Cardiac Muscle; The Heart as a Pump and Function of the Heart Valves

Our discussion of the heart and circulatory system begins in this chapter. The heart, shown in **Figure 9-1**, is actually two separate pumps: a *right heart* that pumps blood through the lungs, and a *left heart* that pumps blood through the systemic circulation that provides blood flow to the other organs and tissues of the body. In turn, each of these hearts is a pulsatile two-chamber pump composed of an *atrium* and a *ventricle.* Each atrium is a weak primer pump for the ventricle, helping to move blood into the ventricle. The ventricles then supply the main pumping force that propels the blood either (1) through the pulmonary circulation by the right ventricle or (2) through the systemic circulation by the left ventricle.

Special mechanisms in the heart cause a continuing succession of heart contractions called *cardiac rhythmicity,* transmitting action potentials throughout the cardiac muscle to cause the heart's rhythmical beat. This rhythmical control system is explained in Chapter 10. In this chapter, we explain how the heart operates as a pump, beginning with the special features of cardiac muscle.
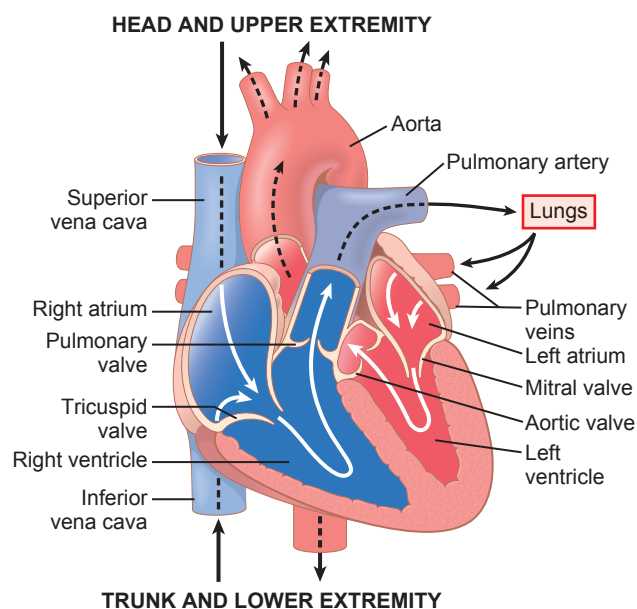

HEAD AND UPPER EXTREMITY

Aorta

Pulmonary artery

Superior vena cava

Lungs

Right atrium

Pulmonary valve

Pulmonary veins

Left atrium

Mitral valve

Tricuspid valve

Aortic valve

Right ventricle

Left ventricle

Inferior vena cava

TRUNK AND LOWER EXTREMITY

Figure 9-1. Structure of the heart and course of blood flow through the heart chambers and heart valves.

PHYSIOLOGY OF CARDIAC MUSCLE

The heart is composed of three major types of cardiac muscle: *atrial muscle, ventricular muscle,* and specialized *excitatory* and *conductive muscle* fibers. The atrial and ventricular types of muscle contract in much the same way as skeletal muscle, except that the duration of contraction is much longer. The specialized excitatory and conductive fibers of the heart, however, contract only feebly because they contain few contractile fibrils; instead, they exhibit either automatic rhythmical electrical discharge in the form of action potentials or conduction of the action potentials through the heart, providing an excitatory system that controls the rhythmical beating of the heart.

PHYSIOLOGIC ANATOMY OF CARDIAC MUSCLE

Figure 9-2 shows the histology of cardiac muscle, demonstrating cardiac muscle fibers arranged in a latticework, with the fibers dividing, recombining, and then spreading again. Note that cardiac muscle is *striated* in the same manner as in skeletal muscle. Further, cardiac muscle has typical myofibrils that contain *actin* and *myosin filaments* almost identical to those found in skeletal muscle; these filaments lie side by side and slide during contraction in the same manner as occurs in skeletal muscle (see Chapter 6). In other ways, however, cardiac muscle is quite different from skeletal muscle, as we shall see.

Cardiac Muscle Is a Syncytium. The dark areas crossing the cardiac muscle fibers in **Figure 9-2** are called *intercalated discs;* they are actually cell membranes that separate individual cardiac muscle cells from one another. That is, cardiac muscle fibers are made up of many individual cells connected in series and in parallel with one another.

At each intercalated disc the cell membranes fuse with one another to form permeable "communicating" junctions (gap junctions) that allow rapid diffusion of ions. Therefore, from a functional point of view, ions move with ease in the intracellular fluid along the longitudinal axes of the cardiac muscle fibers so that action potentials

Figure 9-2. Syncytial, interconnecting nature of cardiac muscle fibers.
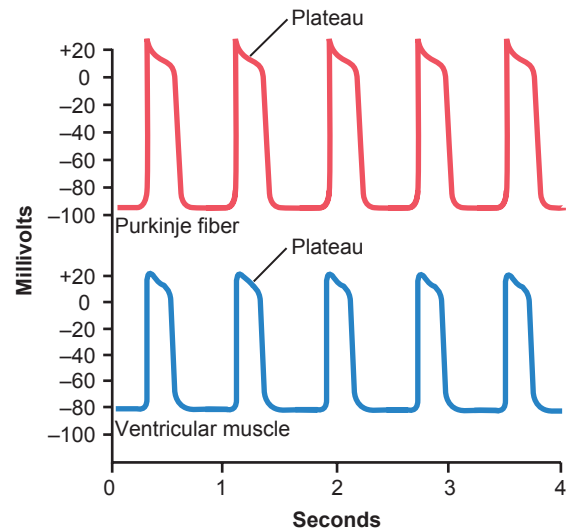

Figure 9-3. Rhythmical action potentials (in millivolts) from a Purkinje fiber and from a ventricular muscle fiber, recorded by means of microelectrodes.

travel easily from one cardiac muscle cell to the next, past the intercalated discs. Thus, cardiac muscle is a *syncytium* of many heart muscle cells in which the cardiac cells are so interconnected that when one cell becomes excited, the action potential rapidly spreads to all of them.

The heart actually is composed of two syncytiums: the *atrial syncytium,* which constitutes the walls of the two atria, and the *ventricular syncytium,* which constitutes the walls of the two ventricles. The atria are separated from the ventricles by fibrous tissue that surrounds the atrioventricular (A-V) valvular openings between the atria and ventricles. Normally, potentials are not conducted from the atrial syncytium into the ventricular syncytium directly through this fibrous tissue. Instead, they are conducted only by way of a specialized conductive system called the *A-V bundle,* a bundle of conductive fibers several millimeters in diameter that is discussed in Chapter 10.

This division of the muscle of the heart into two functional syncytiums allows the atria to contract a short time ahead of ventricular contraction, which is important for effectiveness of heart pumping.

ACTION POTENTIALS IN CARDIAC MUSCLE

The *action potential* recorded in a ventricular muscle fiber, shown in **Figure 9-3**, averages about 105 millivolts, which means that the intracellular potential rises from a very negative value, about −85 millivolts, between beats to a slightly positive value, about +20 millivolts, during each beat. After the initial *spike,* the membrane remains depolarized for about 0.2 second, exhibiting a *plateau*, followed at the end of the plateau by abrupt repolarization. The presence of this plateau in the action potential causes ventricular contraction to last as much as 15 times as long in cardiac muscle as in skeletal muscle.

What Causes the Long Action Potential and the Plateau? Why is the action potential of cardiac muscle

so long and why does it have a plateau, when the action potential of skeletal muscle does not have a plateau? The basic biophysical answers to these questions were presented in Chapter 5, but they merit summarizing here as well.

At least two major differences between the membrane properties of cardiac and skeletal muscle account for the prolonged action potential and the plateau in cardiac muscle. First, the *action potential of skeletal muscle* is caused almost entirely by the sudden opening of large numbers of *fast sodium channels* that allow tremendous numbers of sodium ions to enter the skeletal muscle fiber from the extracellular fluid. These channels are called "fast" channels because they remain open for only a few thousandths of a second and then abruptly close. At the end of this closure, repolarization occurs, and the action potential is over within another thousandth of a second or so.

In cardiac muscle, the action potential is caused by opening of two types of channels: (1) the same *voltage-activated fast sodium channels* as those in skeletal muscle and (2) another entirely different population of *L-type calcium channels (slow calcium channels),* which are also called *calcium-sodium channels.* This second population of channels differs from the fast sodium channels in that they are slower to open and, even more important, remain open for several tenths of a second. During this time, a large quantity of both calcium and sodium ions flows through these channels to the interior of the cardiac muscle fiber, and this activity maintains a prolonged period of depolarization, *causing the plateau* in the action potential. Further, the calcium ions that enter during this plateau phase activate the muscle contractile process, whereas the calcium ions that cause skeletal muscle contraction are derived from the intracellular sarcoplasmic reticulum.

The second major functional difference between cardiac muscle and skeletal muscle that helps account for both the prolonged action potential and its plateau is this: Immediately after the onset of the action potential, the permeability of the cardiac muscle membrane for potassium ions *decreases* about fivefold, an effect that does not occur in skeletal muscle. This decreased potassium permeability may result from the excess calcium influx through the calcium channels just noted. Regardless of the cause, the decreased potassium permeability greatly decreases the outflux of positively charged potassium ions during the action potential plateau and thereby prevents early return of the action potential voltage to its resting level. When the slow calcium-sodium channels do close at the end of 0.2 to 0.3 second and the influx of calcium and sodium ions ceases, the membrane permeability for potassium ions also increases rapidly; this rapid loss of potassium from the fiber immediately returns the membrane potential to its resting level, thus ending the action potential.

Summary of Phases of Cardiac Muscle Action Potential. **Figure 9-4** summarizes the phases of the action potential in cardiac muscle and the ion flows that occur during each phase.

