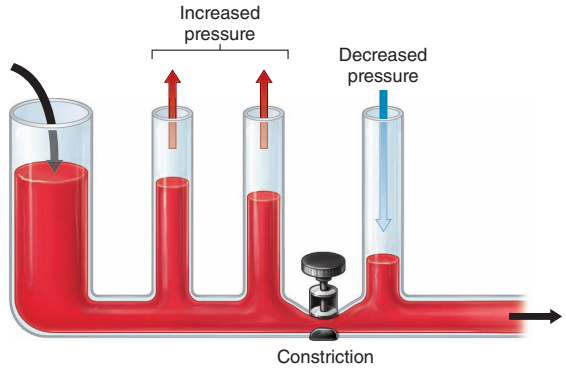
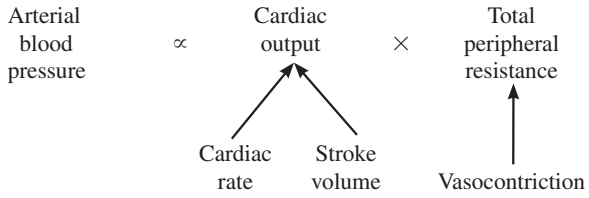


Figure 14.24 The effect of vasoconstriction on blood pressure. A constriction increases blood pressure upstream (analogous to the arterial pressure) and decreases pressure downstream (analogous to capillary and venous pressure).

capillary wall.) The blood pressure upstream of the arterioles—in the medium and large arteries—is correspondingly increased (fig. 14.24).

The total cross-sectional area of capillaries is greater (due to their large number) than the cross-sectional areas of the arteries and arterioles (fig. 14.25), further reducing the capillary blood pressure and flow. Thus, although each capillary is much narrower than each arteriole, the capillary beds served by arterioles do not provide as great a resistance to blood flow as do the arterioles.

Variations in the diameter of arterioles as a result of vasoconstriction and vasodilation thus affect blood flow through capillaries and, simultaneously, the *arterial blood pressure* "upstream" from the capillaries. In this way, an increase in total peripheral resistance due to vasoconstriction of arterioles can raise arterial blood pressure. Blood pressure can also be raised by an increase in the cardiac output. This may be due to elevations in cardiac rate or in stroke volume, which in turn are affected by other factors. The most important variables affecting blood pressure are thus the **cardiac rate, stroke volume** (determined primarily by the **blood volume**), and **total peripheral resistance.** An increase in any of these, if not compensated for by a decrease in another variable, will result in an increased blood pressure.



Blood pressure can be regulated by the kidneys, which control blood volume and thus stroke volume, and by the

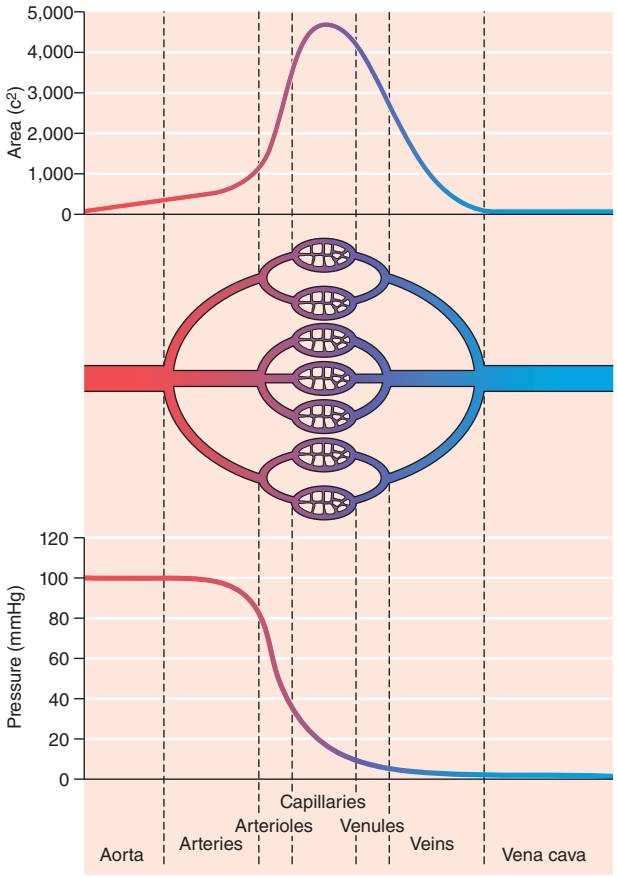


Figure 14.25 The relationship between blood pressure and the cross-sectional area of vessels. As blood passes from the aorta to the smaller arteries, arterioles, and capillaries, the cross-sectional area increases as the pressure decreases.

sympathoadrenal system. Increased activity of the sympathoadrenal system can raise blood pressure by stimulating vasoconstriction of arterioles (thereby raising total peripheral resistance) and by promoting an increased cardiac output. Sympathetic stimulation can also affect blood volume indirectly, by stimulating constriction of renal blood vessels and thus reducing urine output.

Blood pressure is measured in units of **millimeters of mercury (mmHg).** When this measurement is taken, the blood pushes on one surface of a U-shaped column of mercury while the atmosphere pushes on the other surface (see chapter 16, fig. 16.18). If the blood pressure were equal to the atmospheric pressure, the measurement would be 0 mmHg. A mean arterial pressure of 100 mmHg indicates that the blood pressure is 100 mmHg higher than the atmospheric pressure. Instruments used to measure blood pressure, called **sphygmomanometers,** contain mercury or are spring-loaded devices that are calibrated against mercurial instruments.

Clinical Investigation CLUES

Mark trained for running marathons and, because he didn't drink properly, became dehydrated.

- How would dehydration influence blood volume, stroke volume, and cardiac output?
- Through what means would dehydration affect Mark's blood pressure, and in what way?

Baroreceptor Reflex

In order for blood pressure to be maintained within limits, specialized receptors for pressure are needed. These **baroreceptors** are stretch receptors located in the *aortic arch* and in the *carotid sinuses*. The baroreceptors are tonically (constantly) active, producing a baseline frequency of action potentials in their sensory neurons. When blood pressure is increased the walls of the aortic and carotid sinuses stretch, and this produces an increased frequency of action potentials along their sensory nerve fibers (fig. 14.26). A fall in blood pressure below the normal range, by contrast, causes a decreased frequency of action potentials in these sensory fibers.

