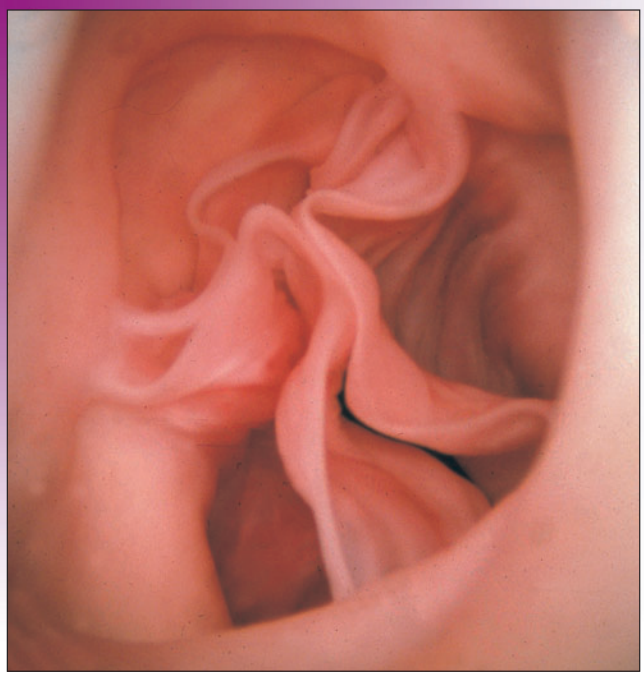


A semilunar valve of the heart (endoscopic photo)

CHAPTER

19

The Circulatory System: The Heart

CHAPTER OUTLINE

INSIGHTS

Brushing Up

To understand this chapter, it is important that you understand or brush up on the following concepts:
- Properties of cardiac muscle (pp. 176, 432)
- Desmosomes and gap junctions (p. 179)
- Ultrastructure of striated muscle (pp. 409–411)
- Excitation-contraction coupling in muscle (p. 417)
- Length-tension relationship in muscle fibers (p. 422)
- Action potentials (p. 458)

We are more conscious of our heart than we are of most organs, and more wary of its failure. Speculation about the heart is at least as old as written history. Some ancient Chinese, Egyptian, Greek, and Roman scholars correctly surmised that the heart is a pump for filling the vessels with blood. Aristotle's views, however, were a step backward. Perhaps because the heart quickens its pace when we are emotionally aroused, and because grief causes "heartache," he regarded it primarily as the seat of emotion, as well as a source of heat to aid digestion. During the Middle Ages, Western medical schools clung dogmatically to the ideas of Aristotle. Perhaps the only significant advance came from Muslim medicine, when thirteenth-century physician Ibn an-Nafis described the role of the coronary blood vessels in nourishing the heart. The sixteenth-century dissections and anatomical charts of Vesalius, however, greatly improved knowledge of cardiovascular anatomy and set the stage for a more scientific study of the heart and treatment of its disorders—the science we now call **cardiology.**[1]

In the early decades of the twentieth century, little could be recommended for heart disease other than bed rest. Then nitroglycerin was found to improve coronary circulation and relieve the pain resulting from physical exertion, digitalis proved effective for treating abnormal heart rhythms, and diuretics were first used to reduce hypertension. Coronary bypass surgery, replacement of diseased valves, clot-dissolving enzymes, heart transplants, artificial pacemakers, and artificial hearts have made cardiology one of the most dramatic and attention-getting fields of medicine in the last quarter-century.

Chapter 19

Gross Anatomy of the Heart

Objectives

When you have completed this section, you should be able to

- describe the relationship of the heart to other thoracic structures;
- identify the chambers and valves of the heart and the features of its wall;
- trace the flow of blood through the heart chambers; and
- describe the blood supply to the heart tissue.

Overview of the Cardiovascular System

The term **circulatory system** refers to the heart, blood vessels, and blood. The term **cardiovascular system,** however, refers only to the passages through which the blood flows—the **heart,** a four-chambered muscular pump; **arteries,** the vessels that carry blood away from the heart; **veins,** the vessels that carry blood back to the heart; and **capillaries,** microscopic blood vessels that connect the smallest arteries to the smallest veins.

[1] *cardio* = heart + *logy* = study

The cardiovascular system has two major divisions: a **pulmonary circuit,** which carries blood to the lungs for gas exchange and then returns it to the heart, and a **systemic circuit,** which supplies blood to every organ of the body (fig. 19.1). The right side of the heart serves the pulmonary circuit. It receives blood that has circulated through the body, unloaded oxygen and nutri-

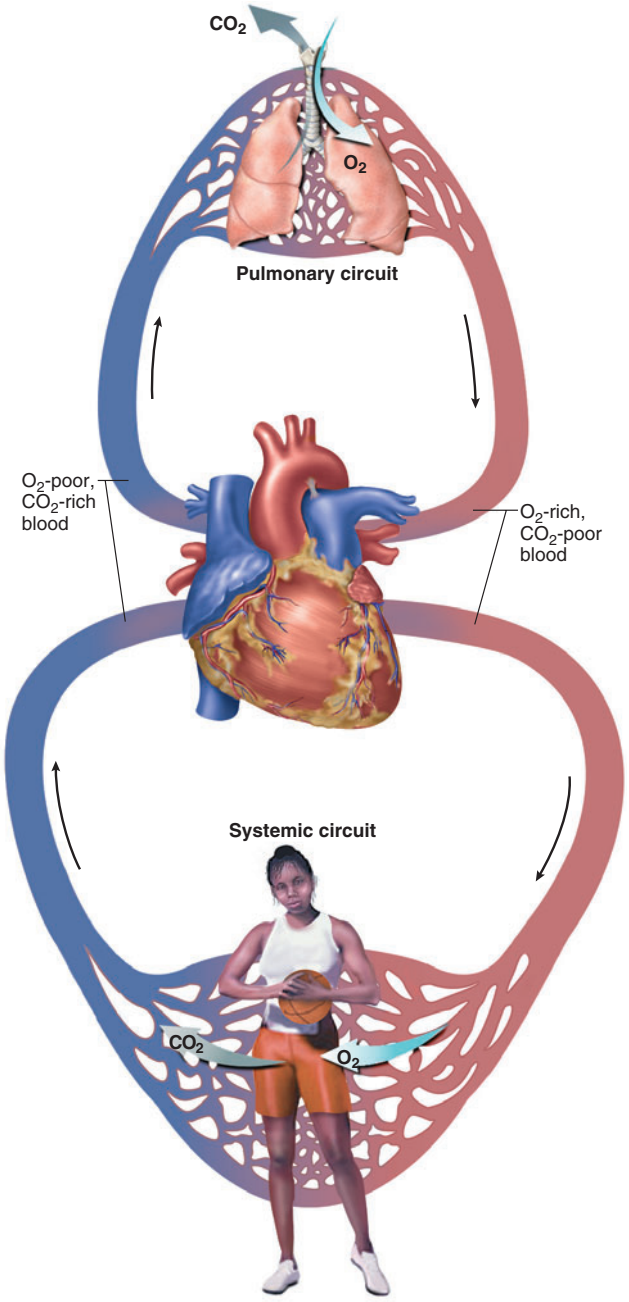


Figure 19.1 General Schematic of the Cardiovascular System.

ents, and picked up a load of carbon dioxide and other wastes. It pumps this oxygen-poor blood into a large artery, the *pulmonary trunk,* which immediately divides into *right* and *left pulmonary arteries.* These transport blood to the lungs, where carbon dioxide is unloaded and oxygen is picked up. The oxygen-rich blood then flows by way of the *pulmonary veins* to the left side of the heart.

The left side of the heart serves the systemic circuit. Oxygenated blood leaves it by way of another large artery, the *aorta.* The aorta takes a sharp U-turn, the *aortic arch,* and passes downward, dorsal to the heart. The aortic arch gives off arteries that supply the head, neck, and upper limbs. The aorta then travels through the thoracic and abdominal cavities and issues smaller arteries to the other organs. After circulating through the body, the now-deoxygenated systemic blood returns to the right side of the heart mainly by way of two large veins, the *superior vena cava* (draining the head, neck, upper limbs, and thoracic organs) and *inferior vena cava* (draining the organs below the diaphragm). The major arteries and veins entering and leaving the heart are called the *great vessels* because of their relatively large diameters.

Size, Shape, and Position of the Heart

The heart is located in the thoracic cavity in the mediastinum, the area between the lungs. About two-thirds of it lies to the left of the median plane (fig. 19.2). The broad superior portion of the heart, called the **base,** is the point of attachment for the great vessels described previously. Its inferior end, the **apex,** tilts to the left and tapers to a blunt point (figs. 19.3 and 19.4). The adult heart is about 9 cm (3.5 in.) wide at the base, 13 cm (5 in.) from base to apex, and 6 cm (2.5 in.) from anterior to posterior at its thickest point—roughly the size of a fist. It weighs about 300 g (10 oz).

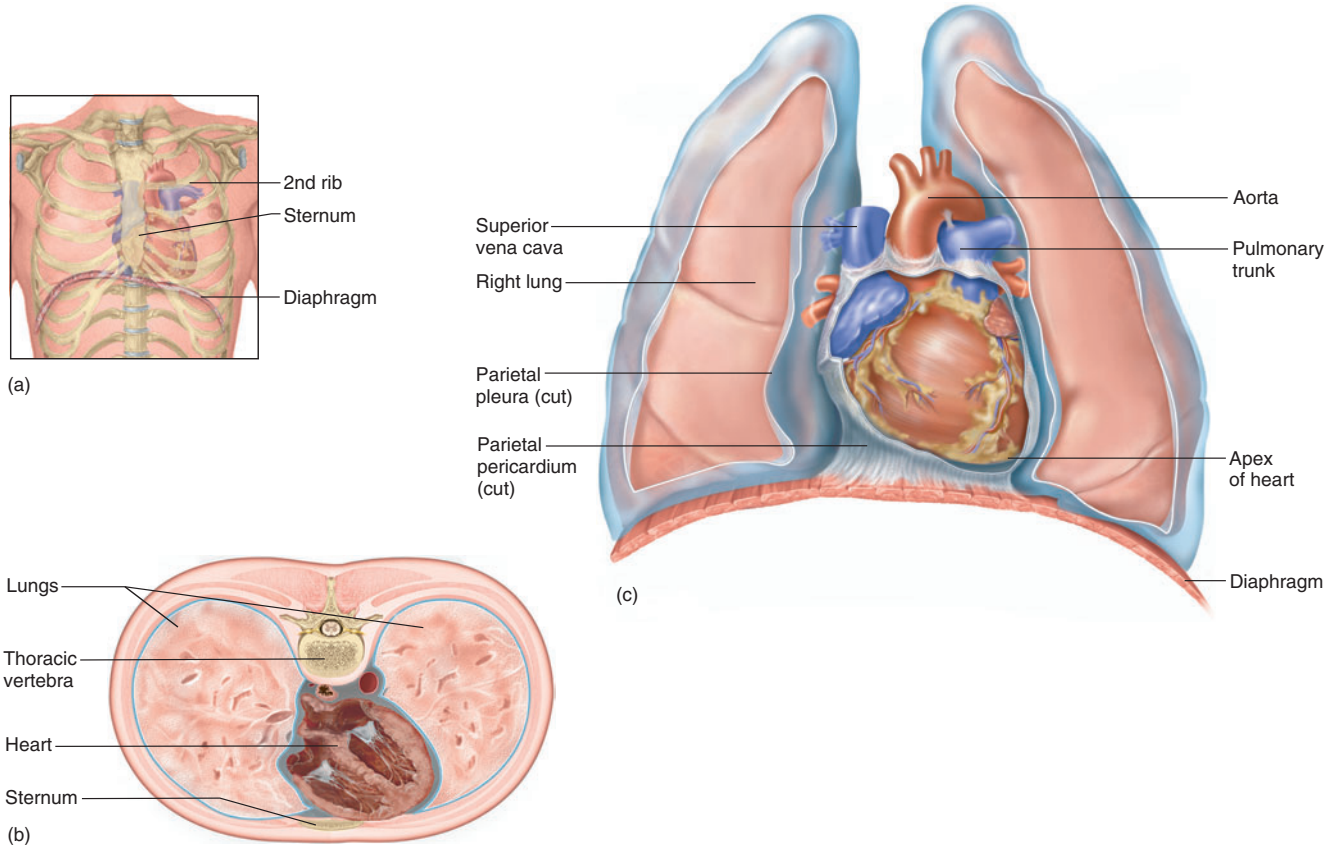


Figure 19.2 Position of the Heart in the Thoracic Cavity. (*a*) Relationship to the thoracic cage; (*b*) cross section of the thorax at the level of the heart; (*c*) frontal section of the thoracic cavity with the lungs slightly retracted and the pericardial sac opened.
Does most of the heart lie to the right or left of the median plane?

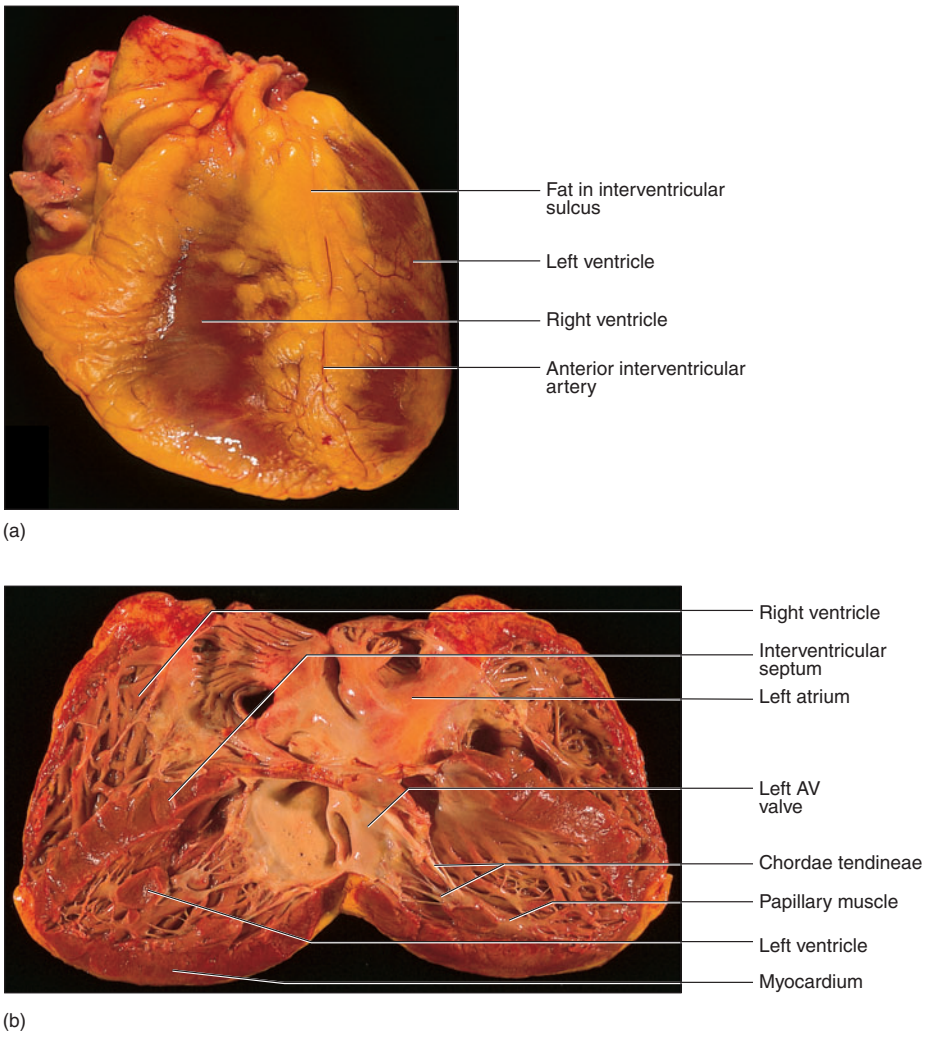


Figure 19.3 The Human Heart. (*a*) Anterior aspect; (*b*) internal anatomy, with the heart in *a* bisected on the frontal plane and folded open like a book.

The Pericardium

The heart is enclosed in a double-walled sac called the **pericardium,**[2] which is anchored to the diaphragm below and to the connective tissue of the great vessels above the heart (fig. 19.5). The **parietal pericardium (pericardial sac)** consists of a tough *fibrous layer* of dense irregular connective tissue and a thin, smooth *serous layer.* The serous layer turns inward at the base of the heart and forms the **visceral pericardium** covering the heart surface. Between the parietal and visceral membranes is a space called the **pericardial cavity.** It contains 5 to 30 mL of **pericardial fluid,** an exudate of the serous pericardium that lubricates the membranes and allows the heart to beat almost without friction. In *pericarditis*—inflammation of the pericardium—the membranes may become dry and produce a painful *friction rub* with each heartbeat. In addition to reducing friction, the pericardium isolates the heart from other thoracic organs, allows the heart room to expand, and resists excessive expansion. (See *cardiac tamponade* in table 19.3.)