Phase 0 (depolarization), fast sodium channels open. When the cardiac cell is stimulated and depolarizes, the membrane potential becomes more positive. Voltage-gated sodium channels (fast sodium channels) open and permit sodium to rapidly flow into the cell and depolarize it. The membrane potential reaches about +20 millivolts before the sodium channels close.

Phase 1 (initial repolarization), fast sodium channels close. The sodium channels close, the cell begins to repolarize, and potassium ions leave the cell through open potassium channels.

Phase 2 (plateau), calcium channels open and fast potassium channels close. A brief initial repolarization occurs and the action potential then plateaus as a result of (1) increased calcium ion permeability and (2) decreased potassium ion permeability. The voltage-gated calcium ion channels open slowly during phases 1 and 0, and calcium enters the cell. Potassium channels then close, and the combination of decreased potassium ion efflux and increased calcium ion influx causes the action potential to plateau.

Phase 3 (rapid repolarization), calcium channels close and slow potassium channels open. The closure of calcium ion channels and increased potassium ion permeability, permitting potassium ions to rapidly exit the cell, ends the plateau and returns the cell membrane potential to its resting level.

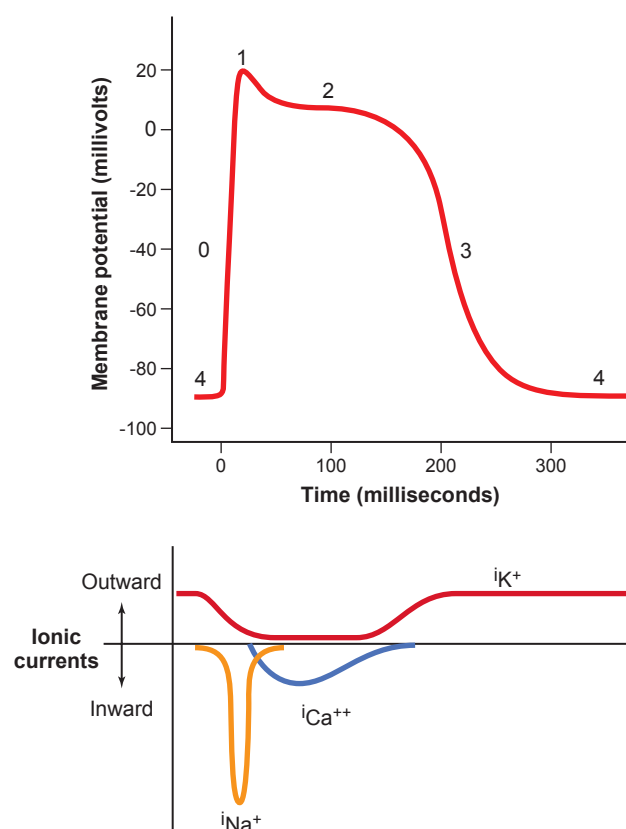*Phase 4 (resting membrane potential) averages about −90 millivolts.*

Figure 9-4. Phases of action potential of cardiac ventricular muscle cell and associated ionic currents for sodium ($^iNa^+$), calcium ($^iCa^{++}$), and potassium ($^iK^+$).

Velocity of Signal Conduction in Cardiac Muscle. The velocity of conduction of the excitatory action potential signal along both *atrial and ventricular muscle fibers* is about 0.3 to 0.5 m/sec, or about 1/250 the velocity in very large nerve fibers and about 1/10 the velocity in skeletal muscle fibers. The velocity of conduction in the specialized heart conductive system—in the *Purkinje fibers*—is as great as 4 m/sec in most parts of the system, which allows reasonably rapid conduction of the excitatory signal to the different parts of the heart, as explained in Chapter 10.

Refractory Period of Cardiac Muscle. Cardiac muscle, like all excitable tissue, is refractory to restimulation during the action potential. Therefore, the refractory period of the heart is the interval of time, as shown to the left in **Figure 9-5**, during which a normal cardiac impulse cannot re-excite an already excited area of cardiac muscle. The normal refractory period of the ventricle is 0.25 to 0.30 second, which is about the duration of the prolonged plateau action potential. There is an additional *relative refractory period* of about 0.05 second during which the muscle is more difficult to excite than normal but nevertheless can be excited by a very strong excitatory signal, as demonstrated by the early "premature" contraction in the second example of **Figure 9-5**. The refractory period of atrial muscle is much shorter than that for the ventricles (about 0.15 second for the atria compared with 0.25 to 0.30 second for the ventricles).
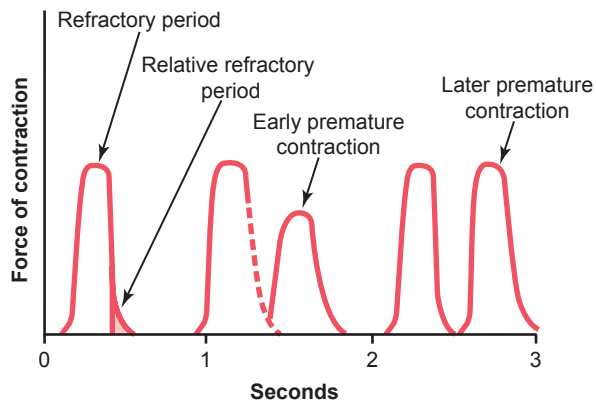
Figure 9-5. Force of ventricular heart muscle contraction, showing also the duration of the refractory period and relative refractory period, plus the effect of premature contraction. Note that premature contractions do not cause wave summation, as occurs in skeletal muscle.

EXCITATION-CONTRACTION COUPLING— FUNCTION OF CALCIUM IONS AND THE *TRANSVERSE TUBULES*

The term "excitation-contraction coupling" refers to the mechanism by which the action potential causes the myofibrils of muscle to contract. This mechanism was discussed for skeletal muscle in Chapter 7. Once again, there are differences in this mechanism in cardiac muscle that have important effects on the characteristics of heart muscle contraction.

As is true for skeletal muscle, when an action potential passes over the cardiac muscle membrane, the action potential spreads to the interior of the cardiac muscle fiber along the membranes of the *transverse (T) tubules.* The T tubule action potentials in turn act on the membranes of the *longitudinal sarcoplasmic tubules* to cause release of calcium ions into the muscle sarcoplasm from the sarcoplasmic reticulum. In another few thousandths of a second, these calcium ions diffuse into the myofibrils and catalyze the chemical reactions that promote sliding of the actin and myosin filaments along one another, which produces the muscle contraction.

Thus far, this mechanism of excitation-contraction coupling is the same as that for skeletal muscle, but there is a second effect that is quite different. In addition to the calcium ions that are released into the sarcoplasm from the cisternae of the sarcoplasmic reticulum, calcium ions also diffuse into the sarcoplasm from the T tubules themselves at the time of the action potential, which opens voltage-dependent calcium channels in the membrane of the T tubule (**Figure 9-6**). Calcium entering the cell then activates *calcium release channels,* also called *ryanodine receptor channels,* in the sarcoplasmic reticulum membrane, triggering the release of calcium into the sarcoplasm. Calcium ions in the sarcoplasm then interact with troponin to initiate cross-bridge formation and contraction by the same basic mechanism as described for skeletal muscle in Chapter 6.

Without the calcium from the T tubules, the strength of cardiac muscle contraction would be reduced considerably because the sarcoplasmic reticulum of cardiac muscle is less well developed than that of skeletal muscle and does not store enough calcium to provide full contraction. The T tubules of cardiac muscle, however, have a diameter five times as great as that of the skeletal muscle tubules, which means a volume 25 times as great. Also, inside the T tubules is a large quantity of mucopolysaccharides that are electronegatively charged and bind an abundant store of calcium ions, keeping them available for diffusion to the interior of the cardiac muscle fiber when a T tubule action potential appears.

The strength of contraction of cardiac muscle depends to a great extent on the concentration of calcium ions in the extracellular fluids. In fact, a heart placed in a calcium-free solution will quickly stop beating. The reason for this response is that the openings of the T tubules pass directly through the cardiac muscle cell membrane into the extracellular spaces surrounding the cells, allowing the same extracellular fluid that is in the cardiac muscle interstitium to percolate through the T tubules. Consequently, the quantity of calcium ions in the T tubule system (i.e., the availability of calcium ions to cause cardiac muscle contraction) depends to a great extent on the extracellular fluid calcium ion concentration.

In contrast, the strength of skeletal muscle contraction is hardly affected by moderate changes in extracellular fluid calcium concentration because skeletal muscle contraction is caused almost entirely by calcium ions released from the sarcoplasmic reticulum *inside* the skeletal muscle fiber.

At the end of the plateau of the cardiac action potential, the influx of calcium ions to the interior of the muscle fiber is suddenly cut off, and calcium ions in the sarcoplasm are rapidly pumped back out of the muscle fibers into both the sarcoplasmic reticulum and the T tubule–extracellular fluid space. Transport of calcium back into the sarcoplasmic reticulum is achieved with the help of a calcium–adenosine triphosphatase (ATPase) pump (see **Figure 9-6**). Calcium ions are also removed from the cell by a sodium-calcium exchanger. The sodium that enters the cell during this exchange is then transported out of the cell by the sodium-potassium ATPase pump. As a result, the contraction ceases until a new action potential comes along.