Sensory nerve activity from the baroreceptors ascends via the vagus (X) and glossopharyngeal (IX) nerves to the medulla oblongata, which directs the autonomic system to respond appropriately. The **vasomotor control center** in the medulla regulates the degree of vasoconstriction/vasodilation, and hence helps to regulate total peripheral resistance. The **cardiac control center** in the medulla regulates the cardiac rate (fig. 14.27).

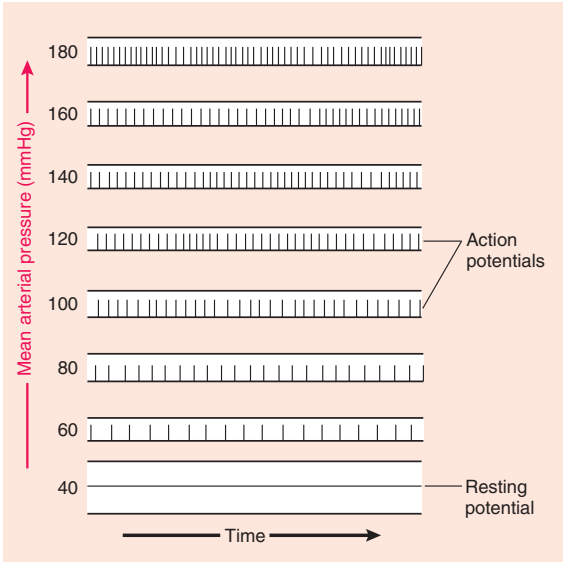


Figure 14.26 The effect of blood pressure on the baroreceptor response. This is a recording of the action potential frequency in sensory nerve fibers from baroreceptors in the carotid sinus and aortic arch. As the blood pressure increases, the baroreceptors become increasingly stretched. This results in a higher frequency of action potentials transmitted to the cardiac and vasomotor control centers in the medulla oblongata.

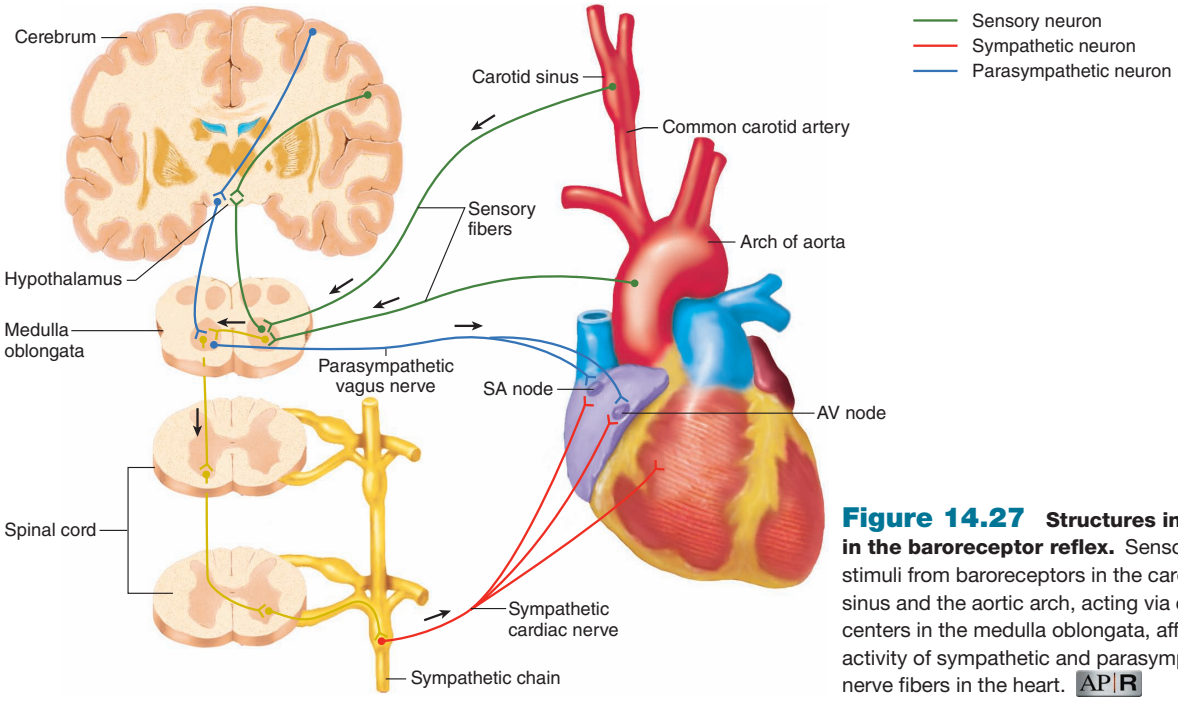


Figure 14.27 Structures involved in the baroreceptor reflex. Sensory stimuli from baroreceptors in the carotid sinus and the aortic arch, acting via control centers in the medulla oblongata, affect the activity of sympathetic and parasympathetic nerve fibers in the heart. AP|R

The **baroreceptor reflex** consists of (1) the aortic arch and carotid sinus baroreceptors as the sensors; (2) the vasomotor and cardiac control centers of the medulla oblongata as the integrating centers; and (3) parasympathetic and sympathetic axons to the heart and blood vessels as the effectors. Acting through the baroreceptor reflex, a fall in blood pressure evokes an increase in sympathetic nerve activity while the activity of the parasympathetic division decreases. As a result, there is a compensatory increase in cardiac output and total peripheral resistance. Conversely, a rise in blood pressure will produce a decline in sympathetic nerve activity while the activity of the parasympathetic division increases. As a result, a rise in blood pressure will evoke a reduction in cardiac output and total peripheral resistance.

The baroreceptor reflex helps maintain normal blood pressure on a beat-to-beat basis (longer-term regulation of blood pressure is achieved by the kidneys, through regulation of blood volume). The reflex is somewhat more sensitive to decreases in pressure than to increases, and is more sensitive to sudden changes in pressure than to more gradual changes. A good example of the importance of the baroreceptor reflex in normal physiology is its activation whenever a person goes from a lying to a standing position.

When a person goes from a lying to a standing position, there is a shift of 500 to 700 ml of blood from the veins of the thoracic cavity to veins in the lower extremities, which expand to contain the extra volume of blood. This pooling of blood in the lower extremities reduces the venous return and cardiac output, but the resulting fall in blood pressure is almost immediately compensated for by the baroreceptor reflex. A decrease in baroreceptor sensory information, traveling in the glossopharyngeal nerve and the vagus nerve to the medulla oblongata, inhibits parasympathetic activity and promotes sympathetic nerve activity. This produces an increase in cardiac rate and vasoconstriction, which help to maintain an adequate blood pressure upon standing (fig. 14.28).