The Heart Wall

The heart wall consists of three layers—the epicardium, myocardium, and endocardium (fig. 19.5). The **epicardium**[3] (= visceral pericardium) is a serous membrane

[2] *peri* = around

[3] *epi* = upon

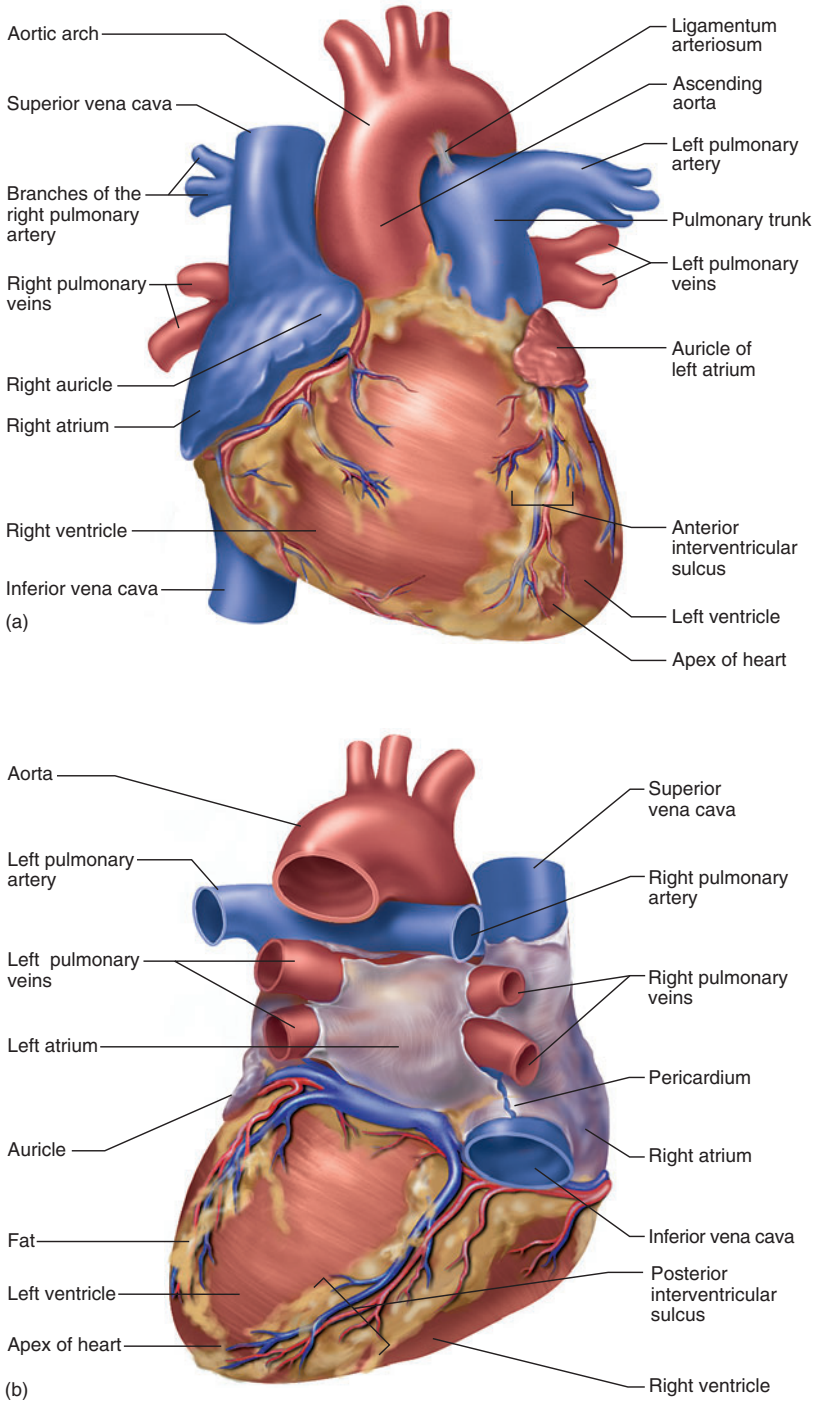


Figure 19.4 External Anatomy of the Heart. (*a*) Anterior aspect; (*b*) posterior aspect. The coronary blood vessels on the heart surface are identified in figure 19.10.

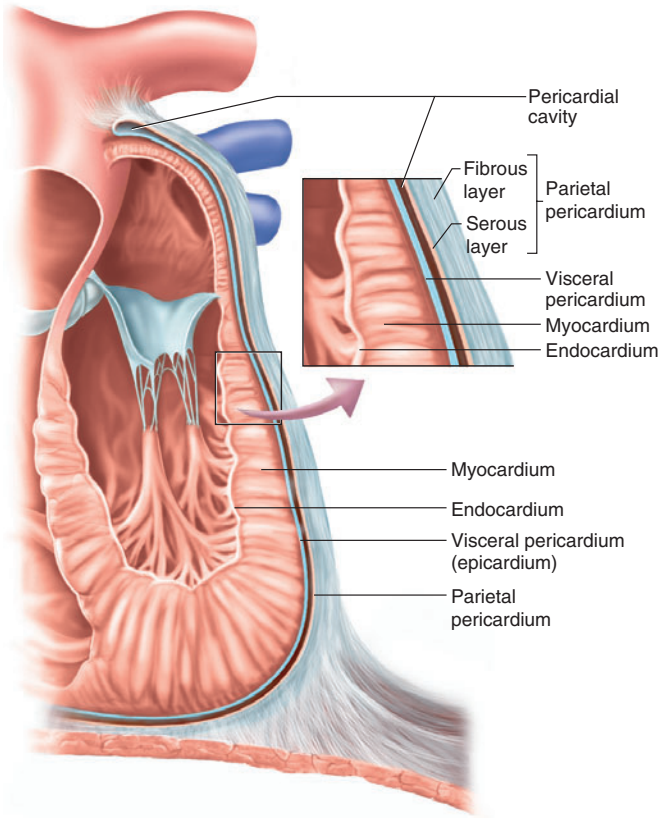


Figure 19.5 The Pericardium and Heart Wall. The inset shows the layers of the heart wall in relationship to the pericardium.

composed of a simple squamous epithelium overlying a thin layer of areolar tissue. Over much of the heart, it has thick deposits of fat that fill grooves in the heart surface and protect the coronary blood vessels. In nonfatty areas, the epicardium is thin and translucent, allowing the myocardium to show through.

The **myocardium,**[4] by far the thickest layer, is composed of cardiac muscle and performs the work of the heart. Its muscle cells spiral around the heart and are bound together by a meshwork of collagenous and elastic fibers that make up the **fibrous skeleton.** The fibrous skeleton has at least three functions: to provide structural support for the heart, especially around the valves and the openings of the great vessels; to give the muscle something to pull against; and, as a nonconductor of electricity, to limit the routes by which electrical excitation travels through the heart. This insulation prevents the atria from stimulating the ventricles directly and is important in the timing and coordination of electrical and contractile activity. Elastic recoil of the fibrous skeleton may also aid in refilling the heart with blood after each beat, but physiologists are not in complete agreement about this.

The **endocardium**[5] consists of a simple squamous endothelium overlying a thin areolar tissue layer. It forms the smooth inner lining of the chambers and valves and is continuous with the endothelium of the blood vessels.

The Chambers

The heart has four chambers (see fig. 19.4). Blood returning to the heart is received by two superior chambers, the **right** and **left atria** (AY-tree-uh; singular *atrium*[6]). These are mostly posterior in position, so only a small portion of each is visible from the anterior aspect. Each atrium has a small earlike extension called an *auricle*[7] that slightly increases its volume. The two inferior chambers, the **right** and **left ventricles,**[8] are the pumps that eject blood into the

[4] *myo* = muscle

[5] *endo* = internal
[6] *atrium* = entryway
[7] *auricle* = little ear
[8] *ventr* = belly, lower part + *icle* = little

arteries. The right ventricle constitutes most of the anterior aspect of the heart, while the left ventricle forms the apex and inferoposterior aspect.

The heart is crisscrossed by sulci (grooves) that mark the boundaries of the four chambers. The sulci are occupied largely by fat and coronary blood vessels. The **atrioventricular (coronary[9]) sulcus** encircles the heart near its base and separates the atria from the ventricles. The **anterior** and **posterior interventricular sulci** extend vertically, from the coronary sulcus toward the apex, externally marking the boundary between the right and left ventricles.

The four chambers are best seen in a frontal section (fig. 19.6). The atria exhibit thin flaccid walls corresponding to their light workload—all they do is pump blood into the ventricles immediately below. They are separated from each other by a wall, the **interatrial septum.** The right atrium and both auricles exhibit internal ridges of myocardium called the **pectinate[10] muscles.** A thicker wall, the **interventricular septum,** separates the right and left ventricles. The right ventricle pumps blood only to the lungs and back, so its wall is only moderately thick and muscular. The left ventricle is two to four times as thick because it bears the greatest workload of all four chambers, pumping blood through the entire body. Both ventricles exhibit internal ridges called **trabeculae carneae**[11] (trah-BEC-you-lee CAR-nee-ee).

The Valves

To pump blood effectively, the heart needs valves that ensure a predominantly one-way flow. There is a valve between each atrium and its ventricle and at the exit from each ventricle into its great artery (figs. 19.6 and 19.7). Each valve consists of two or three fibrous flaps of tissue called **cusps,** covered with endothelium.

[9] *coron* = crown + *ary* = pertaining to

[10] *pectin* = comb + *ate* = like

[11] *trabecula* = little beam + *carne* = flesh, meat

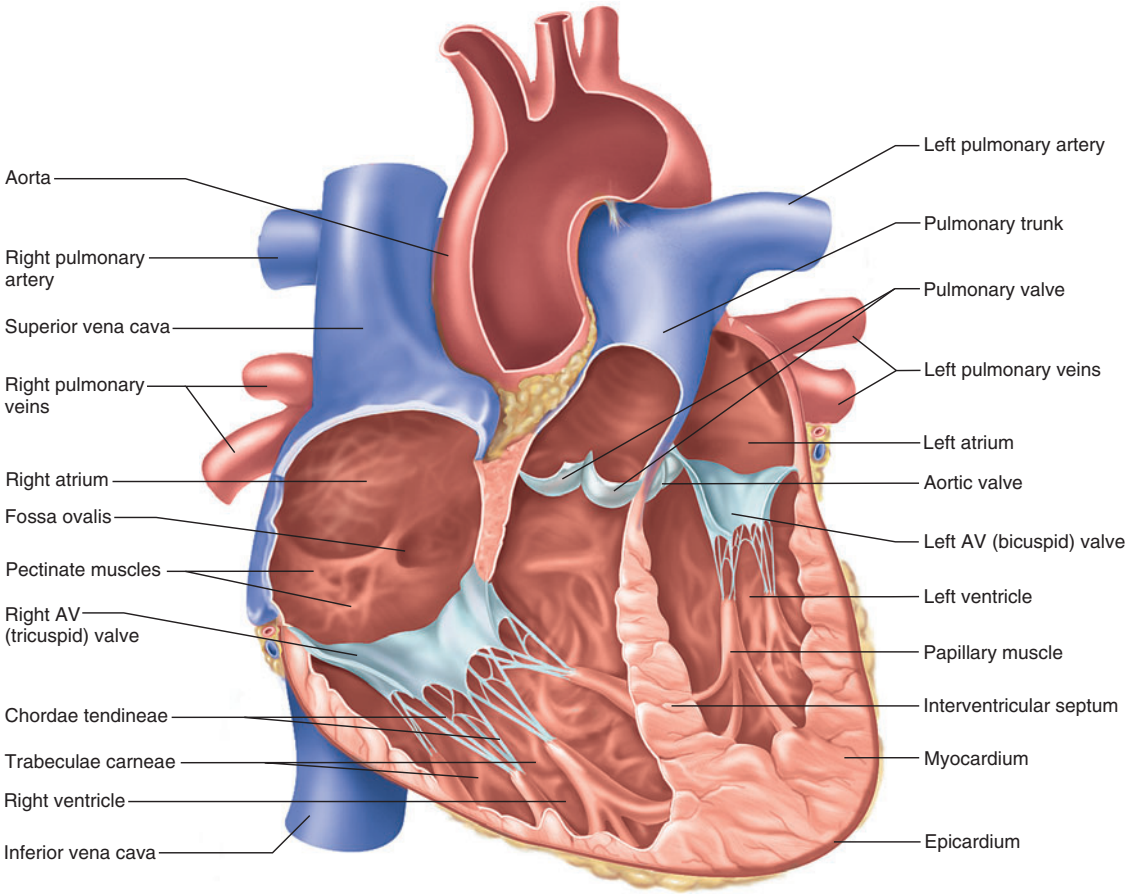


Figure 19.6 **Internal Anatomy of the Heart (anterior aspect).**
Do the atrial pectinate muscles more nearly resemble the ventricular papillary muscles or the trabeculae carneae?

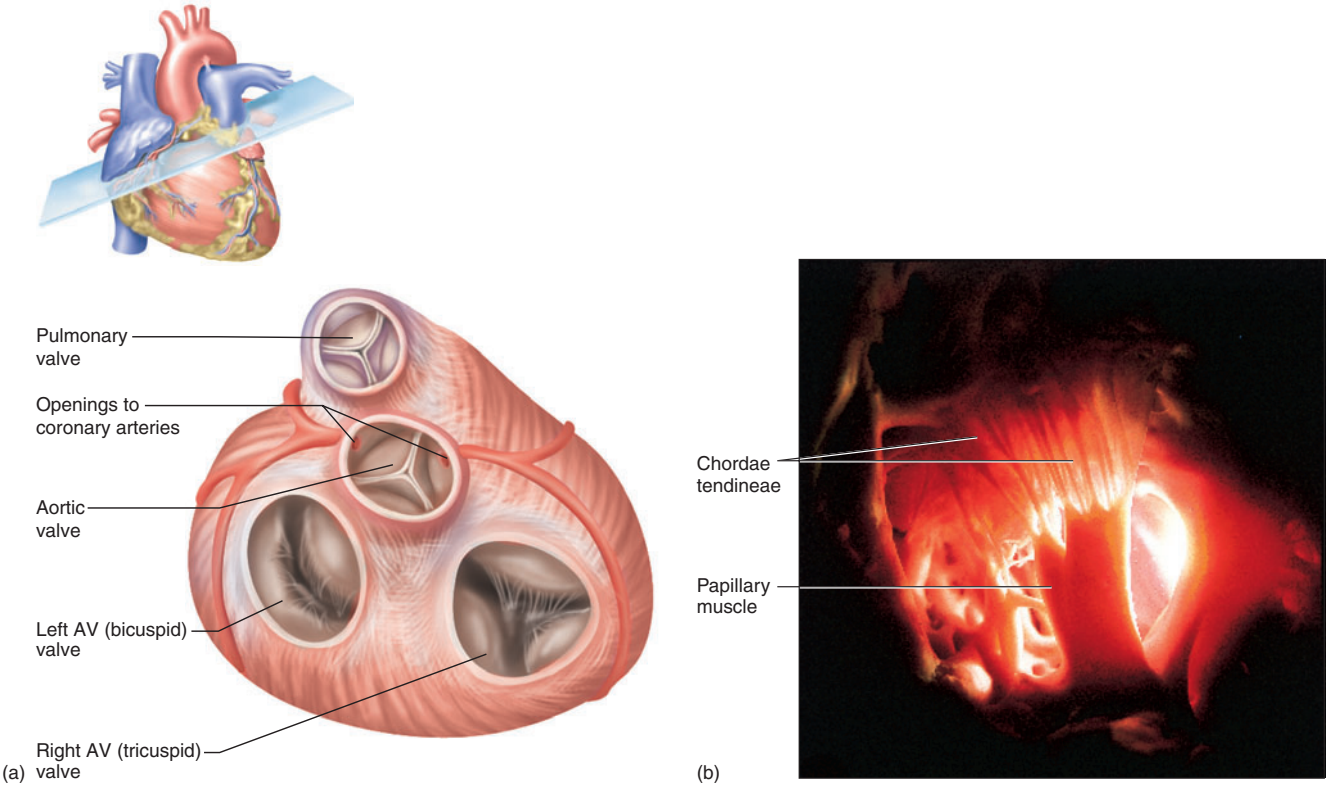


Figure 19.7 The Heart Valves. (*a*) Superior view of the heart with the atria removed; (*b*) papillary muscle and chordae tendineae seen from within the right ventricle. The upper ends of the chordae tendineae are attached to the cusps of the right AV valve.

The **atrioventricular (AV) valves** regulate the openings between the atria and ventricles. The **right AV (tricuspid) valve** has three cusps and the **left AV (bicuspid) valve** has two. The left AV valve is also known as the **mitral** (MY-trul) **valve** after its resemblance to a miter, the headdress of a catholic bishop. Stringlike **chordae tendineae** (COR-dee ten-DIN-ee-ee), reminiscent of the shroud lines of a parachute, connect the AV valve cusps to conical **papillary muscles** on the floor of the ventricle.

The **semilunar**[12] **valves** (pulmonary and aortic valves) regulate the openings between the ventricles and the great arteries. The **pulmonary valve** controls the opening from the right ventricle into the pulmonary trunk, and the **aortic valve** controls the opening from the left ventricle into the aorta. Each has three cusps shaped somewhat like shirt pockets (see photograph on p. 715).

The opening and closing of heart valves is the result of pressure gradients between the "upstream" and "downstream" sides of the valve (fig. 19.8). When the ventricles are relaxed, the AV valve cusps hang down limply, both AV valves are open, and blood flows freely from the atria into the ventricles. When the ventricles have filled with blood and begin to contract, their internal pressure rises and blood surges against the AV valves. This pushes their cusps together, seals the openings, and prevents blood from flowing back into the atria. The papillary muscles contract with the rest of the ventricular myocardium and tug on the chordae tendineae, which prevents the valves from bulging excessively (prolapsing) into the atria or turning inside out like windblown umbrellas (see insight 19.1). When rising "upstream" pressure in the ventricles exceeds the "downstream" blood pressure in the great arteries, the ventricular blood forces the semilunar valves open and blood is ejected from the heart. Then as the ventricles relax again and their pressure falls below that in the arteries, arterial blood briefly flows backward and fills the pocketlike cusps of the semilunar valves. The three cusps meet in the middle of the orifice and seal it, thereby preventing blood from reentering the heart.

Think About It

How would valvular stenosis (see insight 19.1) affect the amount of blood pumped into the aorta? How might this affect a person's physical stamina? Explain your reasoning.