Duration of Contraction. Cardiac muscle begins to contract a few milliseconds after the action potential begins and continues to contract until a few milliseconds after the action potential ends. Therefore, the duration of contraction of cardiac muscle is mainly a function of the duration of the action potential, *including the plateau*—about 0.2 second in atrial muscle and 0.3 second in ventricular muscle.
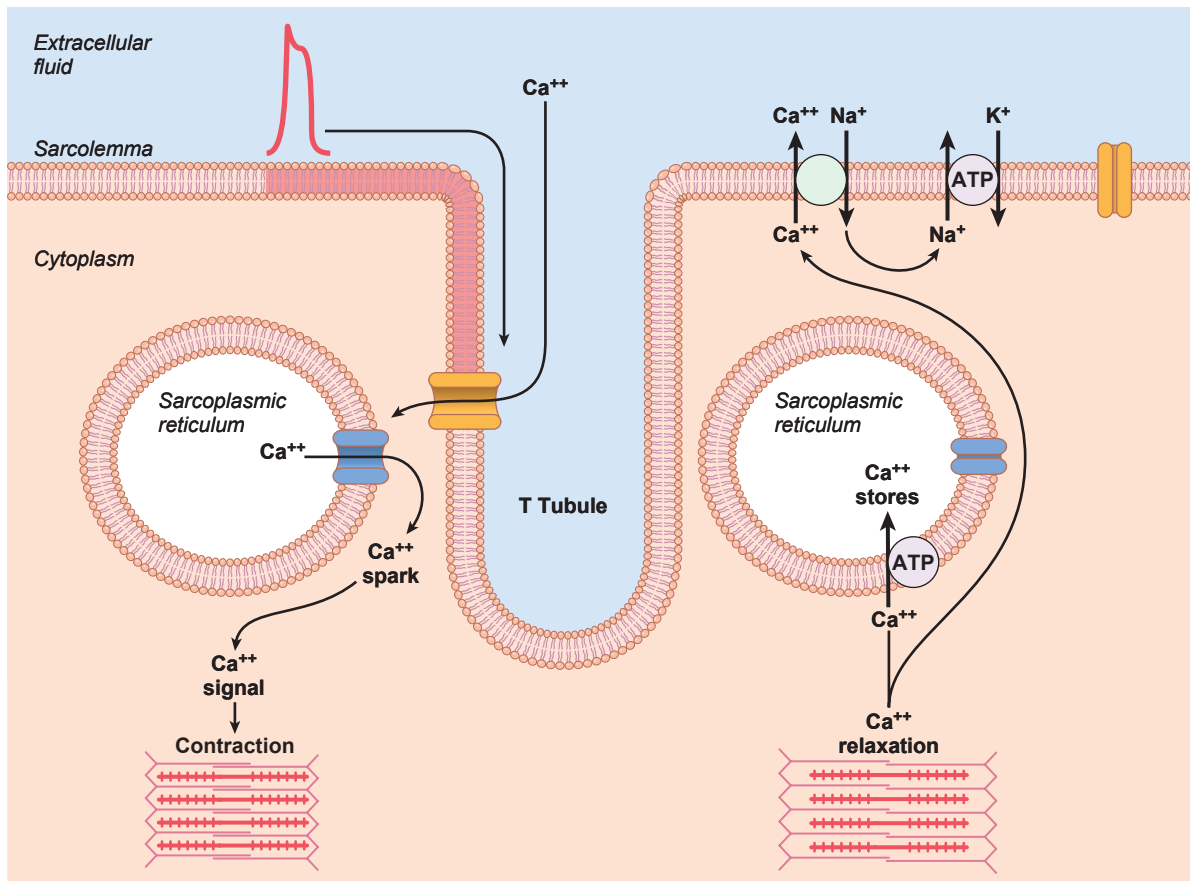
Figure 9-6. Mechanisms of excitation-contraction coupling and relaxation in cardiac muscle. ATP, adenosine triphosphate.

CARDIAC CYCLE

The cardiac events that occur from the beginning of one heartbeat to the beginning of the next are called the *cardiac cycle.* Each cycle is initiated by spontaneous generation of an action potential in the *sinus node,* as explained in Chapter 10. This node is located in the superior lateral wall of the right atrium near the opening of the superior vena cava, and the action potential travels from here rapidly through both atria and then through the A-V bundle into the ventricles. Because of this special arrangement of the conducting system from the atria into the ventricles, there is a delay of more than 0.1 second during passage of the cardiac impulse from the atria into the ventricles. This delay allows the atria to contract ahead of ventricular contraction, thereby pumping blood into the ventricles before the strong ventricular contraction begins. Thus, the atria act as *primer pumps* for the ventricles, and the ventricles in turn provide the major source of power for moving blood through the body's vascular system.

Diastole and Systole

The cardiac cycle consists of a period of relaxation called *diastole,* during which the heart fills with blood, followed by a period of contraction called *systole.*

The total *duration of the cardiac cycle,* including systole and diastole, is the reciprocal of the heart rate. For example, if heart rate is 72 beats/min, the duration of the cardiac cycle is 1/72 min/beat—about 0.0139 minutes per beat, or 0.833 second per beat.

Figure 9-7 shows the different events during the cardiac cycle for the left side of the heart. The top three curves show the pressure changes in the aorta, left ventricle, and left atrium, respectively. The fourth curve depicts the changes in left ventricular volume, the fifth depicts the electrocardiogram, and the sixth depicts a phonocardiogram, which is a recording of the sounds produced by the heart—mainly by the heart valves—as it pumps. It is especially important that the reader study in detail this figure and understand the causes of all the events shown.

Increasing Heart Rate Decreases Duration of Cardiac Cycle. When heart rate increases, the duration of each cardiac cycle decreases, including the contraction and relaxation phases. The duration of the action potential and the period of contraction (systole) also decrease, but not by as great a percentage as does the relaxation phase (diastole). At a normal heart rate of 72 beats/min, systole comprises about 0.4 of the entire cardiac cycle. At three times the normal heart rate, systole is about 0.65 of the
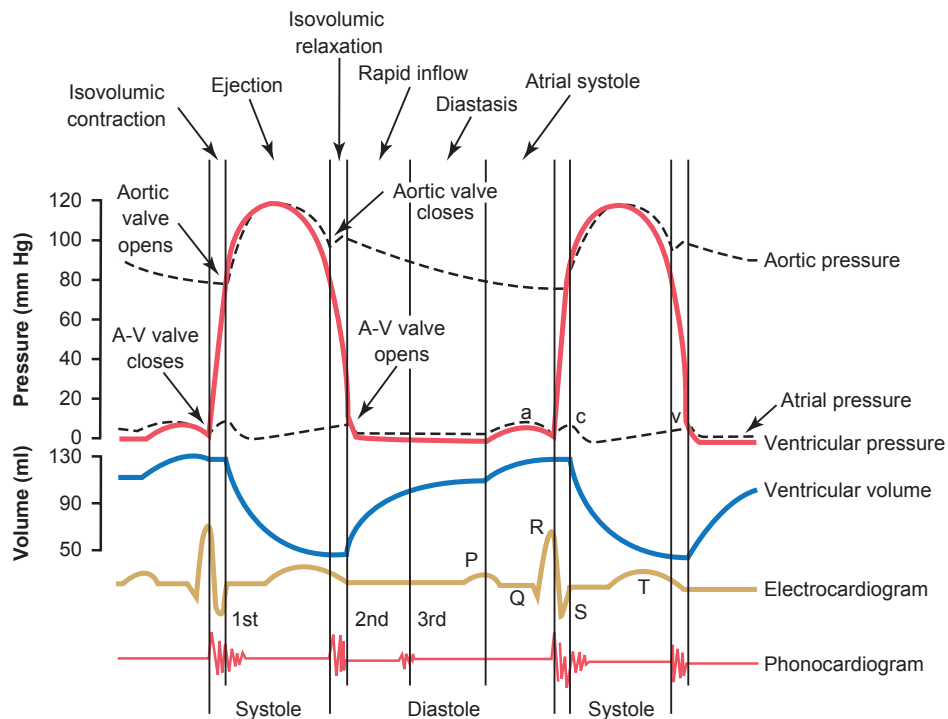
Figure 9-7. Events of the cardiac cycle for left ventricular function, showing changes in left atrial pressure, left ventricular pressure, aortic pressure, ventricular volume, the electrocardiogram, and the phonocardiogram. A-V, atrioventricular.

entire cardiac cycle. This means that the heart beating at a very fast rate does not remain relaxed long enough to allow complete filling of the cardiac chambers before the next contraction.

Relationship of the Electrocardiogram to the Cardiac Cycle

The electrocardiogram in **Figure 9-7** shows the *P, Q, R, S,* and *T waves,* which are discussed in Chapters 11, 12, and 13. They are electrical voltages generated by the heart and recorded by the electrocardiograph from the surface of the body.

The *P wave* is caused by *spread of depolarization* through the atria and is followed by atrial contraction, which causes a slight rise in the atrial pressure curve immediately after the electrocardiographic P wave.

About 0.16 second after the onset of the P wave, the *QRS waves* appear as a result of electrical depolarization of the ventricles, which initiates contraction of the ventricles and causes the ventricular pressure to begin rising. Therefore, the QRS complex begins slightly before the onset of ventricular systole.

Finally, the *ventricular T wave* represents the stage of repolarization of the ventricles when the ventricular muscle fibers begin to relax. Therefore, the T wave occurs slightly before the end of ventricular contraction.

The Atria Function as Primer Pumps for the Ventricles

Blood normally flows continually from the great veins into the atria; about 80 percent of the blood flows directly through the atria into the ventricles even before the atria contract. Then, atrial contraction usually causes an additional 20 percent filling of the ventricles. Therefore, the atria function as primer pumps that increase the ventricular pumping effectiveness as much as 20 percent. However, the heart can continue to operate under most conditions even without this extra 20 percent effectiveness because it normally has the capability of pumping 300 to 400 percent more blood than is required by the resting body. Therefore, when the atria fail to function, the difference is unlikely to be noticed unless a person exercises; then acute signs of heart failure occasionally develop, especially shortness of breath.

Pressure Changes in the Atria—a, c, and v Waves. In the atrial pressure curve of **Figure 9-7**, three minor pressure elevations, called the *a, c,* and *v atrial pressure waves,* are shown.