Input from baroreceptors can also mediate the opposite response. When the blood pressure rises above an individual's normal range, the baroreceptor reflex causes a slowing of the cardiac rate and vasodilation. Manual massage of the carotid sinus, a procedure sometimes employed by physicians to reduce tachycardia and lower blood pressure, also evokes this reflex. Such carotid massage should be used cautiously, however, because the intense vagus-nerve-induced slowing of the cardiac rate could cause loss of consciousness (as occurs in emotional fainting). Manual massage of both carotid sinuses

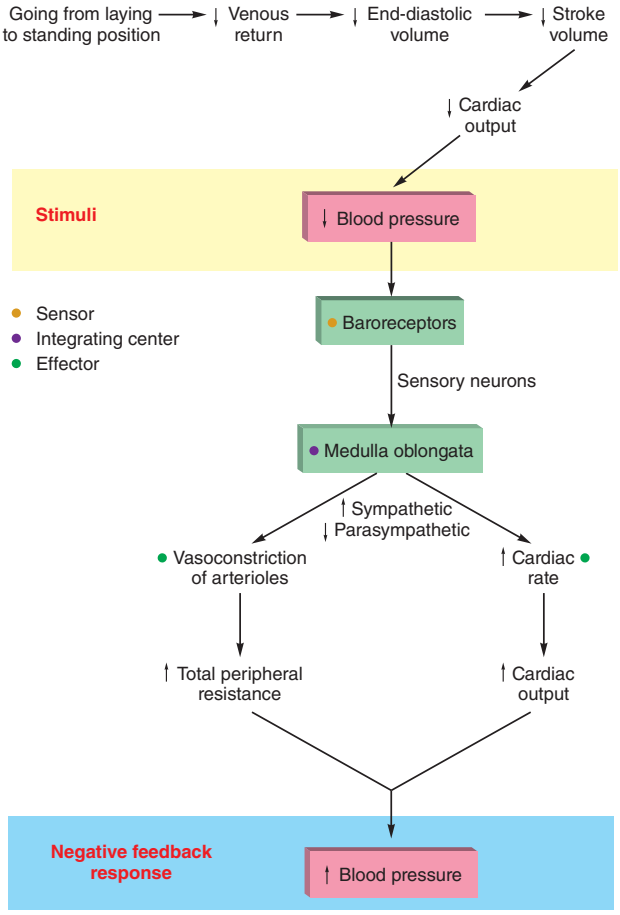


Figure 14.28 **The negative feedback control of blood pressure by the baroreceptor reflex.** This reflex helps to maintain an adequate blood pressure upon standing.

CLINICAL APPLICATION

Orthostatic (or **postural**) **hypotension** is a lowering of blood pressure upon standing that causes a person to feel dizzy and weak, and in extreme cases can even cause fainting (*syncope*). Normally, the baroreceptor reflex compensates for the fall in blood pressure when a person stands, which causes about 700 mL of blood to pool in the lower limbs. However, if a person has low blood pressure because of dehydration, medications (such as beta-adrenergic receptor blockers), or any other cause—including *postprandial hypotension* among the elderly, where the pressure falls after eating—orthostatic hypotension can result.

Clinical Investigation CLUES

Mark experienced dizziness upon standing after he engaged in prolonged exercise without adequate drinking.

- What caused the dizziness upon standing, and how is this normally prevented?
- What condition did Mark have when he got dizzy, and what caused it?

simultaneously can even cause cardiac arrest in susceptible people.

Atrial Stretch Reflexes

In addition to the baroreceptor reflex, several other reflexes help to regulate blood pressure. The reflex control of ADH release by osmoreceptors in the hypothalamus, and the control of angiotensin II production and aldosterone secretion by the juxtaglomerular apparatus of the kidneys, have been previously discussed. Antidiuretic hormone and aldosterone increase blood pressure by increasing blood volume, and angiotensin II stimulates vasoconstriction to cause an increase in blood pressure.

Other reflexes important to blood pressure regulation are initiated by **atrial stretch receptors** located in the atria of the heart. These receptors are activated by increased venous return to the heart and, in response (1) stimulate reflex tachycardia, as a result of increased sympathetic nerve activity; (2) inhibit ADH release, resulting in the excretion of larger volumes of urine and a lowering of blood volume; and (3) promote increased secretion of atrial natriuretic peptide (ANP). The ANP, as previously discussed, lowers blood volume by increasing urinary salt and water excretion.

FITNESS APPLICATION

The **Valsalva maneuver** is a bearing down, as if attempting a forceful exhalation, while preventing air from escaping through the mouth and nose. This raises intrathoracic pressure, compressing thoracic veins and reducing the venous return to the heart. It also briefly raises the aortic pressure, causing a slowing of the heart via the baroreceptor reflex. However, the fall in venous return decreases cardiac output, so that aortic blood pressure then falls, stimulating the baroreceptor reflex and causing the cardiac rate to increase. When the person again breathes, the thoracic pressure falls and the aortic pressure briefly falls (reflexively producing an increase in cardiac rate) before the improved venous return raises aortic pressure and (via the baroreceptor reflex) slows the cardiac rate. Weightlifters attempting to lift a heavy load while holding their breaths, and people straining at stools, also perform this Valsalva maneuver, which can be dangerous in those with coronary heart disease.

Clinical Investigation CLUES

After Mark was diagnosed with essential hypertension, his physician advised him not to hold his breath when lifting heavy weights.

- What sequence of events occurs when a person lifts a heavy weight while holding the breath?
- How is the baroreceptor reflex involved in the these events?

Measurement of Blood Pressure

The first documented measurement of blood pressure was accomplished by Stephen Hales (1677–1761), an English clergyman and physiologist. Hales inserted a cannula into the artery of a horse and measured the heights to which blood would rise in the vertical tube. The height of this blood column bounced between the **systolic pressure** at its highest and the **diastolic pressure** at its lowest, as the heart went through its cycle of systole and diastole. Modern clinical blood pressure measurements, fortunately, are less direct. The indirect, or **auscultatory,** method is based on the correlation of blood pressure and arterial sounds first described by the Russian physician Nicolai Korotkoff in 1905.

In the auscultatory method, an inflatable rubber bladder within a cloth cuff is wrapped around the upper arm, and a stethoscope is applied over the brachial artery (fig. 14.29). The artery is normally silent before inflation of the cuff, because blood travels smoothly through the arteries. **Laminar flow** occurs when all parts of a fluid move in the same direction, parallel to the axis of the vessel. The term *laminar* means "layered"—blood in the central axial stream moves the fastest, and blood flowing closer to the artery wall moves more slowly. If flow is perfectly laminar, there is no transverse movement between these layers that would produce mixing. The blood flows smoothly and doesn't produce vibrations of the artery wall that would cause sounds. By contrast, **turbulent flow** is when some parts of the fluid move in different directions, churning and mixing the blood. Turbulent flow causes vibrations of the vessel, which may produce sounds. Before the blood pressure cuff is inflated, blood flow in the brachial artery has very little turbulence and so is silent.