[12] *semi* = half + *lunar* = like the moon

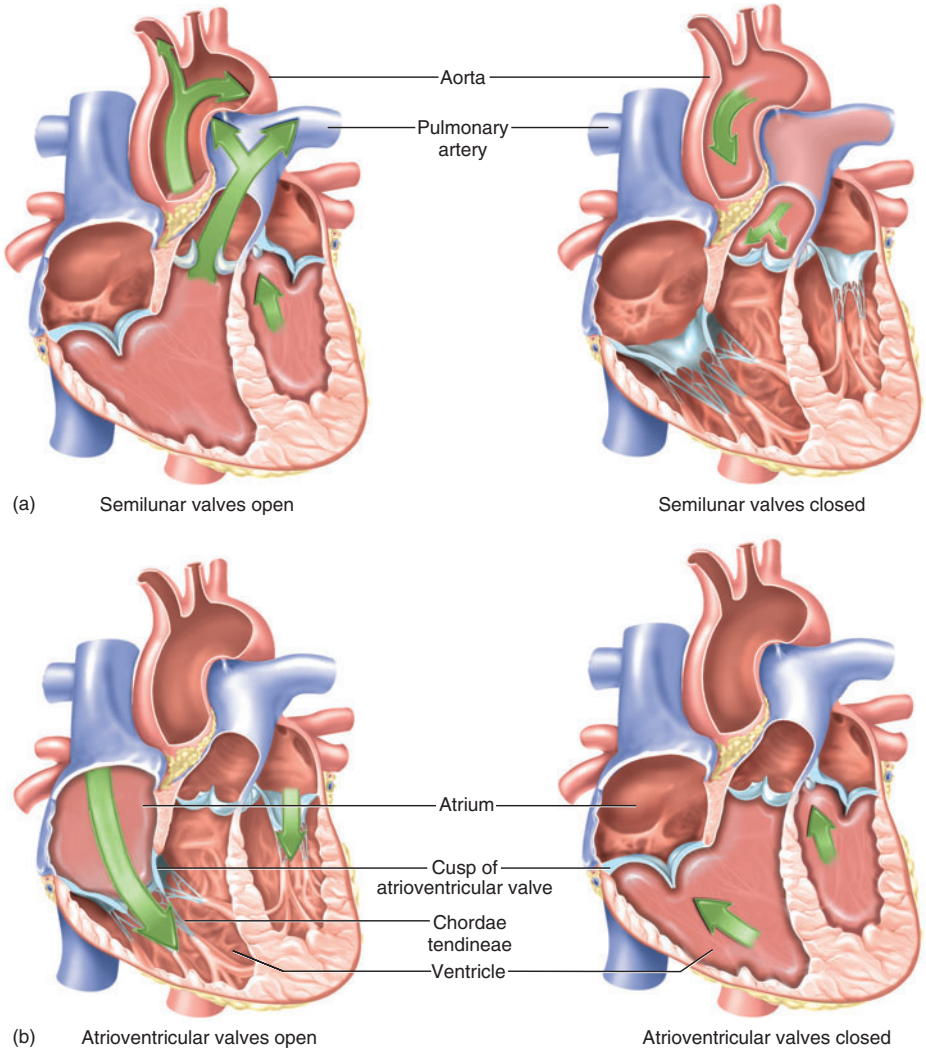


Figure 19.8 Operation of the Heart Valves. (*a*) The semilunar valves. When the pressure in the ventricle is greater than the pressure in the artery, the valve is forced open and blood is ejected. When ventricular pressure is lower than arterial pressure, arterial blood holds the valve closed. (*b*) The atrioventricular valves. When atrial pressure is greater than ventricular pressure, the valve opens and blood flows through. When ventricular pressure rises above atrial pressure, the blood in the ventricle pushes the valve cusps closed.

Insight 19.1 Clinical Application

Valvular Insufficiency

Valvular insufficiency (incompetence) refers to any failure of a valve to prevent *reflux (regurgitation)*—the backward flow of blood. *Valvular stenosis*[13] is a form of insufficiency in which the cusps are stiffened and the opening is constricted by scar tissue. It frequently results from rheumatic fever, an autoimmune disease in which antibodies produced to fight a bacterial infection also attack the mitral and aortic valves. As the valves become scarred and constricted, the heart is overworked by the effort to force blood through the openings and may become enlarged. Regurgitation of blood through the incompetent valves creates turbulence that can be heard as a *heart murmur.*

Mitral valve prolapse (MVP) is an insufficiency in which one or both mitral valve cusps bulge into the atrium during ventricular contraction. It is often hereditary and affects about 1 out of 40 people, especially young women. In many cases, it causes no serious dysfunction, but in some people it causes chest pain, fatigue, and shortness of breath. An incompetent valve can eventually lead to heart failure. A defective valve can be replaced with an artificial valve or a valve transplanted from a pig heart.

[13] *steno* = narrow

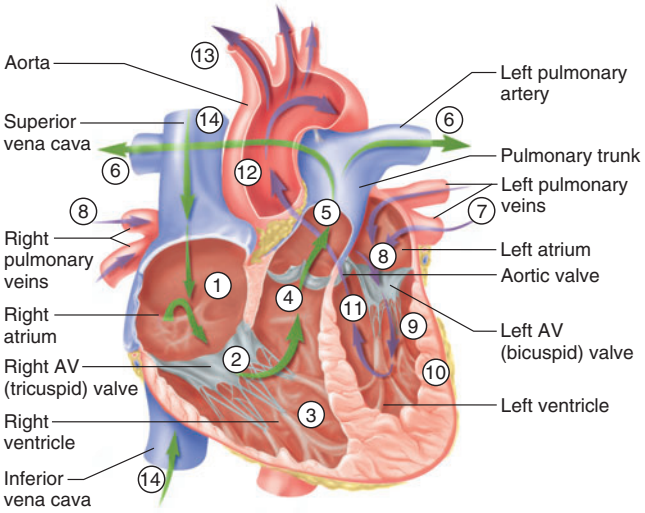


Figure 19.9 The Pathway of Blood from the Right Atrium and Back. (*1*) Right atrium → (*2*) right AV valve → (*3*) right ventricle → (*4*) pulmonary valve → (*5*) pulmonary trunk → (*6*) pulmonary arteries to lungs → (*7*) pulmonary veins returning from lungs → (*8*) left atrium → (*9*) left AV valve → (*10*) left ventricle → (*11*) aortic valve → (*12*) aorta → (*13*) other systemic vessels → (*14*) inferior and superior venae cavae → (*1*) back to the right atrium. The pathway from *5* to *7* is the pulmonary circuit, and the pathway from *12* to *14* is the systemic circuit.

Chapter 19

Blood Flow Through the Heart

Until the sixteenth century, blood was thought to flow directly from the right ventricle into the left through invisible pores in the septum. This of course is not true. Blood on the right and left sides of the heart is kept entirely separate. Figure 19.9 shows the pathway of the blood as it travels from the right atrium through the body and back to the starting point.

The Coronary Circulation

If your heart beats an average of 75 times a minute for 80 years, it will beat more than 3 billion times and pump more than 200 million liters of blood. Understandably, it requires an abundant supply of oxygen and nutrients. Even though the heart is only 0.5% of the body's weight, it uses 5% of the circulating blood to meet its own metabolic needs. The cardiac muscle is not nourished to any great extent by the blood flowing through the heart chambers. Instead, it has its own supply of arteries and capillaries that deliver blood to every cell of the myocardium. The blood vessels of the heart wall constitute the **coronary circulation.** At rest, these vessels supply the myocardium with about 250 mL of blood per minute.

Arterial Supply

Immediately after the aorta leaves the left ventricle, it gives off right and left coronary arteries (fig. 19.10). Each coronary artery begins at an opening deep in the cup formed by a cusp of the aortic valve, like a hole in the bottom of a pocket. The **left coronary artery** passes under the left auricle and divides into two branches:

1. The **anterior interventricular artery** travels down the anterior interventricular sulcus toward the apex. It issues smaller branches to the interventricular septum and anterior walls of both ventricles. Clinically, this vessel is also called the *left anterior descending (LAD) artery.*
2. The **circumflex artery** continues around the left side of the heart in the coronary sulcus. It supplies blood to the left atrium and posterior wall of the left ventricle.

The **right coronary artery** supplies the right atrium, continues along the coronary sulcus under the right auricle, and then gives off two branches:

1. The **marginal artery** supplies the lateral aspect of the right atrium and ventricle.
2. The **posterior interventricular artery** travels down the corresponding sulcus and supplies the posterior walls of both ventricles.

Think About It

Which ventricle receives the greater coronary blood supply? Why should it receive a greater supply than the other? List the vessels that supply it.

The energy demand of the cardiac muscle is so critical that an interruption of the blood supply to any part of the myocardium can cause necrosis within minutes. A fatty deposit or blood clot in a coronary artery can cause a **myocardial infarction**[14] **(MI),** the sudden death of a patch of tissue deprived of its blood flow (see insight 19.2). The coronary circulation has a defense against such an occurrence—points called *anastomoses* (ah-NASS-tih-MO-seez) where two arteries come together and combine their blood flow to points farther downstream. Thus, if one artery becomes obstructed, some blood continues to reach myocardial tissue through the alternative route. The most important anastomosis is the point at which the circumflex artery and right coronary artery meet on the posterior side of the heart; they combine their blood flow into the posterior interventricular artery. Another is the meeting of the anterior and posterior interventricular arteries at the apex of the heart.

[14] *infarct* = to stuff

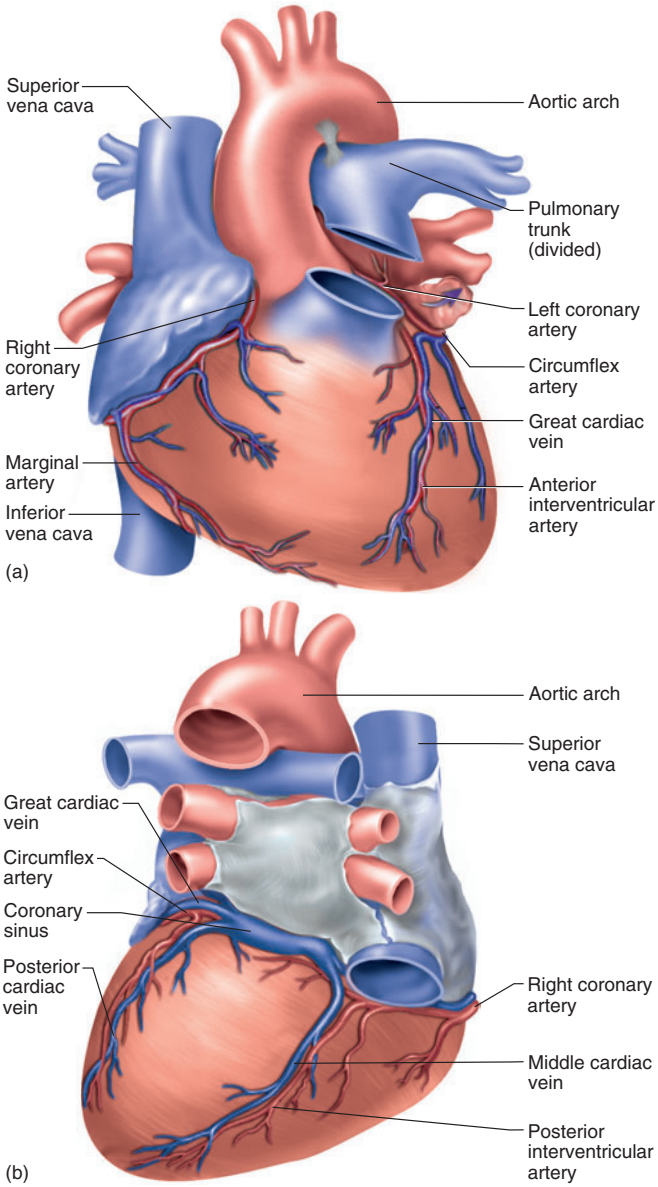


Figure 19.10 The Coronary Blood Vessels. (*a*) Anterior aspect; (*b*) posterior aspect.

Venous Drainage

Venous drainage refers to the route by which blood leaves an organ. After flowing through capillaries of the myocardium, about 20% of the coronary blood empties directly from small veins into the right ventricle. The other 80% returns to the right atrium by the following route (fig. 19.10):

- The **great cardiac vein** collects blood from the anterior aspect of the heart and travels alongside the anterior interventricular artery. It carries blood from the apex of the heart toward the atrioventricular sulcus.
- The **middle cardiac vein,** found in the posterior sulcus, collects blood from the posterior aspect of the heart. It, too, carries blood from the apex upward.
- The **coronary sinus** collects blood from these and smaller cardiac veins. It passes across the posterior aspect of the heart in the coronary sulcus and empties blood into the right atrium.

Insight 19.2 Clinical Application

Myocardial Infarction and Angina Pectoris

A *myocardial infarction (MI)*—what most people call a heart attack—is the sudden death of a patch of myocardium resulting from *ischemia*[15] (iss-KEE-me-uh), the loss of blood flow. It occurs when a coronary artery becomes obstructed by a blood clot or a fatty deposit (atherosclerosis; see insight 19.5 at the end of this chapter). The myocardium downstream from the obstruction dies from *hypoxia* (oxygen deficiency). This tissue necrosis is felt as a sense of heavy pressure or squeezing pain in the chest, often radiating to the shoulder and arm. Infarctions weaken the heart wall and disrupt electrical conduction pathways, potentially leading to fibrillation and cardiac arrest (discussed later in this chapter). Myocardial infarction is responsible for about half of all deaths in the United States.

A temporary and reversible myocardial ischemia produces a sense of heaviness or pain called *angina pectoris*[16] (an-JY-na PEC-toe-riss). As the myocardium becomes hypoxic, it relies increasingly on anaerobic fermentation. This generates lactic acid, which stimulates pain receptors.

[15] *isch* = to hold back + *em* = blood
[16] *angina* = to choke, strangle + *pectoris* = of the chest

Coronary Flow in Relation to the Cardiac Cycle

Most organs receive more arterial blood flow when the ventricles contract than when they relax, but the opposite is true in the coronary arteries. There are two reasons for this. First, contraction of the myocardium compresses the arteries and obstructs blood flow. Second, when the ventricles relax, blood in the aorta surges back toward the heart and fills the semilunar valve cusps. Since the coronary arteries open at the bottom of the pockets created by the cusps, they are filled by this backflow.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

1. Make a two-color sketch of the pericardium; use one color for the fibrous pericardium and another for the serous pericardium and show their relationship to the heart wall.

2. Trace the flow of blood through the heart, naming each chamber and valve in order.
3. Define *pulmonary* and *systemic circuit.*
4. Trace the flow of blood from the left coronary artery to the apex and then to the coronary sinus.

Cardiac Muscle and the Cardiac Conduction System

Objectives

When you have completed this section, you should be able to

- contrast the structure of cardiac and skeletal muscle;
- describe the physiological properties of cardiac muscle and relate its structure to its function;
- explain why the heart does not fatigue; and
- describe the heart's electrical conduction system.

Structure of Cardiac Muscle

Cardiac muscle is striated like skeletal muscle but otherwise differs from it in many structural and physiological ways. Cardiac myocytes (muscle cells), or *cardiocytes,* are relatively short, thick, branched cells, typically 50 to 100 μm long and 10 to 20 μm wide (fig. 19.11). They usually have only one, centrally placed nucleus. The sarcoplasmic reticulum (SR) is less developed than in skeletal muscle. It lacks terminal cisternae, although it does have footlike sacs associated with the T tubules. The T tubules are much larger than in skeletal muscle and admit supplemental calcium ions from the extracellular fluid into the cell during excitation.

The myocytes are joined end to end by thick connections called **intercalated** (in-TUR-kuh-LAY-ted) **discs,** which appear as dark lines (thicker than the striations) in properly stained tissue sections. An intercalated disc is a complex steplike structure with three distinctive features:

1. **Interdigitating folds.** The plasma membrane at the end of the cell is folded somewhat like an egg carton. The folds of adjoining cells interlock with each other and increase the surface area of intercellular contact.
2. **Mechanical junctions.** The cells are tightly joined by two types of mechanical junctions—the fascia adherens and desmosomes. The *fascia adherens*[17] (FASH-ee-ah ad-HEER-enz) is the most extensive. It is a broad band in which the actin of the thin myofilaments is anchored to the plasma membrane and, via transmembrane proteins, one cell is linked to the next. The fascia adherens is interrupted here and there by desmosomes. (Desmosomes and gap junctions, described next, are illustrated in fig. 5.29, p. 178.) These mechanical junctions prevent the myocytes from pulling apart when the heart contracts.
3. **Electrical junctions.** The myocytes are electrically coupled by *gap junctions,* which form channels that allow ions to flow from one cell directly into the next. These junctions enable each myocyte to electrically stimulate its neighbors, so the entire myocardium of the atria, and that of the ventricles, each acts almost as if it were a single cell. This unified action is essential for the effective pumping of a heart chamber.

Cardiac myocytes have, at best, limited capability for mitosis. Furthermore, cardiac muscle lacks satellite cells, which, in skeletal muscle, can divide and replace dead muscle cells to some extent. Thus, the repair of damaged cardiac muscle is almost entirely by fibrosis (scarring).

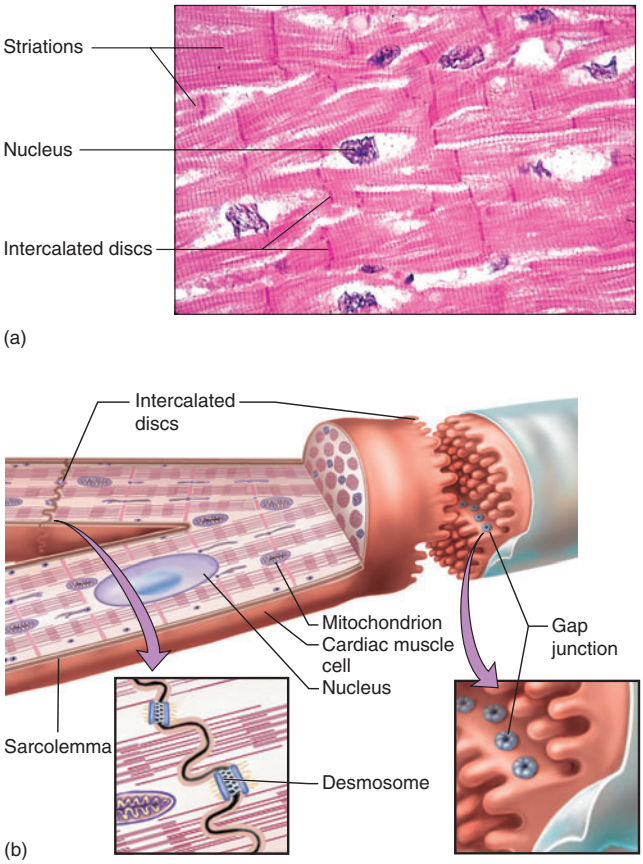


Figure 19.11 Cardiac Muscle. (*a*) Light micrograph, (*b*) cardiac myocytes and intercalated discs.