The *a wave* is caused by atrial contraction. Ordinarily, the *right* atrial pressure increases 4 to 6 mm Hg during atrial contraction, and the *left* atrial pressure increases about 7 to 8 mm Hg.

The *c wave* occurs when the ventricles begin to contract; it is caused partly by slight backflow of blood into the atria at the onset of ventricular contraction but mainly by bulging of the A-V valves backward toward the atria because of increasing pressure in the ventricles.

The *v wave* occurs toward the end of ventricular contraction; it results from slow flow of blood into the atria from the veins while the A-V valves are closed during ventricular contraction. Then, when ventricular contraction is

over, the A-V valves open, allowing this stored atrial blood to flow rapidly into the ventricles and causing the v wave to disappear.

FUNCTION OF THE VENTRICLES AS PUMPS

The Ventricles Fill With Blood During Diastole. During ventricular systole, large amounts of blood accumulate in the right and left atria because of the closed A-V valves. Therefore, as soon as systole is over and the ventricular pressures fall again to their low diastolic values, the moderately increased pressures that have developed in the atria during ventricular systole immediately push the A-V valves open and allow blood to flow rapidly into the ventricles, as shown by the rise of the left *ventricular volume curve* in **Figure 9-7**. This period is called the *period of rapid filling of the ventricles.*

The period of rapid filling lasts for about the first third of diastole. During the middle third of diastole, only a small amount of blood normally flows into the ventricles; this is blood that continues to empty into the atria from the veins and passes through the atria directly into the ventricles.

During the last third of diastole, the atria contract and give an additional thrust to the inflow of blood into the ventricles. This mechanism accounts for about 20 percent of the filling of the ventricles during each heart cycle.

Outflow of Blood From the Ventricles During Systole

Period of Isovolumic (Isometric) Contraction. Immediately after ventricular contraction begins, the ventricular pressure rises abruptly, as shown in **Figure 9-7**, causing the A-V valves to close. Then an additional 0.02 to 0.03 second is required for the ventricle to build up sufficient pressure to push the semilunar (aortic and pulmonary) valves open against the pressures in the aorta and pulmonary artery. Therefore, during this period, contraction is occurring in the ventricles, but no emptying occurs. This period is called the period of *isovolumic* or *isometric contraction,* meaning that cardiac muscle tension is increasing but little or no shortening of the muscle fibers is occurring.

Period of Ejection. When the left ventricular pressure rises slightly above 80 mm Hg (and the right ventricular pressure rises slightly above 8 mm Hg), the ventricular pressures push the semilunar valves open. Immediately, blood begins to pour out of the ventricles. Approximately 60 percent of the blood in the ventricle at the end of diastole is ejected during systole; about 70 percent of this portion flows out during the first third of the ejection period, with the remaining 30 percent emptying during the next two thirds. Therefore, the first third is called the *period of rapid ejection,* and the last two thirds are called the *period of slow ejection.*

Period of Isovolumic (Isometric) Relaxation. At the end of systole, ventricular relaxation begins suddenly, allowing both the right and left *intraventricular pressures* to decrease rapidly. The elevated pressures in the distended large arteries that have just been filled with blood from the contracted ventricles immediately push blood back toward the ventricles, which snaps the aortic and pulmonary valves closed. For another 0.03 to 0.06 second, the ventricular muscle continues to relax, even though the ventricular volume does not change, giving rise to the period of *isovolumic* or *isometric relaxation.* During this period, the intraventricular pressures rapidly decrease back to their low diastolic levels. Then the A-V valves open to begin a new cycle of ventricular pumping.

End-Diastolic Volume, End-Systolic Volume, and Stroke Volume Output. During diastole, normal filling of the ventricles increases the volume of each ventricle to about 110 to 120 milliliters. This volume is called the *end-diastolic volume.* Then, as the ventricles empty during systole, the volume decreases about 70 milliliters, which is called the *stroke volume output.* The remaining volume in each ventricle, about 40 to 50 milliliters, is called the *end-systolic volume.* The fraction of the end-diastolic volume that is ejected is called the *ejection fraction*—usually equal to about 0.6 (or 60 percent).

When the heart contracts strongly, the end-systolic volume may decrease to as little as 10 to 20 milliliters. Conversely, when large amounts of blood flow into the ventricles during diastole, the ventricular end-diastolic volumes can become as great as 150 to 180 milliliters in the healthy heart. By both increasing the end-diastolic volume and decreasing the end-systolic volume, the stroke volume output can be increased to more than double that which is normal.

THE HEART VALVES PREVENT BACKFLOW OF BLOOD DURING SYSTOLE

Atrioventricular Valves. The *A-V valves* (i.e., the *tricuspid* and *mitral* valves) prevent backflow of blood from the ventricles to the atria during systole, and the *semilunar valves* (i.e., the *aortic* and *pulmonary artery* valves) prevent backflow from the aorta and pulmonary arteries into the ventricles during diastole. These valves, shown in **Figure 9-8** for the left ventricle, close and open *passively.* That is, they close when a backward pressure gradient pushes blood backward, and they open when a forward pressure gradient forces blood in the forward direction. For anatomical reasons, the thin, filmy A-V valves require almost no backflow to cause closure, whereas the much heavier semilunar valves require rather rapid backflow for a few milliseconds.
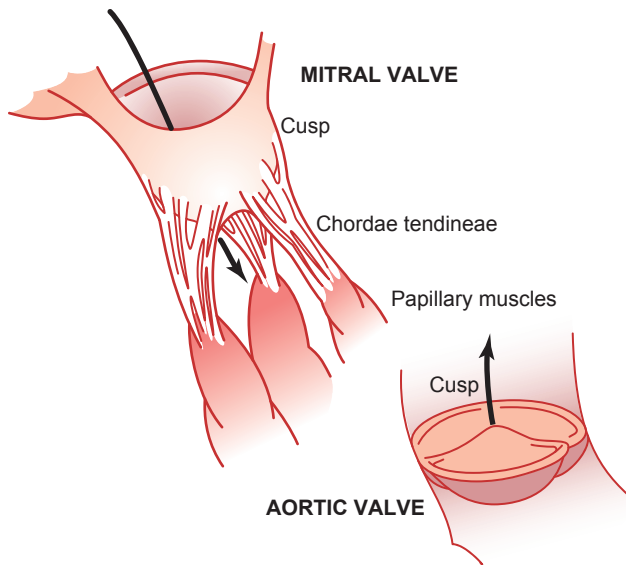
Figure 9-8. Mitral and aortic valves (the left ventricular valves).

Function of the Papillary Muscles. Figure 9-8 also shows papillary muscles that attach to the vanes of the A-V valves by the *chordae tendineae.* The papillary muscles contract when the ventricular walls contract, but contrary to what might be expected, they *do not* help the valves to close. Instead, they pull the vanes of the valves inward toward the ventricles to prevent their bulging too far backward toward the atria during ventricular contraction. If a chorda tendinea becomes ruptured or if one of the papillary muscles becomes paralyzed, the valve bulges far backward during ventricular contraction, sometimes so far that it leaks severely and results in severe or even lethal cardiac incapacity.

Aortic and Pulmonary Artery Valves. The aortic and pulmonary artery semilunar valves function quite differently from the A-V valves. First, the high pressures in the arteries at the end of systole cause the semilunar valves to snap closed, in contrast to the much softer closure of the A-V valves. Second, because of smaller openings, the velocity of blood ejection through the aortic and pulmonary valves is far greater than that through the much larger A-V valves. Also, because of the rapid closure and rapid ejection, the edges of the aortic and pulmonary valves are subjected to much greater mechanical abrasion than are the A-V valves. Finally, the A-V valves are supported by the chordae tendineae, which is not true for the semilunar valves. It is obvious from the anatomy of the aortic and pulmonary valves (as shown for the aortic valve at the bottom of **Figure 9-8**) that they must be constructed with an especially strong yet very pliable fibrous tissue to withstand the extra physical stresses.

AORTIC PRESSURE CURVE

When the left ventricle contracts, the ventricular pressure increases rapidly until the aortic valve opens. Then, after

the valve opens, the pressure in the ventricle rises much less rapidly, as shown in **Figure 9-6**, because blood immediately flows out of the ventricle into the aorta and then into the systemic distribution arteries.

The entry of blood into the arteries during systole causes the walls of these arteries to stretch and the pressure to increase to about 120 mm Hg.

Next, at the end of systole, after the left ventricle stops ejecting blood and the aortic valve closes, the elastic walls of the arteries maintain a high pressure in the arteries, even during diastole.

An *incisura* occurs in the aortic pressure curve when the aortic valve closes. This is caused by a short period of backward flow of blood immediately before closure of the valve, followed by sudden cessation of the backflow.

After the aortic valve has closed, the pressure in the aorta decreases slowly throughout diastole because the blood stored in the distended elastic arteries flows continually through the peripheral vessels back to the veins. Before the ventricle contracts again, the aortic pressure usually has fallen to about 80 mm Hg (diastolic pressure), which is two thirds the maximal pressure of 120 mm Hg (systolic pressure) that occurs in the aorta during ventricular contraction.

The pressure curves in the *right ventricle* and *pulmonary artery* are similar to those in the aorta, except that the pressures are only about one sixth as great, as discussed in Chapter 14.

Relationship of the Heart Sounds to Heart Pumping

When listening to the heart with a stethoscope, one does not hear the opening of the valves because this is a relatively slow process that normally makes no noise. However, when the valves close, the vanes of the valves and the surrounding fluids vibrate under the influence of sudden pressure changes, giving off sound that travels in all directions through the chest.

When the ventricles contract, one first hears a sound caused by closure of the A-V valves. The vibration pitch is low and relatively long-lasting and is known as the *first heart sound.* When the aortic and pulmonary valves close at the end of systole, one hears a rapid snap because these valves close rapidly, and the surroundings vibrate for a short period. This sound is called the *second heart sound.* The precise causes of the heart sounds are discussed more fully in Chapter 23, in relation to listening to the sounds with the stethoscope.