When the artery is pinched, however, blood flow through the constriction becomes turbulent. This causes the artery to produce sounds, much like the sounds produced by water flowing through a kink in a garden hose. The ability of the cuff pressure to constrict the artery is opposed by the blood pressure. So the cuff pressure must be greater than the diastolic pressure to constrict the artery during diastole. If the cuff pressure is also

Figure 14.29 A pressure cuff and sphygmomanometer are used to measure blood pressure. The examiner is listening for the Korotkoff sounds.

greater than the systolic pressure, the artery will be closed off and silent during both diastole and systole. Turbulent flow, and the sounds produced by the artery as a result of this flow, can occur only when the cuff pressure is greater than the diastolic pressure (to constrict the artery during diastole) but less than the systolic pressure. The constriction can then partially open at each systole and allow turbulent blood flow.

Let's say that a person has a systolic pressure of 120 mmHg and a diastolic pressure of 80 mmHg. When the cuff pressure is between 80 and 120 mmHg, the artery will be closed during diastole and open during systole. As the artery begins to open with every systole, turbulent flow of blood through the constriction will create sounds that are known as the **sounds of Korotkoff,** as shown in figure 14.30. These are usually "tapping" sounds because the artery becomes constricted, blood flow stops, and silence is restored with every diastole. It should be understood that the sounds of Korotkoff are *not* "lub-dub" sounds produced by closing of the heart valves (those sounds can be heard only on the chest, not on the brachial artery).

Initially, the cuff is usually inflated to produce a pressure greater than the systolic pressure, so that the artery is pinched off and silent. The pressure in the cuff is read from an attached meter called a *sphygmomanometer.* A valve is then turned to allow the release of air from the cuff, causing a gradual decrease in cuff pressure. When the cuff pressure is equal to the systolic pressure, the **first Korotkoff sound** is heard as blood passes in a turbulent flow through the constricted opening of the artery.

Korotkoff sounds will continue to be heard at every systole as long as the cuff pressure remains greater than the diastolic pressure. When the cuff pressure becomes equal to or less than the diastolic pressure, the sounds disappear because the artery remains open and laminar flow resumes (fig. 14.31). The **last Korotkoff sound** thus occurs when the cuff pressure is equal to the diastolic pressure.

Different phases in the measurement of blood pressure are identified on the basis of the quality of the Korotkoff sounds (fig. 14.32). In some people, the Korotkoff sounds do not disappear even when the cuff pressure is reduced to zero (zero pressure means that it is equal to atmospheric pressure). In these cases—and often routinely—the onset of muffling of the sounds (phase 4 in fig. 14.32) is used as an indication of diastolic pressure rather than the onset of silence (phase 5).

The average arterial blood pressure in the systemic circulation is 120/80 mmHg, whereas the average pulmonary arterial blood pressure is only 22/8 mmHg. Because of the Frank-Starling relationship, the cardiac output from the right ventricle into the pulmonary circulation is matched to that of the

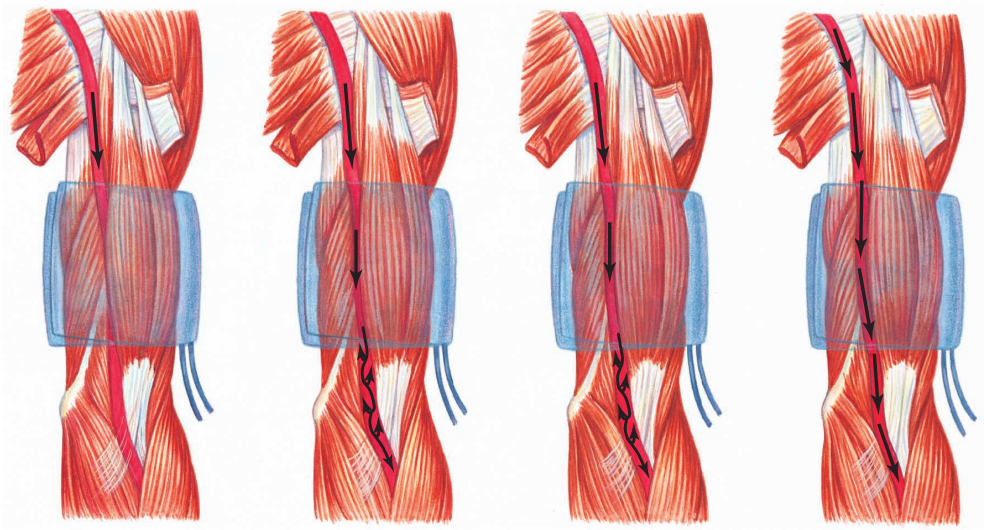


Figure 14.30 **The blood flow and Korotkoff sounds during a blood pressure measurement.** When the cuff pressure is above the systolic pressure, the artery is constricted. When the cuff pressure is below the diastolic pressure, the artery is open and flow is laminar. When the cuff pressure is between the diastolic and systolic pressure, blood flow is turbulent and the Korotkoff sounds are heard with each systole.

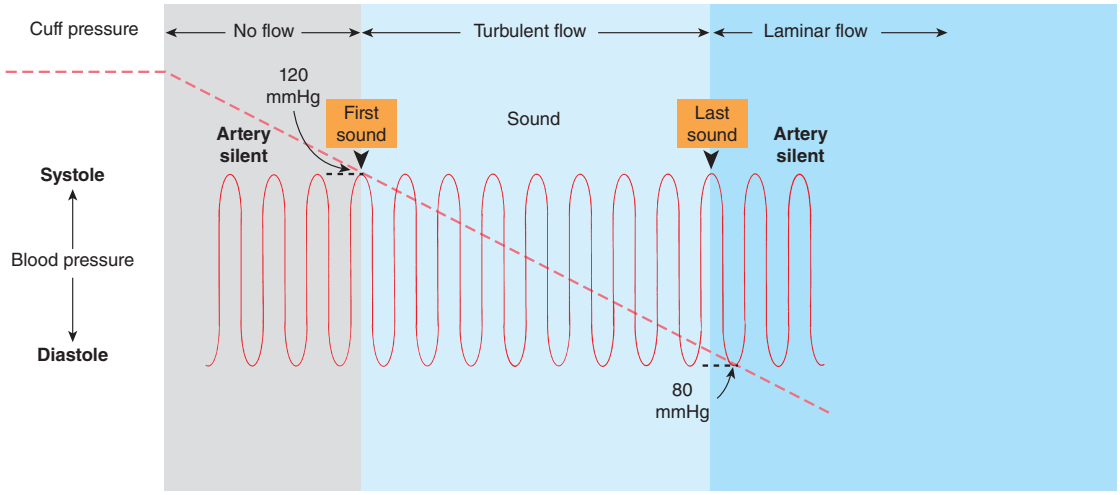


Figure 14.31 The indirect, or auscultatory, method of blood pressure measurement. The first Korotkoff sound is heard when the cuff pressure is equal to the systolic blood pressure, and the last sound is heard when the cuff pressure is equal to the diastolic pressure. The dashed line indicates the cuff pressure.