[17] *fascia* = band + *adherens* = adhering

Chapter 19

Metabolism of Cardiac Muscle

Cardiac muscle depends almost exclusively on aerobic respiration to make ATP. It is very rich in myoglobin (a short-term source of stored oxygen for aerobic respiration) and glycogen (stored energy). It also has especially large mitochondria, which fill about 25% of the myocyte; skeletal muscle fibers, by comparison, have much smaller mitochondria that occupy only 2% of the fiber. Cardiac muscle is relatively adaptable with respect to the organic fuels used. At rest, the heart gets about 60% of its energy from fatty acids, 35% from glucose, and 5% from other fuels such as ketones, lactic acid, and amino acids. Cardiac muscle is more vulnerable to an oxygen deficiency than it is to the lack of any specific fuel. Because it makes little use of anaerobic fermentation or the oxygen debt mechanism, it is not prone to fatigue. You can easily appreciate this fact by clenching and opening your fist once every second for a minute or two. You will soon feel weakness and fatigue in your skeletal muscles and perhaps feel all the more grateful that cardiac muscle can maintain its rhythm, without fatigue, for a lifetime.

The Cardiac Conduction System

Among invertebrates such as clams, crabs, and insects, each heartbeat is triggered by a pacemaker in the nervous system. The vertebrate heartbeat, however, is said to be *myogenic*[18] because the signal originates within the heart itself, in pacemaker cells derived from cardiac muscle. Autonomic nerve fibers to the heart modify its rhythm, but they do not create it—the heart goes on beating even if all nerve connections to it are severed. Indeed, we can remove a vertebrate heart from the body, keep it in aerated saline, and it will beat for hours. Cut the heart into little pieces, and each piece continues its own rhythmic pulsations.

Cardiac myocytes are said to be **autorhythmic**[19] because they depolarize spontaneously at regular time intervals. Some of them lose the ability to contract and become specialized, instead, for generating action potentials. These constitute the **cardiac conduction system,** which controls the route and timing of electrical conduction to ensure that the four chambers are coordinated with each other. The conduction system consists of the following components (fig. 19.12):

- The **sinoatrial (SA) node,** a patch of modified myocytes in the right atrium, just under the epicardium near the superior vena cava. This is the **pacemaker** that initiates each heartbeat and determines the heart rate. Signals from the SA node spread throughout the atria, as shown by the yellow arrows in figure 19.12.

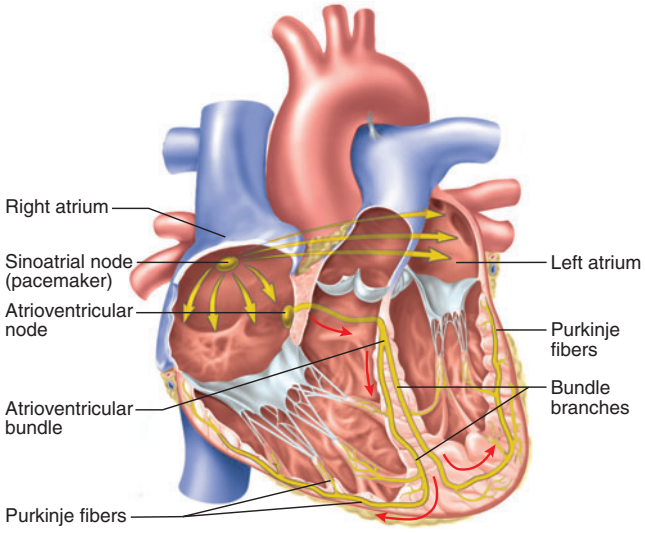


Figure 19.12 The Cardiac Conduction System. Electrical signals travel along the pathway indicated by the *arrows*.
Which atrium is first to receive the signal that induces it to contract?

- The **atrioventricular (AV) node,** located near the right AV valve at the lower end of the interatrial septum. This node acts as an electrical gateway to the ventricles; the fibrous skeleton acts as an insulator to prevent currents from getting to the ventricles by any other route.
- The **atrioventricular (AV) bundle** *(bundle of His*[20]*),* a pathway by which signals leave the AV node.
- The **right** and **left bundle branches,** divisions of the AV bundle that enter the interventricular septum and descend toward the apex.
- **Purkinje**[21] (pur-KIN-jee) **fibers,** nervelike processes that arise from the bundle branches near the apex of the heart and then turn upward and spread throughout the ventricular myocardium. Purkinje fibers distribute the electrical excitation to the myocytes of the ventricles. They form a more elaborate network in the left ventricle than in the right.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

5. What organelle(s) are less developed in cardiac muscle than in skeletal muscle? What organelle(s) are more developed? What is the functional significance of these differences?

[18] *myo* = muscle + *genic* = arising from
[19] *auto* = self
[20] Wilhelm His, Jr. (1863–1934), German physiologist
[21] Johannes E. Purkinje (1787–1869), Bohemian physiologist

6. Name two types of cell junctions in the intercalated discs and explain their functional importance.
7. Why is the human heart described as myogenic? Where is its pacemaker and what is it called?
8. List the components of the cardiac conduction system in the order traveled by signals from the pacemaker.

Electrical and Contractile Activity of the Heart

Objectives

When you have completed this section, you should be able to

- explain why the SA node fires spontaneously and rhythmically;
- explain how the SA node excites the myocardium;
- describe the unusual action potentials of cardiac muscle and relate them to the contractile behavior of the heart; and
- interpret a normal electrocardiogram.

In this section, we examine how the electrical events in the heart produce its cycle of contraction and relaxation. Contraction is called **systole** (SIS-toe-lee) and relaxation is **diastole** (dy-ASS-toe-lee). These terms can refer to a specific part of the heart (for example, atrial systole), but if no particular chamber is specified, they usually refer to the more conspicuous and important ventricular action, which ejects blood from the heart.

The Cardiac Rhythm

The normal heartbeat, triggered by the SA node, is called the **sinus rhythm.** At rest, the adult heart rate is usually around 70 to 80 beats per minute (bpm). Left to itself, the SA node would fire more often than this, but the vagus nerves inhibit it and hold it down to this rate at rest.

Stimuli such as hypoxia, electrolyte imbalances, caffeine, nicotine, and other drugs can cause other parts of the conduction system to fire before the SA node does, setting off an extra heartbeat *(extrasystole).* Any region of spontaneous firing other than the SA node is called an **ectopic**[22] **focus.** If the SA node is damaged, an ectopic focus may take over the governance of the heart rhythm. The most common ectopic focus is the AV node, which produces a slower heartbeat of 40 to 50 bpm called a **nodal rhythm.** If neither the SA nor AV node is functioning, other ectopic foci fire at rates of 20 to 40 bpm. The nodal rhythm is sufficient to sustain life, but a rate of 20 to 40 bpm provides too little flow to the brain to be survivable. This condition calls for an artificial pacemaker.

Any abnormal cardiac rhythm is called **arrhythmia**[23] (see insight 19.3). One cause of arrhythmia is a **heart block**—the failure of any part of the cardiac conduction system to transmit signals, usually as a result of disease and degeneration of conduction system fibers. A *bundle branch block,* for example, is due to damage to one or both bundle branches. Damage to the AV node causes *total heart block,* in which signals from the atria fail to reach the ventricles and the ventricles beat at their own intrinsic rhythm of 20 to 40 bpm.

[22] *ec* = out of + *top* = place
[23] *a* = without + rhythm + *ia* = condition

Physiology of the SA Node

Why does the SA node spontaneously fire 70 or 80 times per minute? Unlike skeletal muscle or neurons, the cells of the SA node do not have a stable resting membrane potential. Their membrane potential starts at about −60 mV and drifts upward, showing a gradual depolarization called the **pacemaker potential** (fig. 19.13). This is thought to result from a slow inflow of Na^+ without a compensating outflow of K^+.

When the pacemaker potential reaches a threshold of −40 mV, voltage-regulated **fast calcium channels** open and Ca^{2+} flows in from the extracellular fluid (ECF). This produces the rising (depolarizing) phase of the action potential, which peaks slightly above 0 mV. At that point, K^+ channels open and potassium ions leave the cell. This makes the cytosol increasingly negative and creates the falling (repolarizing) phase of the action potential. When repolarization is complete, the K^+ channels close and the pacemaker potential starts over, on its way to producing the next heartbeat. Each depolarization of the SA node sets off one heartbeat. When the SA node fires, it excites the other components in the conduction system; thus, the SA node serves as the system's pacemaker. At rest, it fires every 0.8 second or so, creating a heart rate of about 75 bpm.

Impulse Conduction to the Myocardium

Firing of the SA node excites atrial myocytes and stimulates the two atria to contract almost simultaneously. The signal travels at a speed of about 1 m/sec through the atrial myocardium and reaches the AV node in about 50 msec. In the AV node, the signal slows down to about 0.05 m/sec, partly because the myocytes here are thinner but more importantly because they have fewer gap junctions over which the signal can be transmitted. This delays the signal at the AV node for about 100 msec—like highway traffic slowing down at a small town. This delay is essential because it gives the ventricles time to fill with blood before they begin to contract.

The ventricular myocardium has a conduction speed of only 0.3 to 0.5 m/sec. If this were the only route of travel for the excitatory signal, some myocytes would be stimulated much sooner than others. Ventricular contraction would not be synchronized and the pumping effectiveness

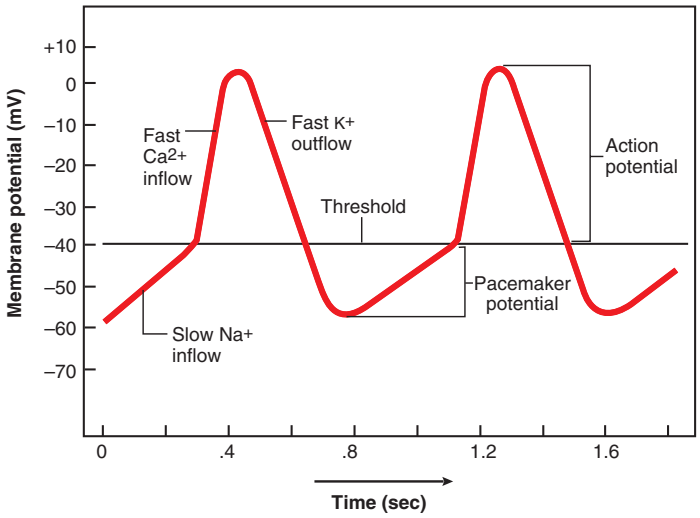


Figure 19.13 **Pacemaker Potentials and Action Potentials of the SA Node.**

of the ventricles would be severely compromised. But signals travel through the AV bundle and Purkinje fibers at a speed of 4 m/sec, the fastest in the conduction system. Consequently, the entire ventricular myocardium depolarizes within 200 msec after the SA node fires, causing the ventricles to contract in near unison.

Signals reach the papillary muscles before the rest of the myocardium. Thus, these muscles contract and begin taking up slack in the chordae tendineae an instant before ventricular contraction causes blood to surge against the AV valves. Ventricular systole begins at the apex of the heart, which is first to be stimulated, and progresses upward—pushing the blood upward toward the semilunar valves. Because of the spiral arrangement of ventricular myocytes, the ventricles twist slightly as they contract, like someone wringing out a towel.

Electrical Behavior of the Myocardium

The action potentials of cardiac muscle are significantly different from those of neurons and skeletal muscle (fig. 19.14). Cardiac muscle has a stable resting potential of −90 mV and depolarizes only when stimulated, unlike the autorhythmic cells of the SA node. A stimulus opens voltage-regulated sodium gates, causing an Na^+ inflow and depolarizing the cell to its threshold. The threshold voltage rapidly opens additional Na^+ gates and triggers a positive feedback cycle like the one seen in the firing of a neuron (see p. 458). The action potential peaks at nearly +30 mV. The Na^+ gates close quickly, and the rising phase of the action potential is very brief.

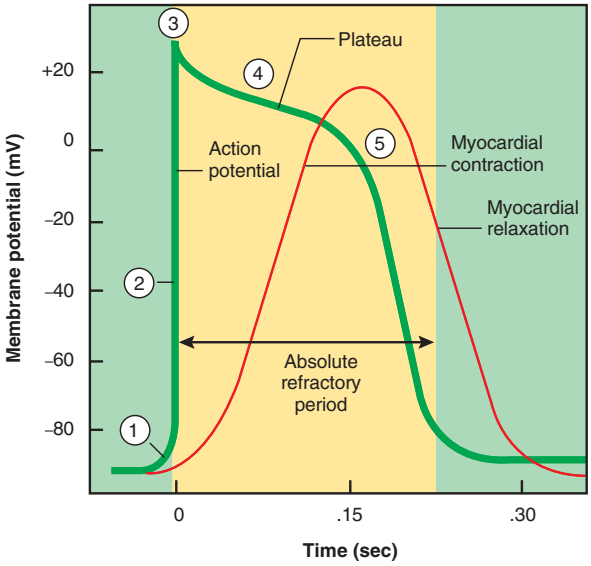
As action potentials spread over the plasma membrane, they open voltage-gated slow calcium channels, which admit a small amount of calcium from the extracellular fluid into the cell. This calcium binds to ligand-gated calcium channels on the sarcoplasmic reticulum (SR), opening them and releasing a greater quantity of Ca^{2+} from the SR into the cytosol. This second wave of Ca^{2+} binds to troponin and triggers contraction in the same way as it does in skeletal muscle (see chapter 11). The SR provides 90% to 98% of the Ca^{2+} needed for myocardial contraction.

In skeletal muscle and neurons, an action potential falls back to the resting potential within 2 msec. In cardiac muscle, however, the depolarization is prolonged for 200 to 250 msec (at a heart rate of 70–80 bpm) producing a long plateau in the action potential—perhaps because the Ca^{2+} channels of the SR are slow to close or because the SR is slow to remove Ca^{2+} from the cytosol.

As long as the action potential is in its plateau, the myocytes contract. Thus, in figure 19.14, you can see the development of muscle tension (myocardial contraction) following closely behind the depolarization and plateau. Rather than showing a brief twitch like skeletal muscle, cardiac muscle has a more sustained contraction necessary for expulsion of blood from the heart chambers. Both atrial and ventricular myocytes exhibit these plateaus, but they are more pronounced in the ventricles.

At the end of the plateau, Ca^{2+} channels close and K^+ channels open. Potassium diffuses rapidly out of the cell and Ca^{2+} is transported back into the extracellular fluid and SR. Membrane voltage drops rapidly, and muscle tension declines soon afterward.

Cardiac muscle has an *absolute refractory period* of 250 msec, compared with 1 to 2 msec in skeletal muscle. This long refractory period prevents wave summation and tetanus, which would stop the pumping action of the heart.



1. Voltage-gated sodium channels open.
2. Na^+ inflow depolarizes the membrane and triggers the opening of still more Na^+ channels, creating a positive feedback cycle and a rapidly rising membrane voltage.
3. Na^+ channels close when the cell depolarizes, and the voltage peaks at nearly +30 mV.
4. Ca^{2+} entering through slow calcium channels prolongs depolarization of membrane, creating a plateau. Plateau falls slightly because of some K^+ leakage, but most K^+ channels remain closed until end of plateau.
5. Ca^{2+} channels close and Ca^{2+} is transported out of cell. K^+ channels open, and rapid K^+ outflow returns membrane to its resting potential.

Figure 19.14 Action Potential of a Ventricular Myocyte. The *red curve* represents rising and falling muscle tension as the myocardium contracts and relaxes.
What is the advantage of having such a long absolute refractory period in cardiac muscle?

Think About It

With regard to the ions involved, how does the falling (repolarization) phase of a myocardial action potential differ from that of a neuron's action potential?
(See p. 458.)

The Electrocardiogram

We can detect electrical currents in the heart by means of electrodes (leads) applied to the skin. An instrument called the *electrocardiograph* amplifies these signals and produces a record, usually on a moving paper chart, called an **electrocardiogram**[24] **(ECG** or **EKG**[25]**).** To record an ECG, electrodes are typically attached to the wrists, ankles, and six locations on the chest. Several simultaneous recordings can be made from electrodes at different distances from the heart; collectively, they provide a comprehensive image of the heart's electrical activity. An ECG is a composite recording of all the action potentials produced by the nodal and myocardial cells—it should not be misconstrued as a tracing of a single action potential.

Figure 19.15 shows a typical ECG. It shows three principal deflections above and below the baseline: the *P wave, QRS complex,* and *T wave.* Figure 19.16 shows how these correspond to regions of the heart undergoing depolarization and repolarization.

The **P wave** is produced when a signal from the SA node spreads through the atria and depolarizes them. Atrial systole begins about 100 msec after the P wave begins, during the *P–Q segment.* This segment is about 160 msec long and represents the time required for impulses to travel from the SA node to the AV node.

The **QRS complex** consists of a small downward deflection (Q), a tall sharp peak (R), and a final downward deflection (S). It marks the firing of the AV node and the onset of ventricular depolarization. Its complex shape is due to the different sizes of the two ventricles and the different times required for them to depolarize. Ventricular systole begins shortly after the QRS complex in the *S–T segment.* Atrial repolarization and diastole also occur during the QRS interval, but atrial repolarization sends a relatively weak signal that is obscured by the electrical activity of the more muscular ventricles. The S–T segment corresponds to the plateau in the myocardial action potential and thus represents the time during which the ventricles contract and eject blood.

The **T wave** is generated by ventricular repolarization immediately before diastole. The ventricles take longer to repolarize than to depolarize; the T wave is therefore smaller and more spread out than the QRS complex, and it has a rounder peak. Even in cases where the T wave is taller than the QRS complex, it can be recognized by its relatively rounded peak.