Work Output of the Heart

The *stroke work output* of the heart is the amount of energy that the heart converts to work during each heartbeat while pumping blood into the arteries. *Minute work output* is the total amount of energy converted to work in 1 minute; this is equal to the stroke work output times the heart rate per minute.

Work output of the heart is in two forms. First, by far the major proportion is used to move the blood from the

low-pressure veins to the high-pressure arteries. This is called *volume-pressure work* or *external work.* Second, a minor proportion of the energy is used to accelerate the blood to its velocity of ejection through the aortic and pulmonary valves, which is the *kinetic energy of blood flow* component of the work output.

Right ventricular external work output is normally about one sixth the work output of the left ventricle because of the sixfold difference in systolic pressures that the two ventricles pump. The additional work output of each ventricle required to create kinetic energy of blood flow is proportional to the mass of blood ejected times the square of velocity of ejection.

Ordinarily, the work output of the left ventricle required to create kinetic energy of blood flow is only about 1 percent of the total work output of the ventricle and therefore is ignored in the calculation of the total stroke work output. In certain abnormal conditions, however, such as aortic stenosis, in which blood flows with great velocity through the stenosed valve, more than 50 percent of the total work output may be required to create kinetic energy of blood flow.

GRAPHICAL ANALYSIS OF VENTRICULAR PUMPING

Figure 9-9 shows a diagram that is especially useful in explaining the pumping mechanics of the *left* ventricle. The most important components of the diagram are the two curves labeled "diastolic pressure" and "systolic pressure." These curves are volume-pressure curves.

The diastolic pressure curve is determined by filling the heart with progressively greater volumes of blood and then measuring the diastolic pressure immediately before ventricular contraction occurs, which is the *end-diastolic pressure* of the ventricle.

The systolic pressure curve is determined by recording the systolic pressure achieved during ventricular contraction at each volume of filling.

Until the volume of the noncontracting ventricle rises above about 150 milliliters, the "diastolic" pressure does not increase greatly. Therefore, up to this volume, blood can flow easily into the ventricle from the atrium. Above 150 milliliters, the ventricular diastolic pressure increases rapidly, partly because of fibrous tissue in the heart that will stretch no more and partly because the pericardium that surrounds the heart becomes filled nearly to its limit.

During ventricular contraction, the systolic pressure increases even at low ventricular volumes and reaches a maximum at a ventricular volume of 150 to 170 milliliters. Then, as the volume increases still further, the systolic pressure actually decreases under some conditions, as demonstrated by the falling systolic pressure curve in **Figure 9-9**, because at these great volumes, the actin and myosin filaments of the cardiac muscle fibers are pulled apart far enough that the strength of each cardiac fiber contraction becomes less than optimal.
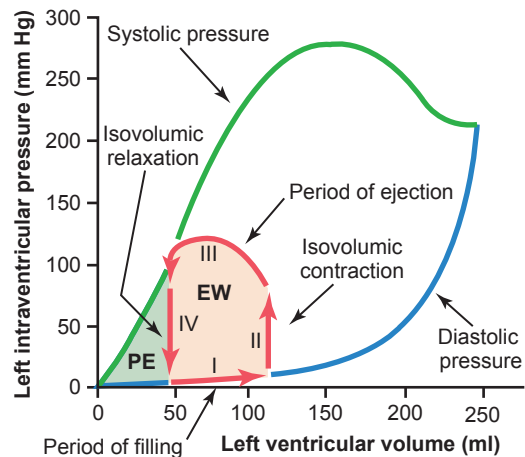

Figure 9-9. Relationship between left ventricular volume and intraventricular pressure during diastole and systole. Also shown by the red lines is the "volume-pressure diagram," demonstrating changes in intraventricular volume and pressure during the normal cardiac cycle. EW, net external work; PE, potential energy.

Note especially in the figure that the maximum systolic pressure for the normal *left* ventricle is between 250 and 300 mm Hg, but this varies widely with each person's heart strength and degree of heart stimulation by cardiac nerves. For the normal *right* ventricle, the maximum systolic pressure is between 60 and 80 mm Hg.

"Volume-Pressure Diagram" During the Cardiac Cycle; Cardiac Work Output. The red lines in **Figure 9-9** form a loop called the *volume-pressure diagram* of the cardiac cycle for normal function of the *left* ventricle. A more detailed version of this loop is shown in **Figure 9-10**. It is divided into four phases.

Phase I: Period of filling. Phase I in the volume-pressure diagram begins at a ventricular volume of about 50 milliliters and a diastolic pressure of 2 to 3 mm Hg. The amount of blood that remains in the ventricle after the previous heartbeat, 50 milliliters, is called the *end-systolic volume.* As venous blood flows into the ventricle from the left atrium, the ventricular volume normally increases to about 120 milliliters, called the *end-diastolic volume,* an increase of 70 milliliters. Therefore, the volume-pressure diagram during phase I extends along the line in **Figure 9-9** labeled "I," and from point A to point B in **Figure 9-10**, with the volume increasing to 120 milliliters and the diastolic pressure rising to about 5 to 7 mm Hg.

Phase II: Period of isovolumic contraction. During isovolumic contraction, the volume of the ventricle does not change because all valves are closed. However, the pressure inside the ventricle increases to equal the pressure in the aorta, at a pressure value of about 80 mm Hg, as depicted by point C (**Figure 9-10**).

Phase III: Period of ejection. During ejection, the systolic pressure rises even higher because of still more contraction of the ventricle. At the same time, the volume of the ventricle decreases because the aortic valve has now opened and blood flows out of the ventricle into the aorta.
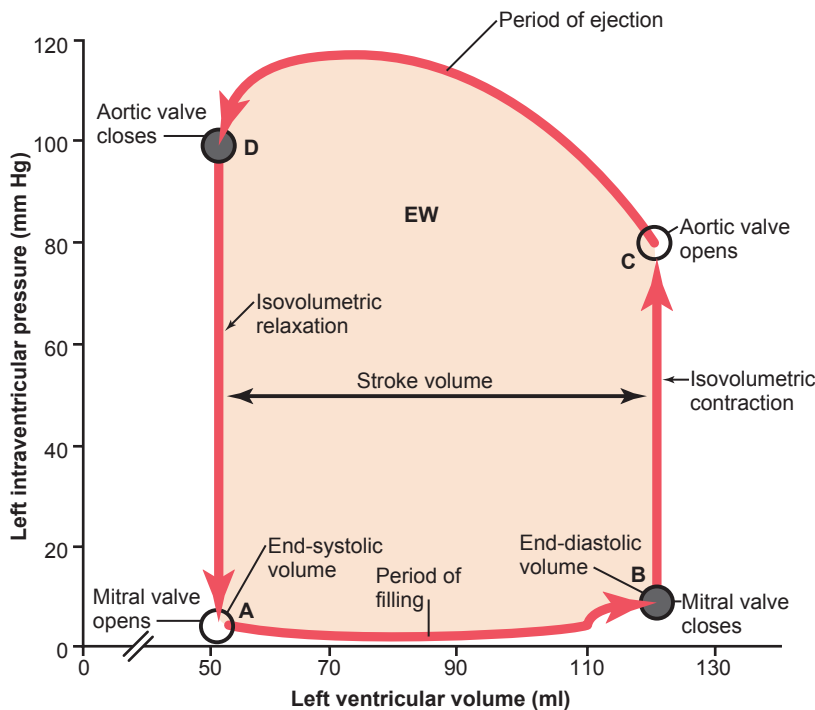
Figure 9-10. The volume-pressure diagram demonstrating changes in intraventricular volume and pressure during a single cardiac cycle *(red line)*. The shaded area represents the net external work (*EW*) output by the left ventricle during the cardiac cycle.

Therefore, in **Figure 9-9** the curve labeled "III," or "period of ejection," traces the changes in volume and systolic pressure during this period of ejection.

Phase IV: Period of isovolumic relaxation. At the end of the period of ejection (point D; **Figure 9-10**), the aortic valve closes and the ventricular pressure falls back to the diastolic pressure level. The line labeled "IV" (**Figure 9-9**) traces this decrease in intraventricular pressure without any change in volume. Thus, the ventricle returns to its starting point, with about 50 milliliters of blood left in the ventricle and at an atrial pressure of 2 to 3 mm Hg.

The area subtended by this functional volume-pressure diagram (the shaded area, labeled "EW") represents the *net external work output* of the ventricle during its contraction cycle. In experimental studies of cardiac contraction, this diagram is used for calculating cardiac work output.

When the heart pumps large quantities of blood, the area of the work diagram becomes much larger. That is, it extends far to the right because the ventricle fills with more blood during diastole, it rises much higher because the ventricle contracts with greater pressure, and it usually extends farther to the left because the ventricle contracts to a smaller volume—especially if the ventricle is stimulated to increased activity by the sympathetic nervous system.

Concepts of Preload and Afterload. In assessing the contractile properties of muscle, it is important to specify the degree of tension on the muscle when it begins to contract, which is called the *preload,* and to specify the load against which the muscle exerts its contractile force, which is called the *afterload.*

For cardiac contraction, the *preload* is usually considered to be the end-diastolic pressure when the ventricle has become filled.

The *afterload* of the ventricle is the pressure in the aorta leading from the ventricle. In **Figure 9-9**, this corresponds to the systolic pressure described by the phase III curve of the volume-pressure diagram. (Sometimes the afterload is loosely considered to be the resistance in the circulation rather than the pressure.)

The importance of the concepts of preload and afterload is that in many abnormal functional states of the heart or circulation, the pressure during filling of the ventricle (the preload), the arterial pressure against which the ventricle must contract (the afterload), or both are altered from normal to a severe degree.