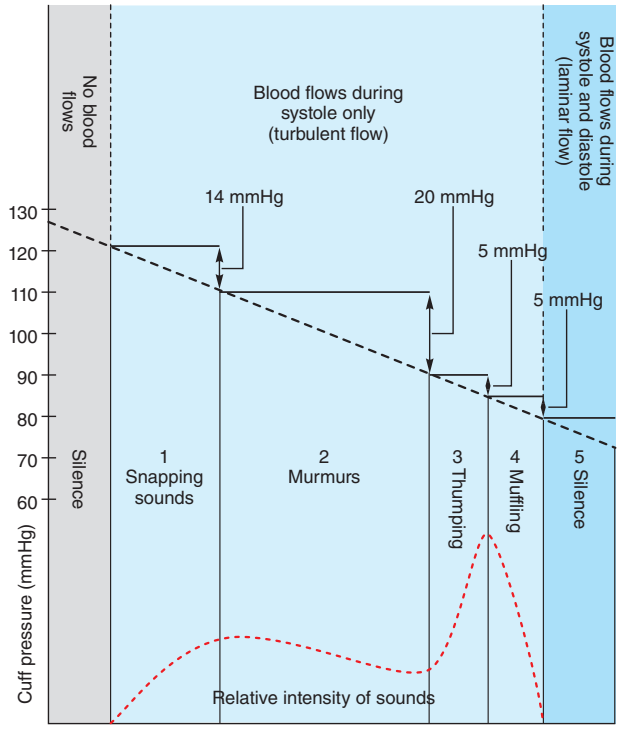


Figure 14.32 The five phases of blood pressure measurement. Not all phases are heard in all people. The cuff pressure is indicated by the falling dashed black line.

left ventricle into the systemic circulation. Since the cardiac outputs are the same, the lower pulmonary blood pressure must be caused by a lower peripheral resistance in the pulmonary circulation. Because the right ventricle pumps blood against a lower resistance, it has a lighter workload and its walls are thinner than those of the left ventricle.

Pulse Pressure and Mean Arterial Pressure

When someone "takes a pulse," he or she palpates an artery (for example, the radial artery) and feels the expansion of the artery occur in response to the beating of the heart; the pulse rate is thus a measure of the cardiac rate. The expansion of the artery with each pulse occurs as a result of the rise in blood pressure within the artery as the artery receives the volume of blood ejected from the left ventricle.

Because the pulse is produced by the rise in pressure from diastolic to systolic levels, the difference between these two pressures is known as the **pulse pressure.** A person with a blood pressure of 120/80 (systolic/diastolic) would therefore have a pulse pressure of 40 mmHg.

Pulse pressure = systolic pressure − diastolic pressure

At diastole in this example, the aortic pressure equals 80 mmHg. When the left ventricle contracts, the intraventricular pressure rises above 80 mmHg and ejection begins. As a result, the amount of blood in the aorta increases by the amount ejected from the left ventricle (the stroke volume). Due to the increase in volume, there is an increase in blood pressure. The

pressure in the brachial artery, where blood pressure measurements are commonly taken, therefore increases to 120 mmHg in this example. The rise in pressure from diastolic to systolic levels (pulse pressure) is thus a reflection of the stroke volume.

The **mean arterial pressure** represents the average arterial pressure during the cardiac cycle. This value is significant because it is the difference between this pressure and the venous pressure that drives blood through the capillary beds of organs. The mean arterial pressure is not a simple arithmetic average because the period of diastole is longer than the period of systole. Mean arterial pressure can be approximated by adding one-third of the pulse pressure to the diastolic pressure. For a person with a blood pressure of 120/80, the mean arterial pressure would be approximately 80 + 1/3 (40) = 93 mmHg.

Mean arterial pressure = diastolic pressure + 1/3 pulse pressure

A rise in total peripheral resistance and cardiac rate increases the diastolic pressure more than it increases the systolic pressure. When the baroreceptor reflex is activated by going from a lying to a standing position, for example, the diastolic pressure usually increases by 5 to 10 mmHg, whereas the systolic pressure either remains unchanged or is slightly reduced (as a result of decreased venous return). People with hypertension (high blood pressure), who usually have elevated total peripheral resistance and cardiac rates, likewise have a greater increase in diastolic than in systolic pressure. Dehydration or blood loss results in decreased cardiac output, and thus also produces a decrease in pulse pressure.

An increase in cardiac output, by contrast, raises the systolic pressure more than it raises the diastolic pressure (although both pressures do rise). This occurs during exercise, for example, when the blood pressure may rise to values as high as 200/100 (yielding a pulse pressure of 100 mmHg).

CHECKPOINT

12a. Describe the relationship between blood pressure and the total cross-sectional area of arteries, arterioles, and capillaries. Describe how arterioles influence blood flow through capillaries and arterial blood pressure.

12b. Explain how the baroreceptor reflex helps to compensate for a fall in blood pressure. Why will a person who is severely dehydrated have a rapid pulse?

13a. Describe how the sounds of Korotkoff are produced and explain how these sounds are used to measure blood pressure.

13b. Define *pulse pressure* and explain the physiological significance of this measurement.

14.7 HYPERTENSION, SHOCK, AND CONGESTIVE HEART FAILURE

An understanding of the normal physiology of the cardiovascular system is prerequisite to the study of its pathophysiology, or mechanisms of abnormal function. Studying the mechanisms of abnormal cardiovascular function is important medically and can improve our understanding of normal physiology.