The ECG affords a wealth of information about the normal electrical activity of the heart. Deviations from normal are invaluable for diagnosing abnormalities in the conduction pathways, myocardial infarction, enlargement

[24] *graph* = recording instrument; *graphy* = recording procedure; *gram* = record of
[25] EKG is from the German spelling, Elektrokardiogramm

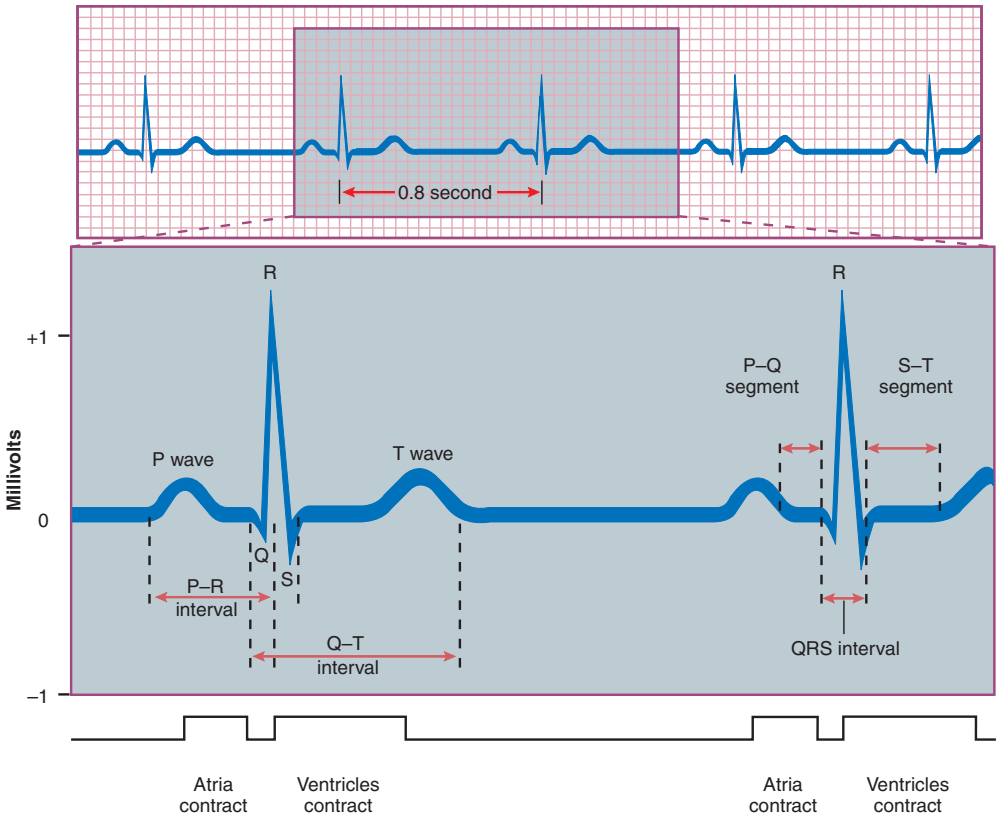
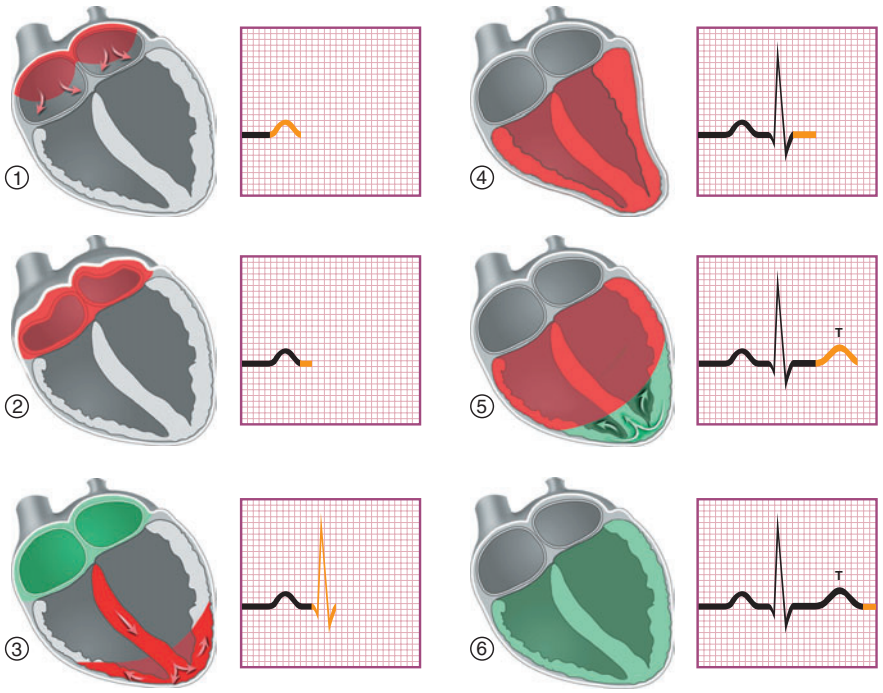


Figure 19.15 The Normal Electrocardiogram.



1. Atria begin depolarizing.
2. Atrial depolarization complete.
3. Ventricular depolarization begins at apex and progresses superiorly as atria repolarize.
4. Ventricular depolarization complete.
5. Ventricular repolarization begins at apex and progresses superiorly.
6. Ventricular repolarization complete; heart is ready for the next cycle.

Figure 19.16 **Relationship of the Electrocardiogram (ECG) to Electrical Activity and Contraction of the Myocardium.** Each heart diagram indicates the events occurring at the time of the colored segment of the ECG. *Red* indicates depolarizing or depolarized myocardium, and *green* indicates repolarizing or repolarized myocardium. *Arrows* indicate the direction in which a wave of depolarization or repolarization is traveling.

Table 19.1 Examples of the Diagnostic Interpretation of Abnormal Electrocardiograms

Appearance	Suggested Meaning
Enlarged P wave	Atrial hypertrophy, often a result of mitral valve stenosis
Missing or inverted P wave	SA node damage; AV node has taken over pacemaker role
Two or more P waves per cycle	Extrasystole; heart block
Extra, misshapen, sometimes inverted QRS not preceded by P wave	Premature ventricular contraction (PVC) (extrasystole)
Enlarged Q wave	Myocardial infarction
Enlarged R wave	Ventricular hypertrophy
Abnormal T waves	Flattened in hypoxia; elevated in hyperkalemia (K^+ excess)
Abnormally long P–Q segment	Scarring of atrial myocardium, forcing impulses to bypass normal conduction pathways and take slower alternative routes to AV node
Abnormal S–T segment	Elevated above baseline in myocardial infarction; depressed in myocardial hypoxia

of the heart, and electrolyte and hormone imbalances. A few examples of abnormal ECGs are given in table 19.1 and figure 19.17.

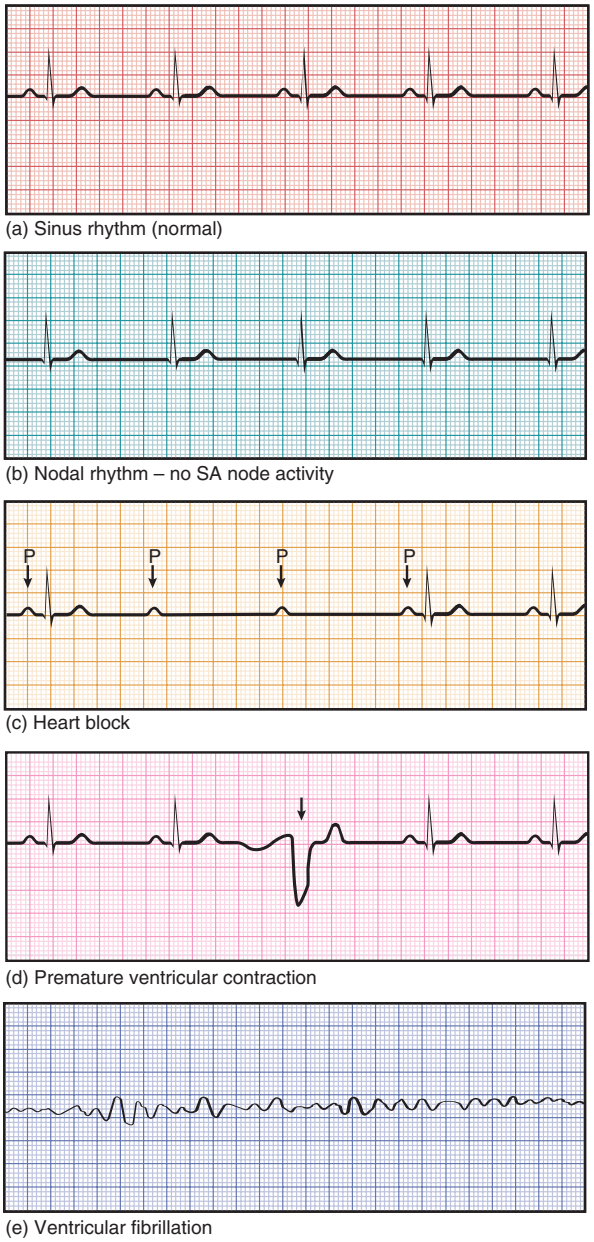
Insight 19.3 Clinical Application

Cardiac Arrhythmias

Atrial flutter, premature ventricular contractions, and ventricular fibrillation are common cardiac arrhythmias. *Atrial flutter* occurs when ectopic foci in the atria set off extra contractions and the atria beat 200 to 400 times per minute. *Premature ventricular contractions (PVCs)* occur singly or in bursts as a result of early firing of an ectopic focus (see fig. 19.17*d*). PVCs are often due to irritation of the heart by stimulants, emotional stress, or lack of sleep, but they sometimes indicate more serious pathology.

Ventricular fibrillation (see fig. 19.17*e*) is a serious arrhythmia caused by electrical signals arriving at different regions of the myocardium at widely different times. A fibrillating ventricle exhibits squirming, uncoordinated contractions; it has been described as looking like a "bag of worms." Since a fibrillating heart does not pump blood, there is no coronary perfusion (blood flow) and the myocardium rapidly dies of ischemia. *Cardiac arrest* is the cessation of cardiac output, with the ventricles either motionless or in fibrillation.

Fibrillation kills quickly if it is not stopped. *Defibrillation* is an emergency procedure in which the heart is given a strong electrical shock



(a) Sinus rhythm (normal)
(b) Nodal rhythm – no SA node activity
(c) Heart block
(d) Premature ventricular contraction
(e) Ventricular fibrillation

Figure 19.17 Normal and Pathological Electrocardiograms. (*a*) Normal sinus rhythm. (*b*) Nodal rhythm generated by the AV node in the absence of SA node activity; note the lack of P waves. (*c*) Heart block, in which some P waves are not transmitted through the AV node and do not generate QRS complexes. (*d*) Premature ventricular contraction (PVC), or extrasystole; note the inverted QRS complex, misshapen QRS and T, and absence of a P wave preceding this contraction. (*e*) Ventricular fibrillation, with grossly irregular waves of depolarization.

with a pair of electrodes. The purpose is to depolarize the entire myocardium and stop the fibrillation, with the hope that the SA node will resume its sinus rhythm. This does not correct the underlying cause of the arrhythmia, but it may sustain a patient's life long enough to allow for other corrective action.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

9. Define *systole* and *diastole*.
10. How does the pacemaker potential of the SA node differ from the resting membrane potential of a neuron? Why is this important in creating the heart rhythm?
11. How does excitation-contraction coupling in cardiac muscle resemble that of skeletal muscle? How is it different?
12. What produces the plateau in the action potentials of cardiac myocytes? Why is this important to the pumping ability of the heart?
13. Name the waves of the ECG and explain what myocardial events produce each wave.

Blood Flow, Heart Sounds, and the Cardiac Cycle

Objectives

When you have completed this section, you should be able to

- explain how pressure and resistance determine the flow of a fluid;
- explain what causes the sounds of the heartbeat;
- describe in detail one complete cycle of heart contraction and relaxation; and
- relate the events of the cardiac cycle to the volume of blood entering and leaving the heart.

A **cardiac cycle** consists of one complete contraction and relaxation of all four heart chambers. We will examine these events in detail to see how they relate to the entry and expulsion of blood, but first we consider two related issues: (1) some general principles of pressure changes and how they affect the flow of blood, and (2) the heart sounds produced during the cardiac cycle, which we can then relate to the stages of the cycle.

Principles of Pressure and Flow

A fluid is any liquid or gas—a state of matter that can flow in bulk from one place to another. In this and some forthcoming chapters, we are concerned with factors that govern the flow of fluids such as blood, lymph, air, and urine. Some basic principles of fluid movement *(fluid dynamics)* are therefore important to understand at this time. Fluid dynamics are governed by pressure, which can cause a fluid to flow, and resistance, which opposes flow.

Measurement of Pressure

Pressure is often measured by observing how high it can push a column of mercury (Hg) up an evacuated tube called a *manometer*. Mercury is used because it is very dense and enables us to measure pressure with shorter columns than we would need with a less dense liquid such as water. Because pressures are compared to the force generated by a column of mercury, they are expressed in terms of millimeters of mercury (mmHg). Blood pressure is usually measured with a **sphygmomanometer**[26] (SFIG-mo-ma-NOM-eh-tur)—a calibrated tube filled with mercury and attached to an inflatable pressure cuff wrapped around the arm. Blood pressure and the method of measuring it are discussed in greater detail in chapter 20.

Pressure Gradients and Flow

Any change in the volume of a container creates a **pressure gradient,** or difference, between the inside and outside of the container. If there is an opening in the container, fluid flows in or out, "down the gradient," from point A, where pressure is higher, to point B, where pressure is lower. The pressure at point B rises and the pressure at point A falls until the two are equal. At that time, there is no more pressure gradient and flow stops. Flow also stops, of course, if it is obstructed by the closure of a passage between point A and B—a matter of obvious relevance where the heart valves are concerned.

Suppose you pull back the plunger of a syringe, for example. The volume in the syringe barrel increases and its pressure falls (fig. 19.18). Since pressure outside the syringe is greater than the pressure inside, air flows into it until the pressures inside and outside are equal. If you then push the plunger in, pressure inside rises above the pressure outside, and air flows out—again following a gradient from high pressure to low.

The syringe barrel is analogous to a heart chamber such as the left ventricle. When the ventricle is expanding, its internal pressure falls. If the AV valve is open, blood flows into the ventricle from the atrium above. When the ventricle contracts, its internal pressure rises. When the aortic valve opens, blood is ejected from the ventricle into the aorta.

A pressure difference does not guarantee that a fluid will flow. There is always a positive blood pressure in the aorta, and if it is greater than the pressure in the ventricle, it holds the aortic valve closed and prevents the expulsion of blood. When continuing contraction causes ventricular pressure to rise above aortic pressure, however, the valve is forced open and blood is ejected into the aorta.

[26] *sphygmo* = pulse + *mano* = rare, sparse, roomy

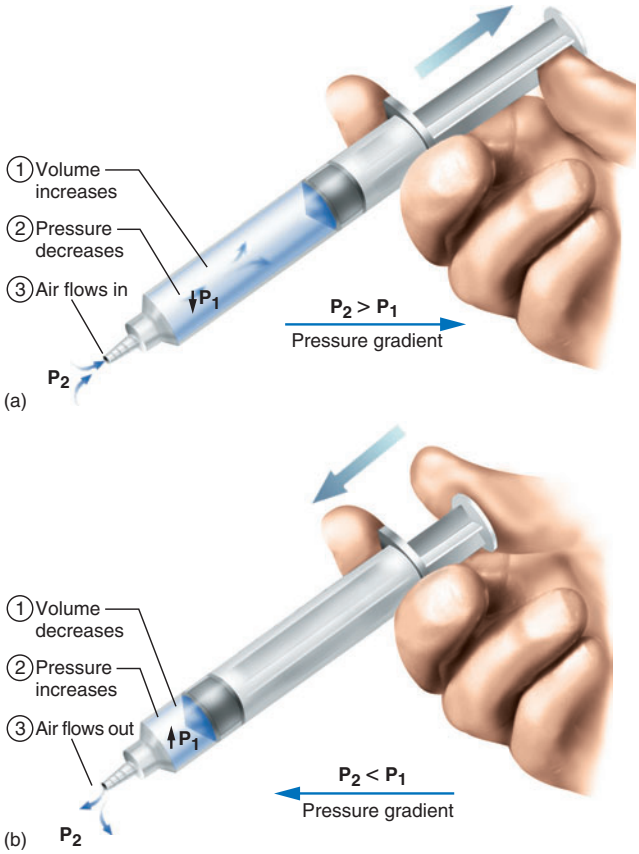


Figure 19.18 Principles of Volume, Pressure, and Flow Illustrated with a Syringe. (*a*) As the plunger is pulled back, the volume of the enclosed space increases, its pressure falls, and pressure inside the syringe (P_1) is lower than the pressure outside (P_2). The pressure gradient causes air to flow inward until the pressures are equal. This is analogous to the filling of an expanding heart chamber. (*b*) As the plunger is depressed, the volume of the enclosed space decreases, P_1 rises above P_2, and air flows out until the pressures are equal. This is analogous to the ejection of blood from a contracting heart chamber. In both cases, fluids flow down their pressure gradients.

Heart Sounds

As we follow events through the cardiac cycle, we will note the occurrence of *heart sounds.* Listening to sounds made by the body is called **auscultation** (AWS-cul-TAY-shun). Each cardiac cycle generates two or three sounds that are audible with a stethoscope. The **first** and **second heart sounds,** symbolized S1 and S2, are often described as a "lubb-dupp"—S1 is louder and longer and S2 a little softer and sharper. In children and adolescents, it is normal to hear a **third heart sound** (S3). This is rarely audible in people older than 30, but when it is, the heartbeat is said to show a *triple rhythm* or *gallop.* If the normal rhythm is roughly simulated by drumming two fingers on a table, a triple rhythm sounds a little like drumming with three fingers. The heart valves themselves operate silently, but S1 and S2 occur in conjunction with the closing of the valves as a result of turbulence in the bloodstream and movements of the heart wall. The cause of each sound is not known with certainty, but the probable factors are discussed in the respective phases of the cardiac cycle.