Chemical Energy Required for Cardiac Contraction: Oxygen Utilization by the Heart

Heart muscle, like skeletal muscle, uses chemical energy to provide the work of contraction. Approximately 70 to 90 percent of this energy is normally derived from oxidative metabolism of fatty acids, with about 10 to 30 percent coming from other nutrients, especially lactate and glucose. Therefore, the rate of oxygen consumption by the heart is an excellent measure of the chemical energy liberated while the heart performs its work. The different chemical reactions that liberate this energy are discussed in Chapters 68 and 69.

Experimental studies have shown that oxygen consumption of the heart and the chemical energy expended during contraction are directly related to the total shaded area in **Figure 9-9**. This shaded portion consists of the *external work* (EW) as explained earlier and an additional

portion called the *potential energy,* labeled "PE". The potential energy represents additional work that could be accomplished by contraction of the ventricle if the ventricle should completely empty all the blood in its chamber with each contraction.

Oxygen consumption has also been shown to be nearly proportional to the *tension* that occurs in the heart muscle during contraction multiplied by the *duration of time* that the contraction persists, called the *tension-time index*. Because tension is high when systolic pressure is high, correspondingly more oxygen is used. Also, much more chemical energy is expended even at normal systolic pressures when the ventricle is abnormally dilated because the heart muscle tension during contraction is proportional to pressure times the diameter of the ventricle. This becomes especially important in heart failure when the heart ventricle is dilated and, paradoxically, the amount of chemical energy required for a given amount of work output is greater than normal even though the heart is already failing.

Efficiency of Cardiac Contraction.   During heart muscle contraction, most of the expended chemical energy is converted into *heat,* and a much smaller portion is converted into *work output*. The ratio of work output to total chemical energy expenditure is called the *efficiency of cardiac contraction,* or simply *efficiency of the heart.* Maximum efficiency of the normal heart is between 20 and 25 percent. In persons with heart failure, this efficiency can decrease to as low as 5 to 10 percent.

REGULATION OF HEART PUMPING

When a person is at rest, the heart pumps only 4 to 6 liters of blood each minute. During strenuous exercise, the heart may be required to pump four to seven times this amount. The basic means by which the volume pumped by the heart is regulated are (1) intrinsic cardiac regulation of pumping in response to changes in volume of blood flowing into the heart and (2) control of heart rate and strength of heart pumping by the autonomic nervous system.

INTRINSIC REGULATION OF HEART PUMPING—THE FRANK-STARLING MECHANISM

In Chapter 20, we will learn that under most conditions, the amount of blood pumped by the heart each minute is normally determined almost entirely by the rate of blood flow into the heart from the veins, which is called *venous return.* That is, each peripheral tissue of the body controls its own local blood flow, and all the local tissue flows combine and return by way of the veins to the right atrium. The heart, in turn, automatically pumps this incoming blood into the arteries so that it can flow around the circuit again.

This intrinsic ability of the heart to adapt to increasing volumes of inflowing blood is called the *Frank-Starling*

mechanism of the heart, in honor of Otto Frank and Ernest Starling, two great physiologists of a century ago. Basically, the Frank-Starling mechanism means that the greater the heart muscle is stretched during filling, the greater is the force of contraction and the greater the quantity of blood pumped into the aorta. Or, stated another way: *Within physiological limits, the heart pumps all the blood that returns to it by way of the veins.*

What Is the Explanation of the Frank-Starling Mechanism?   When an extra amount of blood flows into the ventricles, the cardiac muscle is stretched to a greater length. This stretching in turn causes the muscle to contract with increased force because the actin and myosin filaments are brought to a more nearly optimal degree of overlap for force generation. Therefore, the ventricle, because of its increased pumping, automatically pumps the extra blood into the arteries.

This ability of stretched muscle, up to an optimal length, to contract with increased work output is characteristic of all striated muscle, as explained in Chapter 6, and is not simply a characteristic of cardiac muscle.

In addition to the important effect of lengthening the heart muscle, still another factor increases heart pumping when its volume is increased. Stretch of the right atrial wall directly increases the heart rate by 10 to 20 percent, which also helps increase the amount of blood pumped each minute, although its contribution is much less than that of the Frank-Starling mechanism.

Ventricular Function Curves

One of the best ways to express the functional ability of the ventricles to pump blood is by *ventricular function curves.* **Figure 9-11** shows a type of ventricular function curve called the *stroke work output curve.* Note that as the atrial pressure for each side of the heart increases, the stroke work output for that side increases until it reaches the limit of the ventricle's pumping ability.

Figure 9-12 shows another type of ventricular function curve called the *ventricular volume output curve.*
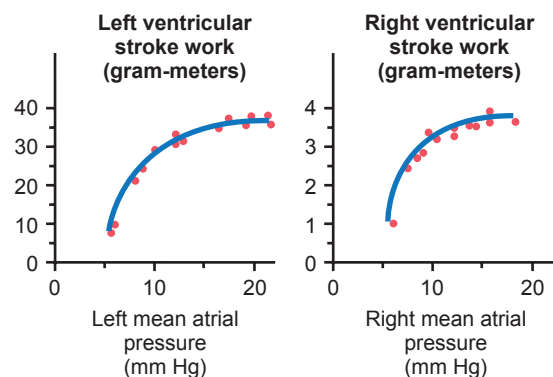
Figure 9-11. Left and right ventricular function curves recorded from dogs, depicting *ventricular stroke work output* as a function of left and right mean atrial pressures. *(Data from Sarnoff SJ: Myocardial contractility as described by ventricular function curves. Physiol Rev 35:107, 1955.)*
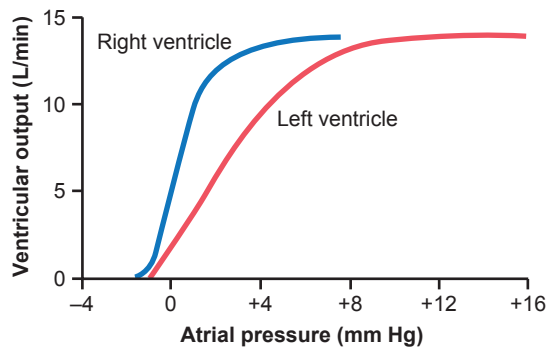
Figure 9-12. Approximate normal right and left *ventricular volume output curves* for the normal resting human heart as extrapolated from data obtained in dogs and data from human beings.
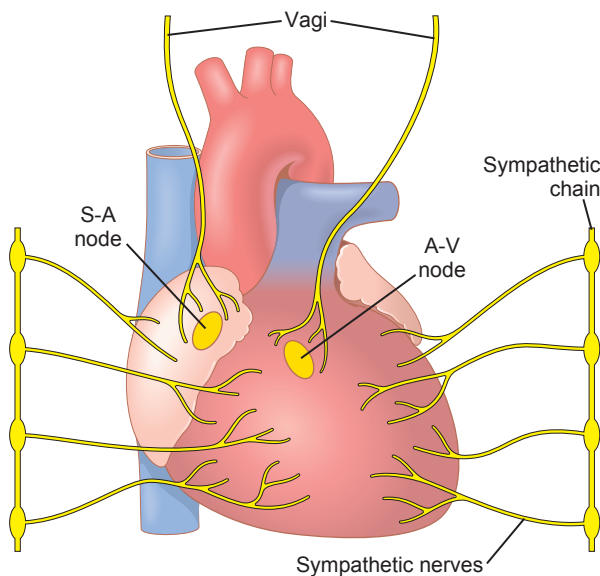

Figure 9-13. Cardiac *sympathetic* and *parasympathetic* nerves. (The vagus nerves to the heart are parasympathetic nerves.) A-V, atrioventricular; S-A, sinoatrial.

The two curves of this figure represent function of the two ventricles of the human heart based on data extrapolated from experimental animal studies. As the right and left atrial pressures increase, the respective ventricular volume outputs per minute also increase.

Thus, *ventricular function curves* are another way of expressing the Frank-Starling mechanism of the heart. That is, as the ventricles fill in response to higher atrial pressures, each ventricular volume and strength of cardiac muscle contraction increase, causing the heart to pump increased quantities of blood into the arteries.

Control of the Heart by the Sympathetic and Parasympathetic Nerves

The pumping effectiveness of the heart also is controlled by the *sympathetic* and *parasympathetic (vagus)* nerves, which abundantly supply the heart, as shown in **Figure 9-13**. For given levels of atrial pressure, the amount of blood pumped each minute *(cardiac output)* often can be increased more than 100 percent by sympathetic

stimulation. By contrast, the output can be decreased to almost zero by vagal (parasympathetic) stimulation.

Mechanisms of Excitation of the Heart by the Sympathetic Nerves. Strong sympathetic stimulation can increase the heart rate in young adult humans from the normal rate of 70 beats/min up to 180 to 200 and, rarely, even 250 beats/min. Also, sympathetic stimulation increases the force of heart contraction to as much as double the normal rate, thereby increasing the volume of blood pumped and increasing the ejection pressure. Thus, sympathetic stimulation often can increase the maximum cardiac output as much as twofold to threefold, in addition to the increased output caused by the Frank-Starling mechanism already discussed.

Conversely, *inhibition* of the sympathetic nerves to the heart can decrease cardiac pumping to a moderate extent. Under normal conditions, the sympathetic nerve fibers to the heart discharge continuously at a slow rate that maintains pumping at about 30 percent above that with no sympathetic stimulation. Therefore, when the activity of the sympathetic nervous system is depressed below normal, both the heart rate and strength of ventricular muscle contraction decrease, thereby decreasing the level of cardiac pumping as much as 30 percent below normal.