LEARNING OUTCOMES

After studying this section, you should be able to:

14. Describe the causes and dangers of hypertension.

15 Describe the causes and dangers of circulatory shock.

16. Explain the events that occur in congestive heart failure.

Hypertension

Hypertension is blood pressure in excess of the normal range; it may be defined as a systolic pressure of 140 mmHg or higher, or a diastolic pressure of 90 or higher (table 14.8). Hypertension that is a result of (secondary to) known disease processes—such as chronic renal failure or an adrenal tumor—is called **secondary hypertension.** Of the hypertensive population, secondary hypertension accounts for only about 5%. Hypertension that is the result of complex and poorly understood processes is called **primary,** or **essential, hypertension.** Newer evidence suggests that cardiovascular risk begins to increase when a person's systolic blood pressure exceeds 115 mmHg or diastolic pressure exceeds 75 mmHg. Although the medical goal for healthy people is a blood pressure that does not exceed 120/80, a panel of experts recently recommended that physicians not prescribe blood pressure medications for patients over age 60 who are otherwise healthy unless their blood pressure is 150/90 or higher, nor for patients between the ages of 30 and 59 unless their blood pressure exceeds 140/90.

Diseases of the kidneys and arteriosclerosis of the renal arteries can cause secondary hypertension because of high blood volume. More commonly, the reduction of renal blood flow can raise blood pressure by stimulating the secretion of vasoactive chemicals from the kidneys. Experiments in which the renal artery is pinched, for example, produce hypertension that is associated (at least initially) with elevated renin secretion. These and other causes of secondary hypertension are summarized in table 14.9.

Essential Hypertension

The vast majority of people with hypertension have essential hypertension. Because their blood pressure is directly proportional to cardiac output and total peripheral resistance, one

Table 14.8 | Blood Pressure Classification in Adults

Blood Pressure Classification	Systolic Blood Pressure		Diastolic Blood Pressure	Drug Therapy
Normal	Under 120 mmHg	and	Under 80 mmHg	No drug therapy
Prehypertension	120–139 mmHg	or	80–89 mmHg	Lifestyle modification;* no antihypertensive drug indicated
Stage 1 Hypertension	140–159 mmHg	or	90–99 mmHg	Lifestyle modification; antihypertensive drugs
Stage 2 Hypertension	160 mmHg or greater	or	100 mmHg or greater	Lifestyle modification; antihypertensive drugs

*Lifestyle modifications include weight reduction; reduction in dietary fat and increased consumption of vegetables and fruit; reduction in dietary sodium (salt); engaging in regular aerobic exercise, such as brisk walking for at least 30 minutes a day, most days of the week; and moderation of alcohol consumption.

Source: From the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. *Journal of the American Medical Association; 289* (2003): 2560–2572.

Table 14.9 | Possible Causes of Secondary Hypertension

System Involved	Examples	Mechanisms
Kidneys	Kidney disease	Decreased urine formation
	Renal artery disease	Secretion of vasoactive chemicals
Endocrine	Excess catecholamines (tumor of adrenal medulla)	Increased cardiac output and total peripheral resistance
	Excess aldosterone (Conn's syndrome)	Excess salt and water retention by the kidneys
Nervous	Increased intracranial pressure	Activation of sympathoadrenal system
	Damage to vasomotor center	Activation of sympathoadrenal system
Cardiovascular	Complete heart block; patent ductus arteriosus	Increased stroke volume
	Arteriosclerosis of aorta; coarctation of aorta	Decreased distensibility of aorta

or both of these must be elevated. It is well established that a diet high in salt is associated with hypertension. A possible explanation for this association is that a high-salt diet causes increased plasma osmolality, which stimulates ADH secretion. Increased ADH then causes increased water reabsorption by the kidneys, increasing blood volume and thereby increasing cardiac output and blood pressure.

This sequence should be prevented by the ability of the kidneys to excrete the excess salt and water. However, the ability of the kidneys to excrete Na^+ declines with age, in part due to a gradual decline in the filtering ability of the kidneys (the glomerular filtration rate, described in chapter 17). Also, there may be inappropriately high levels of aldosterone secretion, stimulating salt and water reabsorption. This is suggested by the observation that some people with essential hypertension (who should have low renin secretion) may have normal or even elevated levels of renin, and thus increased production of angiotensin II, which stimulates aldosterone secretion.

Although hypertension may initially be produced by a rise in blood volume and thus cardiac output, after some time the total peripheral resistance rises to raise the blood pressure as cardiac output declines. The rise in total peripheral resistance appears to involve (1) an increased activity of sympathetic nerves, stimulating vasoconstriction; (2) changes in the secretion of paracrine regulators by the artery endothelium (such as reduced secretion of nitric oxide, which promotes vasodilation, and increased secretion of endothelin, which promotes vasoconstriction); and (3) changes in the structure of the arteries that result in increased resistance to flow.

The interactions between salt intake, sympathetic nerve activity, cardiovascular responses to sympathetic activity, responses to paracrine regulators from the endothelium, and kidney function make it difficult to sort out the cause-and-effect sequence that leads to essential hypertension. Some scientists believe that kidney function may be a "final common pathway" in essential hypertension, in the sense that properly functioning kidneys should be able to lower the blood volume to compensate for elevated blood pressure from any cause.

Newer evidence on dietary NaCl and blood pressure demonstrates a complex relationship. A high-salt diet was especially well correlated with hypertension and cardiovascular disease among older people and people with hypertension, but less well correlated in younger and normotensive people. Lowering salt intake is still recommended for hypertensive patients

who eat a high-salt diet, but for the general population, a diet that is too low in salt may also be unhealthy. However, dietary potassium influences the relationship between dietary salt and hypertension. A diet low in potassium increases the effect of salt on blood pressure, while a diet higher in potassium—as can be obtained by eating fruit and vegetables—may reduce the ability of salt to cause hypertension.

Dangers of Hypertension

If other factors remain constant, blood flow increases as arterial blood pressure increases. The organs of people with hypertension are thus adequately perfused with blood until the excessively high pressure causes vascular damage. Because most patients are asymptomatic (without symptoms) until substantial vascular damage has occurred, hypertension is often referred to as a silent killer.

Hypertension is dangerous for a number of reasons. One problem is that high blood pressure increases the afterload, making it more difficult for the ventricles to eject blood. The ventricles must then work harder, leading to pathological growth of their walls. This abnormal hypertrophy that can result from hypertension, or from valve defects or obesity, increases the risk of arrhythmias and heart failure. Hypertrophy due to these causes differs from the normal left ventricular hypertrophy often seen in well-trained athletes, which relieves wall stress and is believed to be beneficial.