Phases of the Cardiac Cycle

We now examine the phases of the cardiac cycle, the pressure changes that occur, and how the pressure changes and valves govern the flow of blood. A substantial amount of information about these events is summarized in figure 19.19, which is divided into colored bars numbered to correspond to the phases described here. Closely follow the figure as you study the following text. Where to begin when describing a circular chain of events is somewhat arbitrary. However, in this presentation we begin with the filling of the ventricles. Remember that all these events are completed in less than 1 second.

1. **Ventricular filling.** During diastole, the ventricles expand and their pressure drops below that of the atria. As a result, the AV valves open and blood flows into the ventricles, causing ventricular pressure to rise and atrial pressure to fall. Ventricular filling occurs in three phases: (*a*) The first one-third is *rapid ventricular filling,* when blood enters especially quickly. (*b*) The second one-third, called *diastasis* (di-ASS-tuh-sis), is marked by slower filling. The P wave of the electrocardiogram occurs at the end of diastasis, marking the depolarization of the atria. (*c*) In the last one-third, *atrial systole* completes the filling process. The right atrium contracts slightly before the left because it is the first to receive the signal from the SA node. As the ventricles fill, the flaccid cusps of the AV valves float up toward the closed position. At the end of ventricular filling, each ventricle contains an **end-diastolic volume (EDV)** of about 130 mL of blood. Only 40 mL (31%) of this is contributed by atrial systole.
2. **Isovolumetric contraction.** The atria repolarize, relax, and remain in diastole for the rest of the cardiac cycle. The ventricles depolarize, generate the QRS complex, and begin to contract. Pressure in the ventricles rises sharply and reverses the pressure gradient between atria and ventricles. The AV valves close as ventricular blood surges back against the cusps. Heart sound S1 occurs at the beginning of this phase and is produced mainly by the left ventricle; the right ventricle is thought to make little contribution. Causes of the sound are thought to include the tensing of ventricular tissues, acceleration of the ventricular wall, turbulence in the blood as it surges against the closed AV valves, and impact of the heart against the chest wall.

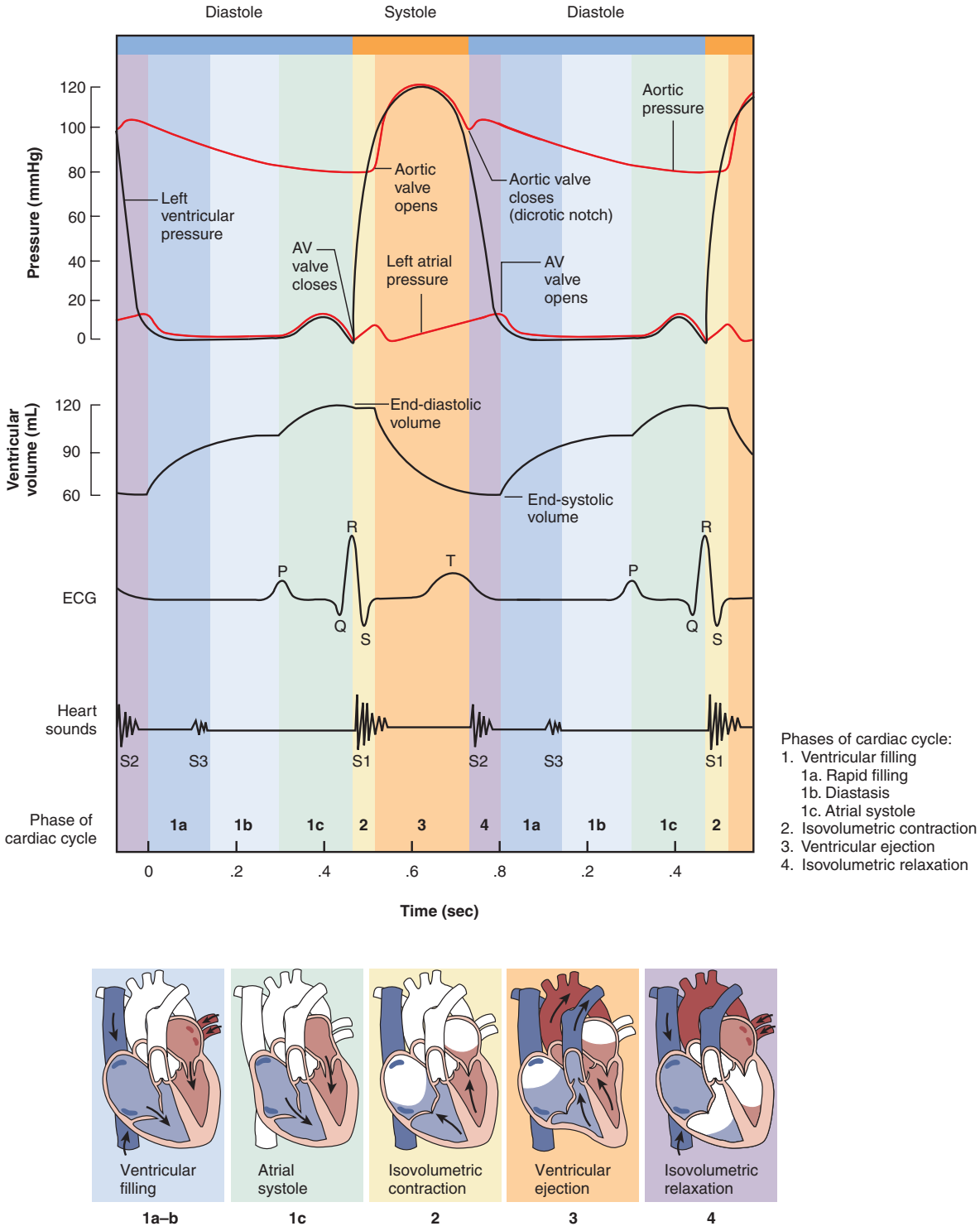


Figure 19.19 Major Events of the Cardiac Cycle. Two complete cycles are shown. The phases are numbered across the bottom to correspond to the text description.

Explain why the aortic pressure curve begins to rise abruptly at about 0.5 second.

This phase is called *isovolumetric*[27] because even though the ventricles contract, they do not eject blood yet, and there is no change in their volume. This is because pressures in the aorta (80 mmHg) and pulmonary trunk (10 mmHg) are still greater than the pressures in the respective ventricles and thus oppose the opening of the semilunar valves. The myocytes exert force, but with all four valves closed, the blood cannot go anywhere.

3. **Ventricular ejection.** The ejection of blood begins when ventricular pressure exceeds arterial pressure and forces the semilunar valves open. The pressure peaks at 120 mmHg in the left ventricle and 25 mmHg in the right. Blood spurts out of each ventricle rapidly at first *(rapid ejection)* and then flows out more slowly under less pressure *(reduced ejection).* By analogy, suppose you were to shake up a bottle of soda pop and remove the cap. The soda would spurt out rapidly at high pressure and then more would dribble out at lower pressure, much like the blood leaving the ventricles. Ventricular ejection lasts about 200 to 250 msec, which corresponds to the plateau of the myocardial action potentials but lags somewhat behind it (review the tension curve in fig. 19.14).

   The ventricles do not expel all their blood. In an average resting heart, each ventricle contains an EDV of 130 mL. The amount ejected, about 70 mL, is called the **stroke volume (SV).** The percentage of the EDV ejected, about 54%, is the **ejection fraction.** The blood remaining behind, about 60 mL in this case, is called the **end-systolic volume (ESV).** Note that EDV − SV = ESV. In vigorous exercise, the ejection fraction may be as high as 90%. Ejection fraction is an important measure of cardiac health. A diseased heart may eject much less than 50% of the blood it contains.
4. **Isovolumetric relaxation.** This is early ventricular diastole, when the T wave appears and the ventricles repolarize and begin to expand. There are competing theories as to how they expand. One is that the blood flowing into the ventricles "inflates" them. Another is that contraction of the ventricles deforms the fibrous skeleton, which subsequently springs back like a rubber ball that has been squeezed and released. This elastic recoil and expansion would cause pressure to drop rapidly and suck blood into the ventricles.

   At the beginning of ventricular diastole, blood from the aorta and pulmonary trunk briefly flows backward through the semilunar valves. The backflow, however, quickly fills the cusps and closes them, creating a slight pressure rebound that appears as the *dicrotic notch* of the aortic pressure curve (fig. 19.19). Heart sound S2 occurs as blood rebounds from the closed semilunar valves and the ventricles expand. This phase is called *isovolumetric* because the semilunar valves are closed, the AV valves have not yet opened, and the ventricles are therefore not taking in blood.

When the valves open, ventricular filling (phase 1) begins again. Heart sound S3, if it occurs, is thought to result from the transition from expansion of the empty ventricles to their sudden filling with blood.

In a resting person, atrial systole lasts about 0.1 second; ventricular systole, 0.3 second; and the *quiescent period* (when all four chambers are in diastole), 0.4 second. Total duration of the cardiac cycle is therefore 0.8 second (800 msec) in a heart beating at 75 bpm.

Overview of Volume Changes

An additional perspective on the cardiac cycle can be gained if we review the volume changes that occur. This "balance sheet" is from the standpoint of the left ventricle, but for reasons explained shortly, these numbers also must be true of the right. The volumes vary somewhat from one person to another and depend on a person's state of activity.

End-systolic volume (ESV, left from previous heartbeat)	60 mL
Passively added to the ventricle during atrial diastole	+ 30 mL
Added by atrial systole	+ 40 mL
Total: end-diastolic volume (EDV)	130 mL
Stroke volume (SV) ejected by ventricular systole	−70 mL
Leaves: end-systolic volume (ESV)	60 mL

Notice that the ventricle pumps as much blood as it received during diastole—70 mL in this example.

Both ventricles eject the same amount of blood even though pressure in the right ventricle is only about one-fifth the pressure in the left. Blood pressure in the pulmonary trunk is relatively low, so the right ventricle does not need to generate very much pressure to overcome it. It is essential that both ventricles have the same output. If the right ventricle pumped more blood into the lungs than the left side of the heart could handle on return, blood would accumulate in the lungs and cause pulmonary hypertension and edema (fig. 19.20). This would put a person at risk of suffocation as fluid filled the lungs and interfered with gas exchange. Conversely, if the left ventricle pumped out more blood than the right heart could handle on return, blood would accumulate in the systemic circuit and cause hypertension and edema there. Over the long term, this could lead to aneurysms (weakened, bulging arteries), stroke, kidney failure, or heart failure (see insight 19.4). To maintain homeostasis, the two ventricles must have equal output.

[27] *iso* = same

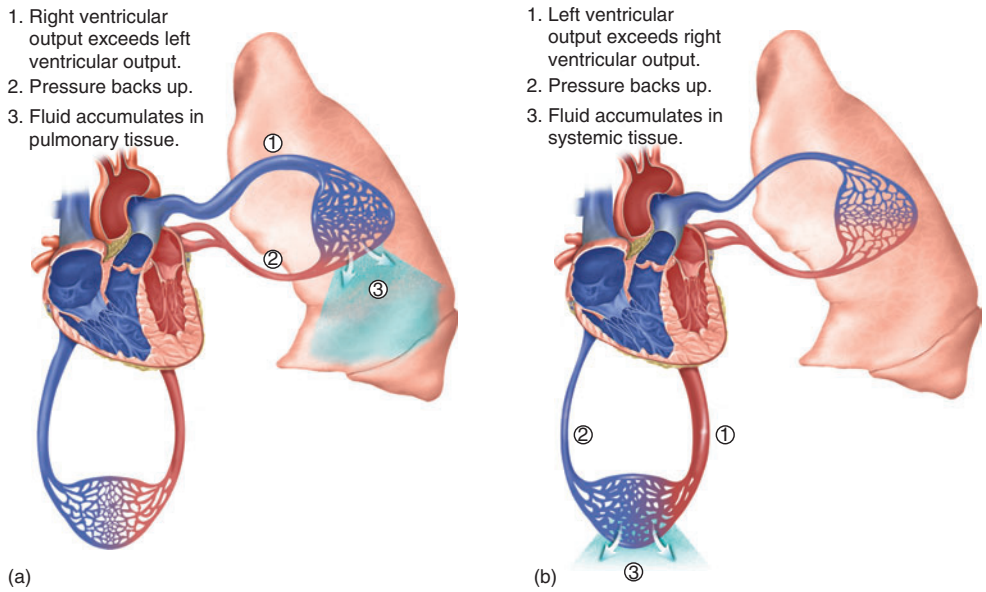


Figure 19.20 The Necessity of Balanced Ventricular Output. (*a*) If the left ventricle pumps less blood than the right, blood pressure backs up into the lungs and causes pulmonary edema. (*b*) If the right ventricle pumps less blood than the left, pressure backs up in the systemic circulation and causes systemic edema. To maintain homeostasis, both ventricles must pump the same average amount of blood.

Insight 19.4 Clinical Application

Congestive Heart Failure

Congestive heart failure (CHF) results from the failure of either ventricle to eject blood effectively. It is usually due to a heart weakened by myocardial infarction, chronic hypertension, valvular insufficiency, or congenital defects in cardiac structure. If the left ventricle fails, blood backs up into the lungs and causes pulmonary edema (fluid in the lungs), shortness of breath, and a sense of suffocation. If the right ventricle fails, blood backs up into the venae cavae and causes systemic, or generalized, edema (formerly called *dropsy*). Systemic edema is marked by enlargement of the liver, ascites (the pooling of fluid in the abdominal cavity), distension of the jugular veins, and swelling of the fingers, ankles, and feet. Failure of one ventricle eventually increases the workload on the other ventricle, which stresses it and leads to its eventual failure as well.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

14. Explain how a pressure gradient across a heart valve determines whether or not a ventricle ejects blood.
15. What factors are thought to cause the first and second heart sounds? When do these sounds occur?
16. What phases of the cardiac cycle are isovolumetric? Explain what this means.

Cardiac Output

Objectives

When you have completed this section, you should be able to

- define *cardiac output* and explain its importance;
- identify the factors that govern cardiac output;
- discuss some of the nervous and chemical factors that alter heart rate, stroke volume, and cardiac output;
- explain how the right and left ventricles achieve balanced output; and
- describe some effects of exercise on cardiac output.

The entire point of all the cardiac physiology we have considered thus far is to eject blood from the heart. The amount ejected by each ventricle in 1 minute is called the **cardiac output (CO).** If HR is heart rate (beats/min) and SV is stroke volume, CO = HR × SV. At typical resting values, CO = 75 beats/min × 70 mL/beat = 5,250 mL/min. Thus, the body's total volume of blood (4–6 L) passes through the heart every minute; or to look at it another way, an RBC leaving the left ventricle will, on average, arrive back at the left ventricle in about 1 minute.

Cardiac output is not constant but varies with the body's state of activity. Vigorous exercise increases CO to as much as 21 L/min in a person in good condition and up to 35 L/min in world-class athletes. The difference between the maximum and resting cardiac output is called **cardiac reserve.** People with severe heart disease may have little or no cardiac reserve and little tolerance of physical exertion.

Given that cardiac output equals HR × SV, you can see that there are only two ways to change it—change the heart rate or change the stroke volume. We will consider factors that influence each of these variables, but bear in mind that heart rate and stroke volume are somewhat interdependent and usually change together.

Heart Rate

Since each beat of the heart produces a surge of pressure in the arteries, the easiest way to measure heart rate is to palpate the **pulse** in a superficial artery and count beats per minute. In newborn infants, the resting heart rate is commonly 120 bpm or greater. It declines steadily with age, averaging 72 to 80 bpm in young adult females and 64 to 72 bpm in young adult males. It rises again in the elderly.

Tachycardia[28] is a persistent, resting adult heart rate above 100 bpm. It can be caused by stress, anxiety, drugs, heart disease, or fever. Heart rate also rises to compensate to some extent for a drop in stroke volume. Thus, the heart races when the body has lost a significant quantity of blood or when there is damage to the myocardium.

Bradycardia[29] is a persistent, resting adult heart rate below 60 bpm. It is common during sleep and in endurance-trained athletes. Endurance training enlarges the heart and increases its stroke volume. Thus, it can maintain the same cardiac output with fewer beats. Hypothermia (low body temperature) also slows the heart rate and may be deliberately induced in preparation for cardiac surgery. Diving mammals such as whales and seals exhibit bradycardia during the dive, as do humans to some extent when the face is immersed in cool water.

Factors that raise the heart rate are called *positive chronotropic*[30] *agents,* and factors that lower it are *negative chronotropic agents.* We next consider some chronotropic effects of the autonomic nervous system, hormones, electrolytes, and blood gases.

Chronotropic Effects of the Autonomic Nervous System

Although the nervous system does not initiate the heartbeat, it does modulate its rhythm and force. The **cardiac center** of the medulla oblongata consists of two neuronal pools, a cardioacceleratory center and cardioinhibitory center. The **cardioacceleratory center** sends signals by way of sympathetic **cardiac accelerator nerves** to the SA node, AV node, and myocardium. These nerves secrete norepinephrine, which binds to β-adrenergic receptors in the heart and increases the heart rate. Cardiac output peaks when the heart rate is 160 to 180 bpm, although the sympathetic nervous system can get the heart rate up to as much as 230 bpm. This limit is set mainly by the refractory period of the SA node; it cannot fire any more frequently. At such a high rate, however, the ventricles beat so rapidly that they have little time to fill between beats; therefore, the stroke volume and cardiac output are less than they are at rest. At a heart rate of 65 bpm, ventricular diastole lasts about 0.62 seconds, but at 200 bpm, it lasts only 0.14 seconds. At that high rate, there is less time available for refilling between beats.

The **cardioinhibitory center** sends signals by way of parasympathetic fibers in the vagus nerves to the SA and AV nodes. The right vagus nerve innervates mainly the SA node, and the left vagus nerve innervates the AV node. The vagus nerves secrete acetylcholine, which binds to muscarinic receptors and opens K^+ channels in the nodal cells. As K^+ leaves the cells, the cells become hyperpolarized and fire less frequently, so the heart slows down.

The vagus nerves maintain a background firing rate called **vagal tone** that inhibits the nodes. If the vagus nerves to the heart are severed, the SA node fires at its own intrinsic frequency of about 100 times per minute. With the vagus nerve intact, however, vagal tone holds the heart rate down to the usual 70 to 80 bpm. Maximum vagal stimulation can reduce the heart rate to as low as 20 bpm.