Parasympathetic (Vagal) Stimulation Reduces Heart Rate and Strength of Contraction. Strong stimulation of the parasympathetic nerve fibers in the vagus nerves to the heart can stop the heartbeat for a few seconds, but then the heart usually "escapes" and beats at a rate of 20 to 40 beats/min as long as the parasympathetic stimulation continues. In addition, strong vagal stimulation can decrease the strength of heart muscle contraction by 20 to 30 percent.

The vagal fibers are distributed mainly to the atria and not much to the ventricles, where the power contraction of the heart occurs. This distribution explains why the effect of vagal stimulation is mainly to decrease the heart rate rather than to decrease greatly the strength of heart contraction. Nevertheless, the great decrease in heart rate combined with a slight decrease in heart contraction strength can decrease ventricular pumping 50 percent or more.

Effect of Sympathetic or Parasympathetic Stimulation on the Cardiac Function Curve. Figure 9-14 shows four cardiac function curves. These curves are similar to the ventricular function curves of **Figure 9-12**. However, they represent function of the entire heart rather than of a single ventricle. They show the relation between right atrial pressure at the input of the right heart and cardiac output from the left ventricle into the aorta.

The curves of **Figure 9-14** demonstrate that at any given right atrial pressure, the cardiac output increases during increased sympathetic stimulation and decreases during increased parasympathetic stimulation. These
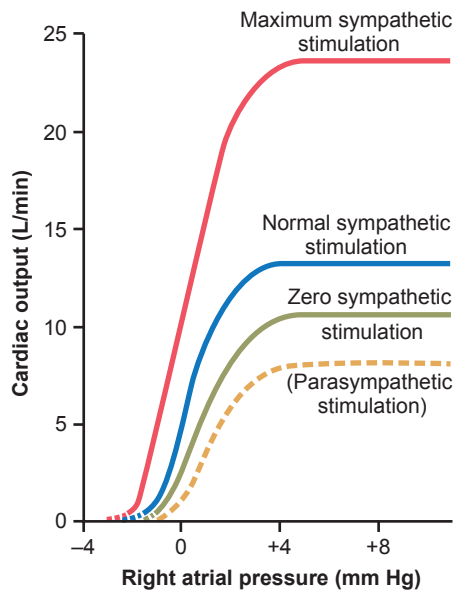
Figure 9-14. Effect on the cardiac output curve of different degrees of sympathetic or parasympathetic stimulation.

Figure 9-15. Constancy of cardiac output up to a pressure level of 160 mm Hg. Only when the arterial pressure rises above this normal limit does the increasing pressure load cause the cardiac output to fall significantly.

changes in output caused by autonomic nervous system stimulation result both from *changes in heart rate* and from *changes in contractile strength of the heart.*

EFFECT OF POTASSIUM AND CALCIUM IONS ON HEART FUNCTION

In the discussion of membrane potentials in Chapter 5, it was pointed out that potassium ions have a marked effect on membrane potentials, and in Chapter 6 it was noted that calcium ions play an especially important role in activating the muscle contractile process. Therefore, it is to be expected that the concentrations of each of these two ions in the extracellular fluids also have important effects on cardiac pumping.

Effect of Potassium Ions. Excess potassium in the extracellular fluids causes the heart to become dilated and flaccid and also slows the heart rate. Large quantities of potassium also can block conduction of the cardiac impulse from the atria to the ventricles through the A-V bundle. Elevation of potassium concentration to only 8 to 12 mEq/L—two to three times the normal value—can cause severe weakness of the heart, abnormal rhythm, and death.

These effects result partially from the fact that a high potassium concentration in the extracellular fluids decreases the resting membrane potential in the cardiac muscle fibers, as explained in Chapter 5. That is, high extracellular fluid potassium concentration partially depolarizes the cell membrane, causing the membrane potential to be less negative. As the membrane potential decreases, the intensity of the action potential also decreases, which makes contraction of the heart progressively weaker.
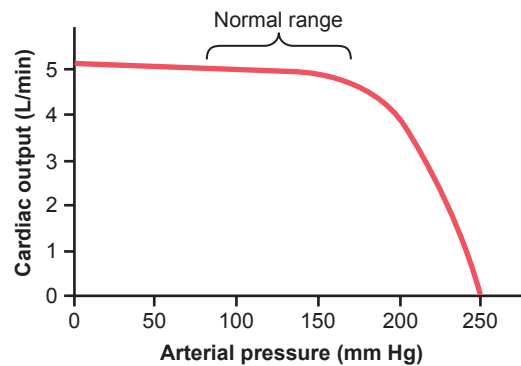
Effect of Calcium Ions. Excess calcium ions cause effects almost exactly opposite to those of potassium ions, causing the heart to move toward spastic contraction. This effect is caused by a direct effect of calcium ions to initiate the cardiac contractile process, as explained earlier in this chapter.

Conversely, deficiency of calcium ions causes cardiac weakness, similar to the effect of high potassium. Fortunately, calcium ion levels in the blood normally are regulated within a very narrow range. Therefore, cardiac effects of abnormal calcium concentrations are seldom of clinical concern.

EFFECT OF TEMPERATURE ON HEART FUNCTION

Increased body temperature, such as that which occurs when one has fever, greatly increases the heart rate, sometimes to double the normal rate. Decreased temperature greatly decreases heart rate, which may fall to as low as a few beats per minute when a person is near death from hypothermia in the body temperature range of 60° to 70°F. These effects presumably result from the fact that heat increases the permeability of the cardiac muscle membrane to ions that control heart rate, resulting in acceleration of the self-excitation process.

Contractile strength of the heart often is enhanced temporarily by a moderate increase in temperature, such as that which occurs during body exercise, but prolonged elevation of temperature exhausts the metabolic systems of the heart and eventually causes weakness. Therefore, optimal function of the heart depends greatly on proper control of body temperature by the temperature control mechanisms explained in Chapter 74.

INCREASING THE ARTERIAL PRESSURE LOAD (UP TO A LIMIT) DOES NOT DECREASE THE CARDIAC OUTPUT

Note in **Figure 9-15** that increasing the arterial pressure in the aorta does not decrease the cardiac output until the

mean arterial pressure rises above about 160 mm Hg. In other words, during normal function of the heart at normal systolic arterial pressures (80 to 140 mm Hg), the cardiac output is determined almost entirely by the ease of blood flow through the body's tissues, which in turn controls *venous return* of blood to the heart. This mechanism is the principal subject of Chapter 20.

Bibliography

Bers DM, Shannon TR: Calcium movements inside the sarcoplasmic reticulum of cardiac myocytes. J Mol Cell Cardiol 58:59, 2013.

Chantler PD, Lakatta EG, Najjar SS: Arterial-ventricular coupling: mechanistic insights into cardiovascular performance at rest and during exercise. J Appl Physiol 105:1342, 2008.

Cingolani HE, Pérez NG, Cingolani OH, Ennis IL: The Anrep effect: 100 years later. Am J Physiol Heart Circ Physiol 304:H175, 2013.

Couchonnal LF, Anderson ME: The role of calmodulin kinase II in myocardial physiology and disease. Physiology (Bethesda) 23:151, 2008.

Doenst T, Nguyen TD, Abel ED: Cardiac metabolism in heart failure: implications beyond ATP production. Circ Res 113:709, 2013.

Eisner D, Caldwell J, Trafford A: Sarcoplasmic reticulum Ca-ATPase and heart failure 20 years later. Circ Res 113:958, 2013.

Guyton AC, Jones CE, Coleman TG: Circulatory Physiology: Cardiac Output and Its Regulation, 2nd ed. Philadelphia: WB Saunders, 1973.

Ibrahim M, Gorelik J, Yacoub MH, Terracciano CM: The structure and function of cardiac t-tubules in health and disease. Proc Biol Sci 278:2714, 2011.

Kho C, Lee A, Hajjar RJ: Altered sarcoplasmic reticulum calcium cycling—targets for heart failure therapy. Nat Rev Cardiol 9:717, 2012.

Korzick DH: From syncytium to regulated pump: a cardiac muscle cellular update. Adv Physiol Educ 35:22, 2011.

Luo M, Anderson ME: Mechanisms of altered Ca^{2+} handling in heart failure. Circ Res 113:690, 2013.

Mangoni ME, Nargeot J: Genesis and regulation of the heart automaticity. Physiol Rev 88:919, 2008.

Marks AR: Calcium cycling proteins and heart failure: mechanisms and therapeutics. J Clin Invest 123:46, 2013.

Puglisi JL, Negroni JA, Chen-Izu Y, Bers DM: The force-frequency relationship: insights from mathematical modeling. Adv Physiol Educ 37:28, 2013.

Sarnoff SJ: Myocardial contractility as described by ventricular function curves. Physiol Rev 35:107, 1955.

Solaro RJ, Henze M, Kobayashi T: Integration of troponin I phosphorylation with cardiac regulatory networks. Circ Res 112:355, 2013.

Starling EH: The Linacre Lecture on the Law of the Heart. London: Longmans Green, 1918.

ter Keurs HE: The interaction of Ca^{2+} with sarcomeric proteins: role in function and dysfunction of the heart. Am J Physiol Heart Circ Physiol 302:H38, 2012.
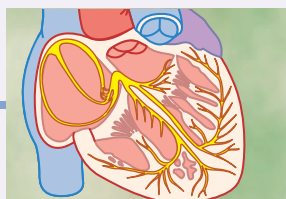
Rhythmical Excitation of the Heart

The human heart has a special system for rhythmic self-excitation and repetitive contraction approximately 100,000 times each day, or 3 billion times in the average human lifetime. This impressive feat is performed by a system that (1) generates rhythmical electrical impulses to initiate rhythmical contraction of the heart muscle and (2) conducts these impulses rapidly through the heart. When this system functions normally, the atria contract about one sixth of a second ahead of ventricular contraction, which allows filling of the ventricles before they pump the blood through the lungs and peripheral circulation. Another special importance of the system is that it allows all portions of the ventricles to contract almost simultaneously, which is essential for the most effective pressure generation in the ventricular chambers.