Additionally, high pressure may damage cerebral blood vessels, leading to cerebrovascular accident, or "stroke." (Stroke is the third leading cause of death in the United States.) Finally, hypertension contributes to the development of atherosclerosis, which can itself lead to heart disease and stroke as previously described.

CLINICAL APPLICATION

Preeclampsia, formerly called *toxemia of pregnancy,* occurs in up to 8% of women worldwide who are pregnant beyond their twentieth week. It is characterized by the new onset of hypertension, but differs from gestational hypertension by evidence of damage to organs such as the liver and kidneys. *Thrombocytopenia* (low platelet count) may occur, and abnormally large amounts of proteins in the urine (*proteinuria*) may be present. Urine normally has little protein, and the presence of proteinuria indicates that plasma proteins are abnormally leaking through the kidneys' filtering units (*glomeruli*) into the urine. This lowers the plasma protein concentration and oncotic pressure (section 14.2), producing edema and swelling of the feet, legs, or hands. The causes of preeclampsia are not well understood, but it is believed to stem from dysfunction of the placenta, perhaps involving vasoconstriction and hypoxia within the uterus/placenta environment. If preeclampsia becomes severe, the hypertension can cause seizures and stroke. The only cure for preeclampsia is delivery of the baby.

Treatment of Hypertension

The first form of treatment that is usually attempted is modification of lifestyle. This modification includes cessation of smoking, moderation of alcohol intake, and weight reduction, if applicable. It can also include programmed exercise and a more moderate sodium intake. People with essential hypertension may have a potassium deficiency, and there is evidence that eating food that is rich in potassium may help lower blood pressure. There is also evidence that supplementing the diet with Ca^{2+} may be of benefit, but this is more controversial.

If lifestyle modifications alone are insufficient, various drugs may be prescribed. These may include *diuretics* that increase urine volume, thus decreasing blood volume and pressure. Drugs that block β_1-adrenergic receptors (such as atenolol) lower blood pressure by decreasing the cardiac rate and are also frequently prescribed. *ACE (angiotensin-converting enzyme) inhibitors,* calcium antagonists, and various vasodilators (table 14.10) may also be used in particular situations.

Another class of drugs, the *angiotensin II-receptor blockers (ARBs),* allows angiotensin II to be formed but blocks the binding of angiotensin II to its receptors. This reduces angiotensin II–induced vasoconstriction and (via angiotensin II stimulation of aldosterone secretion) salt and water retention. ACE inhibitors and ARBs are currently the most widely prescribed drugs for the treatment of hypertension. Newer drugs include those that inhibit renin activity and in other ways reduce the activity of the renin-angiotensin-aldosterone system.

Clinical Investigation CLUES

Mark was diagnosed with essential hypertension, for which he was prescribed an ACE inhibitor.

- What is essential hypertension, and what are its dangers?
- By what mechanisms does an ACE inhibitor lower blood pressure?

Circulatory Shock

Circulatory shock occurs when there is inadequate blood flow and/or oxygen utilization by the tissues. Some of the signs of shock (table 14.11) are a result of inadequate tissue perfusion; other signs of shock are produced by cardiovascular responses that help compensate for the poor tissue perfusion (table 14.12). When these compensations are effective, they (together with emergency medical care) are able to reestablish adequate tissue perfusion. In some cases, however, and for reasons that are not clearly understood, the shock may progress to an irreversible stage and death may result.

Hypovolemic Shock

The term **hypovolemic shock** refers to circulatory shock that is due to low blood volume, as might be caused by hemorrhage

(bleeding), dehydration, or burns. This is accompanied by decreased blood pressure and decreased cardiac output. In response to these changes, the sympathoadrenal system is activated by means of the baroreceptor reflex. As a result, tachycardia is produced and vasoconstriction occurs in the skin, digestive tract, kidneys, and muscles. Decreased blood flow through the kidneys stimulates renin secretion and activation of the renin-angiotensin-aldosterone system. A person in hypovolemic shock thus has low blood pressure, a rapid pulse, cold, clammy skin, and a reduced urine output.

Because the resistance in the coronary and cerebral circulations is not increased, blood is diverted to the heart and brain at the expense of other organs. Interestingly, a similar

Table 14.10 | Mechanisms of Action of Selected Antihypertensive Drugs

Category of Drugs	Examples	Mechanisms
Diuretics	Thiazide; furosemide	Increase volume of urine excreted, thus lowering blood volume
Sympathoadrenal system inhibitors	Clonidine; alpha-methyldopa	Act to decrease sympathoadrenal stimulation by bonding to α2-adrenergic receptors in the brain
	Guanethidine; reserpine	Deplete norepinephrine from sympathetic nerve endings
	Atenolol	Blocks beta-adrenergic receptors, decreasing cardiac output and/or renin secretion
	Phentolamine	Blocks alpha-adrenergic receptors, decreasing sympathetic vasoconstriction
Direct vasodilators	Hydralazine; minoxidil sodium nitroprusside	Cause vasodilation by acting directly on vascular smooth muscle
Calcium channel blockers	Verapamil; diltiazem	Inhibit diffusion of Ca^{2+} into vascular smooth muscle cells, causing vasodilation and reduced peripheral resistance
Angiotensin-converting enzyme (ACE) inhibitors	Captopril; enalapril	Inhibit the conversion of angiotensin I into angiotensin II
Angiotensin II–receptor antagonists	Losartan	Blocks the binding of angiotensin II to its receptor

Table 14.11 | Signs of Shock

	Early Sign	Late Sign
Blood pressure	Decreased pulse pressure	Decreased systolic pressure
	Increased diastolic pressure	
Urine	Decreased Na^+ concentration	Decreased volume
	Increased osmolality	
Blood pH	Increased pH (alkalosis) due to hyperventilation	Decreased pH (acidosis) due to metabolic acids
Effects of poor tissue perfusion	Slight restlessness; occasionally warm, dry skin	Cold, clammy skin; "cloudy" senses

Source: From *Principles and Techniques of Critical Care,* Vol. 1, edited by R. F. Wilson. Copyright © 1977 F. A. Davis Company, Philadelphia, PA. Used by permission.

Table 14.12 | Cardiovascular Reflexes That Help to Compensate for Circulatory Shock

Organ(s)	Compensatory Mechanisms
Heart	Sympathoadrenal stimulation produces increased cardiac rate and increased stroke volume due to a positive inotropic effect on myocardial contractility
Digestive tract and skin	Decreased blood flow due to vasoconstriction as a result of sympathetic nerve stimulation (alpha-adrenergic effect)
Kidneys	Decreased urine production as a result of sympathetic-nerve-induced constriction of renal arterioles; increased salt and water retention due to increased plasma levels of aldosterone and antidiuretic hormone (ADH)

response occurs in diving mammals and, to a lesser degree, in Japanese pearl divers during prolonged submersion. These responses help deliver blood to the two organs that have the highest requirements for aerobic metabolism.