The cardiac center receives and integrates input from multiple sources. Sensory and emotional stimuli can act on the cardiac center by way of the cerebral cortex, limbic system, and hypothalamus; therefore, heart rate can climb even as you anticipate taking the first plunge on a roller coaster, and it is influenced by emotions such as love and anger. The cardiac center also receives input from receptors in the muscles, joints, arteries, and brainstem:

- **Proprioceptors** in the muscles and joints quickly inform the cardiac center of changes in physical activity. Thus, the heart can increase its output even before the metabolic demands of the muscles rise.
- **Baroreceptors (pressoreceptors)** are pressure sensors in the aorta and internal carotid arteries (see fig. 15.1, p. 565). They send a continual stream of signals to the cardiac center. If blood pressure drops, the signaling rate drops and the cardiac center increases the heart rate and raises the blood pressure. If blood pressure rises too high, the signaling rate from the baroreceptors rises and the cardiac center reduces the heart rate.
- **Chemoreceptors** sensitive to blood pH, carbon dioxide, and oxygen are found in the aortic arch, carotid arteries, and medulla oblongata. They are more important in respiratory control than in cardiovascular

[28] *tachy* = speed, fast + *card* = heart + *ia* = condition
[29] *brady* = slow
[30] *chrono* = time + *trop* = turn, change, influence

control but do influence the heart rate. If circulation to the tissues is too slow to remove CO_2 as fast as the tissues produce it, then CO_2 accumulates in the blood and cerebrospinal fluid (CSF) and produces a state of *hypercapnia* (CO_2 excess). Furthermore, CO_2 generates hydrogen ions by reacting with water: $CO_2 + H_2O \rightarrow HCO_3^- + H^+$. The hydrogen ions lower the pH of the blood and CSF and may create a state of acidosis (pH < 7.35). Hypercapnia and acidosis stimulate the cardiac center to increase the heart rate, thus improving perfusion of the tissues and restoring homeostasis. The chemoreceptors also respond to extreme *hypoxemia* (oxygen deficiency), such as in suffocation, but the effect is usually to slow down the heart, perhaps so the heart does not compete with the brain for the limited oxygen supply.

Such responses to fluctuations in blood chemistry and blood pressure, called **chemoreflexes** and **baroreflexes,** are good examples of negative feedback loops. They are discussed more fully in chapter 20.

Chronotropic Effects of Chemicals

Epinephrine and norepinephrine are potent cardiac stimulants. They are secreted by the cardiac accelerator nerves and the adrenal medulla in response to arousal, stress, and exercise. These catecholamines act through cAMP. Caffeine and the related stimulants in coffee, tea, and chocolate produce positive chronotropic effects by inhibiting cAMP breakdown. Nicotine also accelerates the heart by stimulating catecholamine secretion. Thyroid hormone increases the number of adrenergic receptors in the cardiac muscle, making the heart more responsive to sympathetic stimulation and thus increasing the heart rate. Hyperthyroidism causes tachycardia, which in the long run can weaken the heart and cause heart failure.

The ion with the greatest chronotropic effect is potassium (K^+). *Hyperkalemia,*[31] a K^+ excess, is especially dangerous. A rapid rise in K^+ concentration makes the myocardium unusually excitable and subject to systolic arrest (in which the ventricles contract and fail to relax and refill). A slow rise in K^+ makes it less excitable than normal; the heartbeat becomes slow and irregular, and may arrest in diastole. In *hypokalemia,* a K^+ deficiency, myocytes become hyperpolarized—their membrane voltage is lower than normal and it is more difficult to stimulate the cells to threshold. These potassium imbalances are very dangerous and require emergency medical treatment. Chapter 24 further explains the causes and effects of these electrolyte imbalances.

Hypercalcemia (a calcium excess) reduces the heart rate and hypocalcemia (a calcium deficiency) increases it. These calcium imbalances are relatively rare, however, and when they do occur, their primary effect is on contraction strength.

Stroke Volume

Stroke volume is governed by three factors called *preload, contractility,* and *afterload.* Increased preload or contractility increases stroke volume, while increased afterload opposes the emptying of the ventricles and reduces stroke volume.

Preload

The amount of tension in the ventricular myocardium immediately before it begins to contract is called the **preload.** To understand how it influences stroke volume, imagine yourself engaged in heavy exercise. As active muscles massage your veins, they drive more blood back to your heart, increasing *venous return.* As more blood enters your heart, it stretches the myocardium. Due to the length-tension relationship of striated muscle explained in chapter 11, moderate stretch enables the myocytes to generate more tension when they begin to contract—that is, it increases the preload. If the ventricles contract more forcefully, they expel more blood, thus adjusting your cardiac output to the increase in venous return.

This theory is summarized by the **Frank–Starling law of the heart.**[32] In a concise, symbolic way, it states that SV $\propto$ EDV. In other words, the ventricles tend to eject as much blood as they receive. Within limits, the more they are stretched, the harder they contract when stimulated.

While relaxed skeletal muscle is normally at an optimum length for the most forceful contraction, relaxed cardiac muscle is at less than optimum length. Additional stretch therefore produces a significant increase in contraction force on the next beat. This helps balance the output of the two ventricles. For example, if the right ventricle begins to pump an increased amount of blood, this soon arrives at the left ventricle, stretches it more than before, and causes it to increase its stroke volume to match that of the right.

Contractility

The **contractility** of the myocardium refers to its contraction force *for a given preload.* It does not describe an

[31] *kal* = potassium (Latin, *kalium*)

[32] Otto Frank (1865–1944), German physiologist; Ernest Henry Starling (1866–1927), English physiologist

increase in tension resulting from increased stretch but rather an increase caused by factors that make the myocytes more responsive to stimulation. Factors that increase contractility are called *positive inotropic*[33] *agents,* and those that reduce it are *negative inotropic agents.*

Remember that Ca^{2+} is essential to the excitation-contraction coupling of muscle and prolongs the plateau of the myocardial action potential. Calcium therefore has a positive inotropic effect, as do agents that increase its availability to the myofilaments. Epinephrine and norepinephrine act through cAMP to open Ca^{2+} channels. By increasing the supply of Ca^{2+} to the myofilaments, they have a positive inotropic effect. Glucagon acts by stimulating the formation of cAMP; a solution of glucagon and calcium chloride is sometimes used for the emergency treatment of heart attacks. Digitalis, a cardiac stimulant from the foxglove plant, is used to treat congestive heart failure. It acts indirectly by inhibiting the Na^{+}-K^{+} pumps of the myocardium, raising intracellular Na^{+} concentration, and increasing the amount of Ca^{2+} in the sarcoplasm. Hypercalcemia causes more than the usual amount of Ca^{2+} to diffuse into the sarcoplasm and thus produces strong, prolonged contractions. In extreme cases, it can cause cardiac arrest in systole. Hypocalcemia can cause a weak, irregular heartbeat and potentially cause diastolic arrest. However, as explained in chapter 8, severe hypocalcemia is likely to kill through skeletal muscle paralysis and suffocation before the cardiac effects are felt.

The vagus nerves have a negative inotropic effect on the atria, but they provide so little innervation to the ventricular myocytes that they have little effect on the ventricles. Hyperkalemia has a negative inotropic effect because it reduces the strength of myocardial action potentials and thus reduces the release of Ca^{2+} into the sarcoplasm. The heart becomes dilated and flaccid. Hypokalemia, however, has little effect on contractility. There are other chronotropic and inotropic agents too numerous to mention here. The ones we have discussed are summarized in table 19.2.

Table 19.2 Some Chronotropic and Inotropic Agents

Chronotropic Agents	
Positive	**Negative**
Sympathetic stimulation	Parasympathetic stimulation
Epinephrine and norepinephrine	Acetylcholine
Thyroid hormone	Hyperkalemia
Hypocalcemia	Hypokalemia
Hypercapnia and acidosis	Hypercalcemia
Digitalis	Hypoxia
Inotropic Agents	
Positive	**Negative**
Sympathetic stimulation	(Parasympathetic effect negligible)
Epinephrine and norepinephrine	Hyperkalemia
Hypercalcemia	Hypocalcemia
Digitalis	Myocardial hypoxia
Glucagon	Myocardial hypercapnia

Think About It

Suppose a person has a heart rate of 70 bpm and a stroke volume of 70 mL. A negative inotropic agent then reduces the stroke volume to 50 mL. What would the new heart rate have to be to maintain the same cardiac output?

Afterload

The blood pressure in the arteries just outside the semilunar valves, called the **afterload,** opposes the opening of these valves. An increased afterload therefore reduces stroke volume. Anything that impedes arterial circulation can increase the afterload. For example, in some lung diseases, scar tissue forms in the lungs and restricts pulmonary circulation. This increases the afterload in the pulmonary trunk and opposes emptying of the right ventricle. As the ventricle works harder to overcome this resistance, it gets larger like any other muscle. Stress and hypertrophy of a ventricle can eventually cause it to weaken and fail. Right ventricular failure due to obstructed pulmonary circulation is called *cor pulmonale*[34] (CORE PUL-mo-NAY-lee). It is a common complication of emphysema, chronic bronchitis, and black lung disease (see chapter 22).

Exercise and Cardiac Output

It is no secret that exercise makes the heart work harder, and it should come as no surprise that this increases cardiac output. The main reason the heart rate increases at the beginning of exercise is that proprioceptors in the muscles and joints transmit signals to the cardiac center signifying that the muscles are active and will quickly need an increased blood flow. As the exercise progresses, muscular activity increases venous return. This increases the preload on the right ventricle and is soon reflected in the left ventricle as more blood flows through the pulmonary circuit and reaches the left heart. As the heart rate

[33] *ino* = fiber

[34] *cor* = heart + *pulmo* = lung

Table 19.3 Some Disorders of the Heart

Acute pericarditis	Inflammation of the pericardium, sometimes due to infection, radiation therapy, or connective tissue disease, causing pain and friction rub
Cardiac tamponade	Compression of the heart by an abnormal accumulation of fluid in the pericardial cavity, interfering with ventricular filling; may result from pericarditis
Cardiomyopathy	Any disease of the myocardium not resulting from coronary artery disease, valvular dysfunction, or other cardiovascular disorders; can cause dilation and failure of the heart, thinning of the heart wall, or thickening of the interventricular septum
Infective endocarditis	Inflammation of the endocardium, usually due to infection, especially streptococcus and staphylococcus bacterial infections
Myocardial ischemia	Inadequate blood flow to the myocardium, usually because of coronary atherosclerosis; can lead to myocardial infarction
Pericardial effusion	Seepage of fluid from the pericardium into the pericardial cavity, often resulting from pericarditis and sometimes causing cardiac tamponade
Septal defects	Abnormal openings in the interatrial or interventricular septum, resulting in blood from the right atrium flowing directly into the left atrium, or blood from the left ventricle returning to the right ventricle; results in pulmonary hypertension, difficulty breathing, and fatigue. Often fatal in childhood if uncorrected

Disorders described elswhere

Angina pectoris 725	Cor pulmonale 740	Myocardial infarction 725
Atrial flutter 732	Coronary artery disease 741–743	Premature ventricular contraction 732
Bradycardia 738	Familial hypercholesterolemia 742	Tachycardia 738
Bundle branch block 728	Friction rub 718	Total heart block 728
Cardiac arrest 732	Heart murmur 723	Valvular stenosis 723
Congestive heart failure 737	Mitral valve prolapse 723	Ventricular fibrillation 732

and stroke volume rise, cardiac output rises, which compensates for the increased venous return.

A sustained program of exercise causes hypertrophy of the ventricles, which increases their stroke volume. As explained earlier, this allows the heart to beat more slowly and still maintain a normal resting cardiac output. Endurance athletes commonly have resting heart rates as low as 40 to 60 bpm, but because of the higher stroke volume, their resting cardiac output is about the same as that of an untrained person. They have greater cardiac reserve, so they can tolerate more exertion than a sedentary person can.

The effects of aging on the heart are discussed on p. 1111, and some common heart diseases are listed in table 19.3. Disorders of the blood and blood vessels are described in chapters 18 and 20.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

17. Define *cardiac output* in words and with a simple formula.
18. Describe the cardiac center and innervation of the heart.
19. Explain what is meant by positive and negative chronotropic and inotropic agents. Give two examples of each.
20. How do preload, contractility, and afterload influence stroke volume and cardiac output?
21. Explain the principle behind the Frank–Starling law of the heart. How does this mechanism normally prevent pulmonary or systemic congestion?

Insight 19.5 Clinical Application

Coronary Atherosclerosis

Atherosclerosis[35] is a disorder in which fatty deposits form in an artery, obstruct the lumen, and cause deterioration of the arterial wall. It is especially critical when it occurs in the coronary arteries and threatens to cut off the blood supply to the myocardium. Atherosclerosis is also a leading contributor to stroke and kidney failure.

Cause and Pathogenesis

According to one theory, the stage is set for atherosclerosis when the endothelium of a blood vessel is damaged by hypertension, viral infection, diabetes mellitus, or other causes. Monocytes adhere to the damaged endothelium, penetrate beneath it, and transform into macrophages. Macrophages and smooth muscle cells absorb cholesterol and neutral fats from the blood and acquire a frothy appearance; they are then called *foam cells* and are visible as a *fatty streak* on the vessel wall.

Platelets also adhere to areas of endothelial damage, degranulate, and release platelet-derived growth factor (PDGF); some PDGF also comes from macrophages and endothelial cells. PDGF stimulates mitosis of smooth muscle, leading eventually to a mass of lipid, smooth muscle, and macrophages called an *atheroma (atherosclerotic plaque).* The muscular and elastic tissue of the artery become increasingly replaced with scar tissue. When atheromas become calcified, they are called *complicated plaques.* Such plaques cause a state of arterial rigidity called *arteriosclerosis.*

Atherosclerosis is caused primarily by a combination of *low-density lipoproteins (LDLs)* in the blood plasma and defective LDL receptors in

the arteries. LDLs are small protein-coated droplets of cholesterol, neutral fat, free fatty acids, and phospholipids (see chapter 26). Most cells have LDL receptors, take up these droplets from the blood by receptor-mediated endocytosis, and stop when they have enough cholesterol. In atherosclerosis, arterial cells have dysfunctional receptors that continue taking up plasma lipids and cause the cells to accumulate excess cholesterol.

As an atheroma grows, more and more of the arterial lumen becomes obstructed (fig. 19.21). Angina pectoris and other symptoms begin to occur when the lumen of a major coronary artery is reduced by at least 75%. When platelets adhere to lesions of the arterial wall, they release clotting factors, so an atheroma can become a focus for thrombosis. A clot can block what remains of the lumen, or it can break free and become an embolus that travels downstream until it lodges in a smaller artery. Part of an atheroma itself can also break loose and travel as a *fatty embolus.*

Atheromas also contribute to coronary artery spasms. Healthy endothelial cells secrete nitric oxide (NO), which causes the arteries to dilate. Vessels damaged by atherosclerosis release less NO, and the coronary arteries exhibit spasms. With much of the lumen already obstructed by the atheroma and perhaps a thrombus, an arterial spasm can temporarily shut off the remaining flow and precipitate an attack of angina.

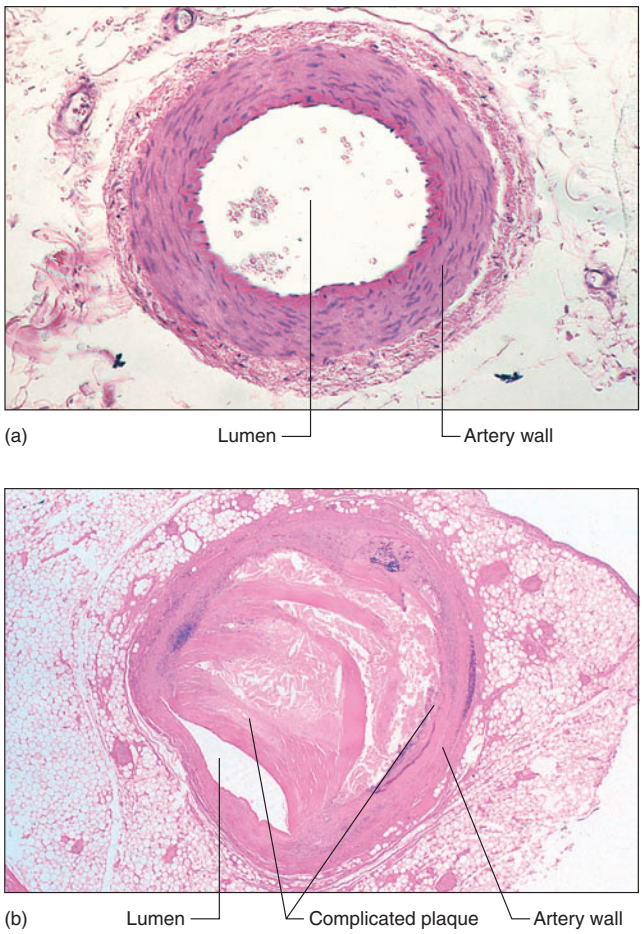


Figure 19.21 Atherosclerosis. (*a*) Cross section of a healthy artery; (*b*) cross section of an artery with advanced atherosclerosis. The lumen is reduced to a small space that can easily be blocked by thrombosis, embolism, or vasoconstriction. Most of the original lumen is obstructed by a complicated plaque composed of calcified scar tissue.

Risk and Prevention

Risk factors are personal characteristics or elements of the environment that predispose an individual to a particular disease. Some risk factors for atherosclerosis cannot be avoided—for example, aging, heredity, and being male. One form of hereditary atherosclerosis is *familial hypercholesterolemia* ("elevated blood cholesterol levels running in the family"). Most people have two recessive alleles *(hh)* of the gene for LDL receptors, which leads to the synthesis of normal receptors. One person in 500 is heterozygous *(Hh)* and makes only half the normal number of LDL receptors; one in a million is homozygous dominant *(HH)* and makes no LDL receptors. When the body's cells have few or no LDL receptors, they fail to absorb LDLs from the blood. LDL levels therefore remain high—six times normal in *HH* individuals. Foam cells, however, absorb LDLs even without these receptors, and with excess LDL in the blood plasma, atheromas grow rapidly. Heterozygous individuals usually suffer heart attacks by age 35, and homozygous dominant individuals usually have heart attacks in childhood, sometimes before age 2.

Most risk factors for atherosclerosis, however, are preventable. A sedentary lifestyle promotes LDL formation, whereas exercise promotes the formation of *high-density lipoproteins (HDLs),* which not only don't contribute to coronary disease but also help to lower blood cholesterol. Obesity is a risk factor that can be reduced by exercise. Aggressiveness, anxiety, and emotional stress promote hypertension and atherosclerosis. Smoking is another avoidable risk factor. The incidence of coronary heart disease is proportional to the number of cigarettes smoked per day and the number of years a person has been a smoker. This is reversible; people who quit smoking drop to normal risk levels within 5 years.

Diet, of course, is an overwhelmingly important factor. Eating animal fat reduces the number of LDL receptors and raises plasma LDL levels. Foods high in soluble fiber (such as beans, apples, and oat bran) lower blood cholesterol by an interesting mechanism. The liver normally converts cholesterol to bile acids, which it secretes into the small intestine to aid fat digestion. The bile acids are reabsorbed farther down the intestine and recycled to the liver for reuse. Soluble fiber, however, binds bile acids and carries them out in the feces. To replace them, the liver must synthesize more, thus using more cholesterol and lowering the blood cholesterol.

In the 1970s, scientists found that the Eskimos of Greenland had unusually low rates of coronary atherosclerosis despite the fact that their diet consisted entirely of meat—averaging a pound of whale meat and a pound of fish per day. Japanese and other groups with large amounts of fish in their diets also show low blood cholesterol levels. It is suspected that this is due to *omega-3 polyunsaturated fatty acids (PUFAs)* in fish oil. PUFAs increase the fluidity of plasma membranes and enable cells to remove more lipid from the blood. However, a daily capsule of fish oil does not hold much promise for controlling cholesterol. Doses of PUFAs high enough to reduce blood cholesterol would be prohibitively expensive and have undesirable side effects, including suppression of the immune system. Studies on the effectiveness of PUFAs remain inconclusive.

Treatment Options

The first pioneering approach to treating atherosclerosis, and still a common standby, is *coronary artery bypass surgery.* Sections of the

great saphenous vein of the leg or small arteries from the thoracic cavity are used to construct a detour from the aorta to a point on a coronary artery beyond the obstruction.

Balloon angioplasty[36] is a technique in which a thin, flexible catheter is threaded into a coronary artery to the point of obstruction, and then a balloon at its tip is inflated to press the atheroma against the arterial wall, opening up the lumen. Its usefulness is limited to well-localized atheromas. In another method, *laser angioplasty,* an illuminated catheter enables the surgeon to see inside a diseased artery on a monitor and to use a laser to vaporize atheromas and reopen the artery. These methods are cheaper and less risky than bypass surgery. However, there is some concern that these procedures may cause new injuries to the arterial walls, which may be foci for the development of new atheromas. Also, angioplasty is often followed by *restenosis*—atheromas grow back and reobstruct the artery months later. Insertion of a tube called a *stent* into the artery can prevent restenosis, ensuring that the vessel remains open.

Clearly, prevention is the least expensive, least risky, and most effective approach to the threat of coronary artery disease.

[35] *athero* = fat, fatty + *sclerosis* = hardening
[36] *angio* = vessel + *plasty* = surgical repair

Chapter Review

Review of Key Concepts

Gross Anatomy of the Heart (p. 716)

1. The *cardiovascular system* consists of the heart and blood vessels; the *circulatory system* consists of these and the blood.
2. The cardiovascular system has two divisions. The *pulmonary circuit* serves the lungs only and the *systemic circuit* serves the entire body (including the lungs).
3. The heart lies in the mediastinum with about two-thirds of it to the left of the median plane.
4. The heart is enclosed in a two-layered fibrous sac, the *pericardium.* The *visceral pericardium* forms the surface layer of the heart (= epicardium) and the *parietal pericardium* forms a loose-fitting *pericardial sac* around the heart. The space between these two layers is lubricated by *pericardial fluid.*
5. The heart wall is composed of epicardium, myocardium, and endocardium.
6. The heart has four chambers—two blood-receiving *atria* and two blood-ejecting *ventricles.* Externally, these are marked by the *atrioventricular sulcus* and the *anterior* and *posterior interventricular sulci,* which harbor the major coronary blood vessels. Internally, they are separated by walls called the *interatrial septum* and *interventricular septum.*
7. *Atrioventricular (AV) valves* regulate blood flow from the atria to the ventricles. The right AV valve is the *tricuspid* valve and the left AV valve is the *bicuspid* valve.
8. *Semilunar valves* regulate the flow of blood from the ventricles into the major arteries—the *pulmonary valve* at the origin of the pulmonary trunk and *aortic valve* at the origin of the aorta.
9. Valves open when pressure on the upstream side exceeds pressure on the downstream side. When closed, they prevent blood from flowing backward through an opening.
10. Systemic blood enters the heart at its right atrium, flows through the right AV valve into the right ventricle, and is pumped from there through the pulmonary valve into the pulmonary circuit. It returns from the lungs to the left atrium, passes through the left AV valve into the left ventricle, and this ventricle pumps it through the aortic valve into the systemic circuit.
11. The cardiac tissue is supplied by a system of *coronary* blood vessels. Blockage of any major coronary artery can cause *myocardial infarction,* death of cardiac muscle due to lack of oxygen.

Cardiac Muscle and the Cardiac Conduction System (p. 726)

1. Cardiac myocytes are short, thick, branched, striated cells. They have a less extensive sarcoplasmic reticulum (SR) than skeletal muscle, but larger T tubules, and obtain Ca^{2+} from the ECF as well as the SR.
2. The myocytes meet end-to-end at *intercalated discs,* which contain mechanical junctions to hold the contracting cells together and electrical gap junctions to enable myocytes to stimulate each other.
3. Cardiac muscle uses almost entirely aerobic respiration, and has large, abundant mitochondria and abundant glycogen and myoglobin to meet this demand. It employs fatty acids, glucose, and other organic fuels.
4. Cardiac myocytes are *autorhythmic,* contracting periodically even without nervous stimulation. Some heart cells have lost the ability to contract and constitute the *cardiac conduction system,* specialized to generate and conduct action potentials.
5. Electrical signals originate in the *SA node* (the usual pacemaker of the cardiac rhythm) and travel via the *AV node, AV bundle, bundle branches,* and *Purkinje fibers* to reach the ventricular myocytes.

Electrical and Contractile Activity of the Heart (p. 728)

1. *Systole* is the contraction of any heart chamber, and *diastole* is relaxation.
2. A cardiac rhythm activated by the SA node is the *sinus rhythm.* Irritation of the heart or damage to the SA node can cause other areas to take over control. When the AV node takes over, the heart beats with a *nodal rhythm* that is slower than the sinus

rhythm. Any abnormal cardiac rhythm is called *arrhythmia.*

3. Cells of the SA node exhibit a *pacemaker potential* in which the membrane voltage starts at −60 mV and drifts spontaneously toward a threshold of −40 mV. At this point, *fast calcium channels* open and the inflow of Ca^{2+} sets off an action potential. In a resting sinus rhythm of 70 to 80 beats/min, this process repeats itself about every 0.8 sec.
4. Firing of the SA node excites the atria and causes atrial systole. The spreading wave of excitation slows down at the AV node, then quickly spreads to the atrial myocytes and triggers ventricular systole.
5. Papillary muscles contract and pull on the chordae tendineae just before the rest of the ventricle contracts; the chordae prevent the AV valves from prolapsing when pressure rises in the ventricles.
6. Ordinary cardiac myocytes have a resting potential of −90 mV. Upon excitation, Na^+ enters the cells and sets off an action potential that peaks around +30 mV. Ca^{2+} channels then open, admitting Ca^{2+} into the cytosol from the ECF and SR and triggering muscle contraction.
7. The action potential of cardiac myocytes has a sustained plateau of 200 to 250 msec, causing prolonged contraction rather than a muscle twitch. The plateau ensures that contraction is sustained long enough to expel blood from the ventricles.
8. At the end of the plateau, Ca^{2+} channels close and K^+ channels open. The membrane potential drops rapidly as K^+ leaves the cell. Contraction is followed by a long refractory period that prevents wave summation and tetanus in the heart.
9. The electrical events of the myocardium as a whole generate the electrocardiogram (ECG). The P wave of the ECG indicates atrial depolarization; atrial systole occurs during the P-Q segment. The QRS complex indicates ventricular depolarization, but atrial repolarization occurs at the same time. Ventricular systole begins in the S-T segment. The T wave indicates ventricular repolarization and is followed by ventricular diastole.

Blood Flow, Heart Sounds, and the Cardiac Cycle (p. 733)

1. Blood and other fluids flow down a *pressure gradient* from a point of high pressure to a point of lower pressure.
2. When the volume of a ventricle increases, its internal pressure drops, and when the AV valve opens, blood flows into the ventricle. When the ventricle contracts, its internal pressure rises, and when the semilunar valve opens, blood is ejected into an artery.
3. Adults normally have two heart sounds, S1 and S2. Listening to these sounds is called *auscultation.*
4. A *cardiac cycle* is one complete cycle of contraction and relaxation. It can be divided into four phases (fig. 19.19).
5. In phase 1, ventricular filling, the ventricles expand, the AV valves open, and blood flows into the ventricles, rapidly at first and then more slowly. The P wave occurs, and the atria contract and contribute the last one-third of the blood to the ventricles. At the end of phase 1, each ventricle contains an *end-diastolic volume* (EDV) of about 130 mL.
6. In phase 2, isovolumetric contraction, the QRS wave occurs, the atria repolarize and relax, and the ventricles begin contracting. The AV valves close and heart sound S1 occurs. The semilunar valves remain closed and no blood is expelled yet.
7. In phase 3, ventricular ejection, the semilunar valves open and blood is ejected, rapidly at first and then more slowly. Each ventricle ejects a *stroke volume* of about 70 mL, which is an *ejection fraction* of about 54% of the EDV. The blood remaining behind, about 60 mL, is the *end-systolic volume* (ESV).
8. In phase 4, isovolumetric relaxation, the T wave occurs and the ventricles repolarize and relax. The semilunar valves close and heart sound S2 occurs. The AV valves remain closed and no blood enters the ventricles until the next phase 1.
9. Each ventricle ejects the same amount of blood. If they ejected unequal amounts, fluid would accumulate in the tissues of either the pulmonary or systemic circuit.

Cardiac Output (p. 737)

1. *Cardiac output (CO)* is the volume of blood pumped by each ventricle in 1 minute. It is a product of heart rate × stroke volume, and averages about 5.25 L/min.
2. Heart rate is typically about 70 to 80 beats/min (bpm) in young adults, but higher in children and the elderly. A persistent high resting heart rate is *tachycardia* and a persistent low resting rate is *bradycardia.*
3. Heart rate is raised or lowered, respectively, by *positive* and *negative chronotropic agents.*
4. The *cardioacceleratory center* raises the heart rate through sympathetic nerves. The *cardioinhibitory center* reduces heart rate through parasympathetic fibers in the vagus nerve. Both centers constitute the *cardiac center* of the medulla oblongata.
5. The cardiac center receives input from proprioceptors, baroreceptors, and chemoreceptors. It adjusts the heart rate to maintain blood pressure, pH, and blood O_2 and CO_2 levels within homeostatic limits.
6. Stroke volume is determined by the relationship of preload, contractility, and afterload. *Preload* is the amount of tension in the myocardium just before contraction; *contractility* is the amount of force that the contracting myocardium generates for a given preload; and *afterload* is resistance from blood pressure in the major arteries attached to the heart.
7. Factors that increase or decrease contractility are called *positive* and *negative inotropic agents,* respectively.
8. The autonomic nervous system, hormones, electrolytes, drugs, and O_2 and CO_2 levels have varied chronotropic and inotropic effects summarized in table 19.2.
9. Exercise influences cardiac output through its effects on the proprioceptors and on the venous return of blood to the heart. Habitual exercise increases ventricular size and stroke volume, and reduces resting heart rate.

Selected Vocabulary

cardiology 716
pulmonary circuit 716
systemic circuit 716
pericardium 718
myocardium 720
atrium 720
ventricle 720
atrioventricular valve 722
pulmonary valve 722
aortic valve 722
myocardial infarction 724
sinoatrial node 727
atrioventricular node 727
atrioventricular bundle 727
systole 728
diastole 728
sinus rhythm 728
electrocardiogram 730
sphygmomanometer 733
stroke volume 736
cardiac output 737
baroreceptor 738
chemoreceptor 738

Testing Your Recall

1. The cardiac conduction system includes all of the following *except*
   a. the SA node.
   b. the AV node.
   c. the bundle branches.
   d. the chordae tendineae.
   e. the Purkinje fibers.

2. To get from the right atrium to the right ventricle, blood flows through
   a. the pulmonary valve.
   b. the tricuspid valve.
   c. the bicuspid valve.
   d. the aortic valve.
   e. the mitral valve.

3. Assume that one ventricle of a child's heart has an EDV of 90 mL, an ESV of 60 mL, and a cardiac output of 2.55 L/min. What are the child's stroke volume (SV), ejection fraction (EF), and heart rate (HR)?
   a. SV = 60 mL; EF = 33%; HR = 85 bpm
   b. SV = 30 mL; EF = 60%; HR = 75 bpm
   c. SV = 150 mL; EF = 67%; HR = 42 bpm
   d. SV = 30 mL; EF = 33%; HR = 85 bpm
   e. There is not enough information to calculate these.

4. A heart rate of 45 bpm and an absence of P waves suggest
   a. damage to the SA node.
   b. ventricular fibrillation.
   c. cor pulmonale.
   d. extrasystole.
   e. heart block.

5. The fast-rising phase of the action potential of the SA node results from
   a. the opening of slow Ca^{2+} channels.
   b. the closing of K^+ channels.
   c. K^+ outflow.
   d. K^+ inflow.
   e. Ca^{2+} inflow.

6. Cardiac muscle does not exhibit tetanus because it has
   a. fast Ca^{2+} channels.
   b. scanty sarcoplasmic reticulum.
   c. a long absolute refractory period.
   d. electrical synapses.
   e. exclusively aerobic respiration.

7. The atria contract during
   a. the first heart sound.
   b. the second heart sound.
   c. the QRS complex.
   d. the P–Q segment.
   e. the S–T segment.

8. Ventricular pressure peaks during
   a. the first heart sound.
   b. the second heart sound.
   c. the QRS complex.
   d. the P–Q segment.
   e. the S–T segment.

9. The blood contained in a ventricle during isovolumetric relaxation is
   a. the end-systolic volume.
   b. the end-diastolic volume.
   c. the stroke volume.
   d. the ejection fraction.
   e. none of these; the ventricle is empty then.

10. Drugs that increase the heart rate have a _____ effect.
    a. myogenic
    b. negative inotropic
    c. positive inotropic
    d. negative chronotropic
    e. positive chronotropic

11. The contraction of any heart chamber is called _____ and its relaxation is called _____.

12. The circulatory route from aorta to the venae cavae is the _____ circuit.

13. The circumflex artery travels in a groove called the _____.

14. The pacemaker potential of the SA node cells results from the slow inflow of _____.

15. Electrical signals pass quickly from one cardiac myocyte to another through the _____ of the intercalated discs.

16. Repolarization of the ventricles produces the _____ of the electrocardiogram.

17. Closing of the _____ valves produces turbulence in the bloodstream, which contributes to heart sound S2.

18. The procedure for listening to the heart sounds is called cardiac _____.

19. The end-diastolic volume of blood stretches the ventricles and creates myocardial tension called the _____.

20. The Frank–Starling law of the heart explains why the _____ of the left ventricle is the same as that of the right ventricle.

Chapter 19

Answers in Appendix B

True or False

Determine which five of the following statements are false, and briefly explain why.

1. The blood supply to the myocardium is the coronary circulation; everything else is called the systemic circuit.
2. There are no valves at the point where venous blood flows into the atria.
3. No blood can enter the ventricles until the atria contract.
4. The vagus nerves reduce the heart rate but have little effect on the strength of ventricular contraction.
5. A high blood CO_2 level and low blood pH stimulate an increase in heart rate.
6. The first heart sound occurs at the time of the P wave of the electrocardiogram.
7. If all nerves to the heart were severed, the heart would instantly stop beating.
8. If the two pulmonary arteries were clamped shut, systemic edema would follow.
9. Ventricular myocytes have a stable resting membrane potential but myocytes of the SA node do not.
10. An electrocardiogram is a tracing of the action potential of a cardiac myocyte.

Answers in Appendix B

Testing Your Comprehension

1. Verapimil is a calcium channel blocker used to treat hypertension. It selectively blocks slow calcium channels. Would you expect it to have a positive or negative inotropic effect? Explain. (See p. 101 to review calcium channel blockers.)
2. To temporarily treat tachycardia and restore the normal resting sinus rhythm, a physician may massage a patient's carotid artery near the angle of the mandible. Propose a mechanism by which this treatment would have the desired effect.
3. Suppose that a patient experienced bleeding into the pericardial cavity because of a ruptured aneurysm. The amount of blood lost was not life-threatening, but about 200 mL of blood accumulated and clotted in the pericardial cavity before the bleeding stopped. Predict how this could affect the heart's end-diastolic volume and stroke volume, and explain your reasoning.
4. In ventricular systole, the left ventricle is the first to begin contracting but the right ventricle is the first to expel blood. Aside from the obvious fact that the pulmonary valve opens before the aortic valve, how can you explain this difference?
5. The action potential of a cardiac myocyte looks very different from the action potential of a neuron. Sketch the two and explain the ionic basis for the differences.

Answers at the Online Learning Center

Answers to Figure Legend Questions

19.2 To the left
19.6 The trabeculae carneae
19.12 The right atrium
19.14 It ensures that wave summation and tetanus will not occur, and thus ensures relaxation and refilling of the heart chambers.
19.19 This is the point at which the aortic valve opens and blood is ejected into the aorta, raising its blood pressure.