Vasoconstriction in organs other than the brain and heart raises total peripheral resistance, which helps (along with the reflex increase in cardiac rate) to compensate for the drop in blood pressure due to low blood volume. Constriction of arterioles also decreases capillary blood flow and capillary filtration pressure. As a result, less filtrate is formed. At the same time, the osmotic return of fluid to the capillaries is either unchanged or increased (during dehydration). The blood volume is thus raised at the expense of tissue fluid volume. Blood volume is also conserved by decreased urine production, which occurs as a result of vasoconstriction in the kidneys and the water-conserving effects of ADH and aldosterone, which are secreted in increased amounts during shock.

Septic Shock

Septic shock refers to a dangerously low blood pressure (hypotension) that may result from sepsis, or infection. This can occur through the action of a bacterial lipopolysaccharide called *endotoxin.* The mortality associated with septic shock is presently very high, estimated at 50% to 70%. According to recent information, endotoxin activates the enzyme nitric oxide synthase within macrophages—cells that play an important role in the immune response (chapter 15). As previously discussed, nitric oxide synthase produces nitric oxide, which promotes vasodilation and, as a result, a fall in blood pressure. Septic shock has recently been treated effectively with drugs that inhibit the production of nitric oxide.

Other Causes of Circulatory Shock

A rapid fall in blood pressure occurs in **anaphylactic shock** as a result of a severe allergic reaction (usually to bee stings or penicillin). This results from the widespread release of histamine, which causes vasodilation and thus decreases total peripheral resistance. A rapid fall in blood pressure also occurs in **neurogenic shock,** in which sympathetic tone is decreased, usually because of upper spinal cord damage or spinal anesthesia. **Cardiogenic shock** results from cardiac failure, as defined by a cardiac output inadequate to maintain tissue perfusion. This commonly results from infarction that causes the loss of a significant proportion of the myocardium. Cardiogenic shock may also result from severe cardiac arrythmias or valve damage.

Congestive Heart Failure

Cardiac failure occurs when the cardiac output is insufficient to maintain the blood flow required by the body. This may be due to heart disease—resulting from myocardial infarction or congenital defects—or to hypertension, which increases the afterload of the heart. The most common causes of left ventricular heart failure are myocardial infarction, aortic valve stenosis, and incompetence of the aortic and bicuspid (mitral) valves. This can become a vicious cycle, where a myocardial infarction causes heart failure that results in heart muscle remodeling, which can in turn promote dangerous arrythmias. Failure of the right ventricle is usually caused by prior failure of the left ventricle.

Heart failure can also result from disturbance in the electrolyte concentrations of the blood. Excessive plasma K^+ concentration decreases the resting membrane potential of myocardial cells, and low blood Ca^{2+} reduces excitation-contraction coupling. High blood K^+ and low blood Ca^{2+} can thus cause the heart to stop in diastole. Conversely, low blood K^+ and high blood Ca^{2+} can arrest the heart in systole.

The term *congestive* is often used in describing heart failure because of the increased venous volume and pressure that results. Failure of the left ventricle, for example, raises the left atrial pressure and produces pulmonary congestion and edema. This causes shortness of breath and fatigue; if severe, pulmonary edema can be fatal. Failure of the right ventricle results in increased right atrial pressure, which produces congestion and edema in the systemic circulation.

The compensatory responses that occur during congestive heart failure are similar to those that occur during hypovolemic shock. Activation of the sympathoadrenal system stimulates cardiac rate, contractility of the ventricles, and constriction of arterioles. As in hypovolemic shock, renin secretion is increased and urine output is reduced. The increased secretion of renin and consequent activation of the renin-angiotensinaldosterone system causes salt and water retention. This occurs despite an increased secretion of atrial natriuretic peptide (which would have the compensatory effect of promoting salt and water excretion).

As a result of these compensations, chronically low cardiac output is associated with elevated blood volume and dilation and hypertrophy of the ventricles. These changes can themselves be dangerous. Elevated blood volume places a work overload on the heart, and the enlarged ventricles have a higher metabolic requirement for oxygen. These problems are often treated with drugs that increase myocardial contractility (such as digitalis, described in chapter 13), drugs that are vasodilators (such as nitroglycerin), drugs that block beta-adrenergic receptors (to reduce the strain on the heart from excessive sympathoadrenal activation), and drugs that reduce the effects of excessive activation of the renin-angiotensin system. The latter includes ACE (angiotensin converting enzyme) inhibitors and ARBs (angiotensin II receptor blockers). Diuretics—drugs that lower blood volume by increasing urine volume (chapter 17, section 17.6)—are also used to alleviate congestive heart failure.

CHECKPOINT

14. Explain how stress and a high-salt diet can contribute to hypertension. Also, explain how different drugs may act to lower blood pressure.

15a. Using a flowchart to show cause and effect, explain why a person in hypovolemic shock may have a fast pulse and cold, clammy skin.

15b. Describe the compensatory mechanisms that act to raise blood volume during cardiovascular shock.

15c. Explain how septic shock may be produced.

16. Describe congestive heart failure and explain the compensatory responses that occur during this condition.

Clinical Investigation SUMMARY

Mark's Crohn's disease caused him to lose proteins through the intestine. This produced a fall in plasma protein concentration (hypoproteinemia) and a fall in his plasma oncotic pressure, so that interstitial fluid was not sufficiently returned to the vascular system and produced edema. His prolonged running made him dehydrated, which gave him orthostatic hypotension that made him dizzy upon standing. He was advised to drink more and to switch from water to sports drinks for prolonged exercise sessions, because he needed to replenish his Na^+, K^+, and Cl^- that were lost in sweat. This would allow him to maintain his blood volume and pressure, so that his baroreceptor reflex could prevent the orthostatic hypotension. He later had essential hypertension and took an ACE inhibitor, which inhibits angiotensin-converting enzyme, reducing angiotensin-II-induced vasoconstriction (increasing peripheral resistance) and lowering the total peripheral resistance. He was advised not to perform the Valsalva maneuver when lifting heavy weights, to avoid the fluctuations in heart rate and blood pressure that this produces, because hypertension is a risk factor for atherosclerosis and coronary heart disease.

See the additional chapter 14 Clinical Investigations on Orthostatic Hypotension and Pheochromocytoma in the Connect site for this text.