This rhythmical and conductive system of the heart is susceptible to damage by heart disease, especially by ischemia of the heart tissues resulting from poor coronary blood flow. The effect is often a bizarre heart rhythm or abnormal sequence of contraction of the heart chambers, and the pumping effectiveness of the heart often is affected severely, even to the extent of causing death.

SPECIALIZED EXCITATORY AND CONDUCTIVE SYSTEM OF THE HEART

Figure 10-1 shows the specialized excitatory and conductive system of the heart that controls cardiac contractions. The figure shows the sinus node (also called sinoatrial or S-A node) in which the normal rhythmical impulses are generated; the internodal pathways that conduct impulses from the sinus node to the atrioventricular (A-V) node; the A-V node in which impulses from the atria are delayed before passing into the ventricles; the A-V bundle, which conducts impulses from the atria into the ventricles; and the left and right bundle branches of Purkinje fibers, which conduct the cardiac impulses to all parts of the ventricles.

SINUS (SINOATRIAL) NODE

The sinus node (also called *sinoatrial node*) is a small, flattened, ellipsoid strip of specialized cardiac muscle about 3 millimeters wide, 15 millimeters long, and 1 millimeter thick. It is located in the superior posterolateral wall of the right atrium immediately below and slightly lateral to the opening of the superior vena cava. The fibers of this node have almost no contractile muscle filaments and are each only 3 to 5 micrometers in diameter, in contrast to a diameter of 10 to 15 micrometers for the surrounding atrial muscle fibers. However, the sinus nodal fibers connect directly with the atrial muscle fibers so that any action potential that begins in the sinus node spreads immediately into the atrial muscle wall.

Automatic Electrical Rhythmicity of the Sinus Fibers

Some cardiac fibers have the capability of *self-excitation*, a process that can cause automatic rhythmical discharge and contraction. This capability is especially true of the fibers of the heart's specialized conducting system, including the fibers of the sinus node. For this reason, the sinus node ordinarily controls the rate of beat of the entire heart, as discussed in detail later in this chapter. First, let us describe this automatic rhythmicity.

Mechanism of Sinus Nodal Rhythmicity. **Figure 10-2** shows action potentials recorded from inside a sinus nodal fiber for three heartbeats and, by comparison, a single ventricular muscle fiber action potential. Note that the "resting membrane potential" of the sinus nodal fiber between discharges has a negativity of about −55 to −60 millivolts, in comparison with −85 to −90 millivolts for the ventricular muscle fiber. The cause of this lesser negativity is that the cell membranes of the sinus fibers are naturally leaky to sodium and calcium ions, and positive charges of the entering sodium and calcium ions neutralize some of the intracellular negativity.

Before we attempt to explain the rhythmicity of the sinus nodal fibers, first recall from the discussions of Chapters 5 and 9 that cardiac muscle has three main types of membrane ion channels that play important roles in causing the voltage changes of the action potential. They are (1) *fast sodium channels*, (2) *L-type calcium channels (slow sodium-calcium channels)*, and (3) *potassium channels*.
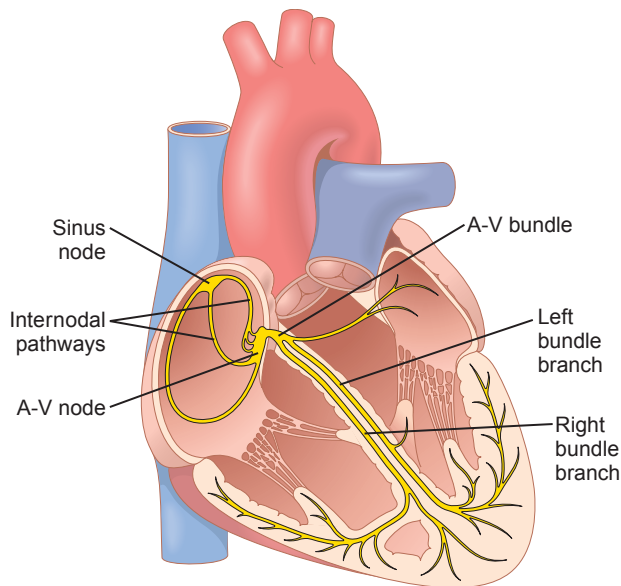
Figure 10-1. Sinus node and the Purkinje system of the heart, showing also the atrioventricular *(A-V)* node, atrial internodal pathways, and ventricular bundle branches.
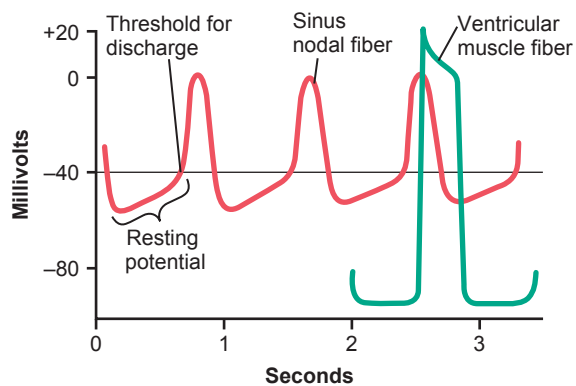

Figure 10-2. Rhythmical discharge of a sinus nodal fiber. Also, the sinus nodal action potential is compared with that of a ventricular muscle fiber.

Opening of the fast sodium channels for a few 10,000ths of a second is responsible for the rapid upstroke spike of the action potential observed in ventricular muscle because of rapid influx of positive sodium ions to the interior of the fiber. Then the "plateau" of the ventricular action potential is caused primarily by slower opening of the slow sodium-calcium channels, which lasts for about 0.3 second. Finally, opening of potassium channels allows diffusion of large amounts of positive potassium ions in the outward direction through the fiber membrane and returns the membrane potential to its resting level.

However, there is a difference in the function of these channels in the sinus nodal fiber because the "resting" potential is much less negative—only −55 millivolts in the nodal fiber instead of the −90 millivolts in the ventricular muscle fiber. At this level of −55 millivolts, the fast sodium channels mainly have already become "inactivated," which means that they have become blocked. The cause of this

is that any time the membrane potential remains less negative than about −55 millivolts for more than a few milliseconds, the inactivation gates on the inside of the cell membrane that close the fast sodium channels become closed and remain so. Therefore, only the slow sodium-calcium channels can open (i.e., can become "activated") and thereby cause the action potential. As a result, the atrial nodal action potential is slower to develop than the action potential of the ventricular muscle. Also, after the action potential does occur, return of the potential to its negative state occurs slowly as well, rather than the abrupt return that occurs for the ventricular fiber.

Self-Excitation of Sinus Nodal Fibers. Because of the high sodium ion concentration in the extracellular fluid outside the nodal fiber, as well as a moderate number of already open sodium channels, positive sodium ions from outside the fibers normally tend to leak to the inside. Therefore, between heartbeats, influx of positively charged sodium ions causes a slow rise in the resting membrane potential in the positive direction. Thus, as shown in **Figure 10-2**, the "resting" potential gradually rises and becomes less negative between each two heartbeats. When the potential reaches a threshold voltage of about −40 millivolts, the L-type calcium channels become "activated," thus causing the action potential. Therefore, basically, the inherent leakiness of the sinus nodal fibers to sodium and calcium ions causes their self-excitation.

Why does this leakiness to sodium and calcium ions not cause the sinus nodal fibers to remain depolarized all the time? Two events occur during the course of the action potential to prevent such a constant state of depolarization. First, the L-type calcium channels become inactivated (i.e., they close) within about 100 to 150 milliseconds after opening, and second, at about the same time, greatly increased numbers of potassium channels open. Therefore, influx of positive calcium and sodium ions through the L-type calcium channels ceases, while at the same time large quantities of positive potassium ions diffuse out of the fiber. Both of these effects reduce the intracellular potential back to its negative resting level and therefore terminate the action potential. Furthermore, the potassium channels remain open for another few tenths of a second, temporarily continuing movement of positive charges out of the cell, with resultant excess negativity inside the fiber; this process is called *hyperpolarization.* The hyperpolarization state initially carries the "resting" membrane potential down to about −55 to −60 millivolts at the termination of the action potential.

Why is this new state of hyperpolarization not maintained forever? The reason is that during the next few tenths of a second after the action potential is over, progressively more and more potassium channels close. The inward-leaking sodium and calcium ions once again overbalance the outward flux of potassium ions, which causes the "resting" potential to drift upward once more, finally reaching the threshold level for discharge at a potential of

about −40 millivolts. Then the entire process begins again: self-excitation to cause the action potential, recovery from the action potential, hyperpolarization after the action potential is over, drift of the "resting" potential to threshold, and finally re-excitation to elicit another cycle. This process continues throughout a person's life.

INTERNODAL AND INTERATRIAL PATHWAYS TRANSMIT CARDIAC IMPULSES THROUGH THE ATRIA

The ends of the sinus nodal fibers connect directly with surrounding atrial muscle fibers. Therefore, action potentials originating in the sinus node travel outward into these atrial muscle fibers. In this way, the action potential spreads through the entire atrial muscle mass and, eventually, to the A-V node. The velocity of conduction in most atrial muscle is about 0.3 m/sec, but conduction is more rapid, about 1 m/sec, in several small bands of atrial fibers. One of these bands, called the *anterior interatrial band,* passes through the anterior walls of the atria to the left atrium. In addition, three other small bands curve through the anterior, lateral, and posterior atrial walls and terminate in the A-V node; shown in **Figures 10-1** and **10-3**, these are called, respectively, the *anterior, middle,* and *posterior internodal pathways.* The cause of more rapid velocity of conduction in these bands is the presence of specialized conduction fibers. These fibers are similar to even more rapidly conducting "Purkinje fibers" of the ventricles, which are discussed as follows.
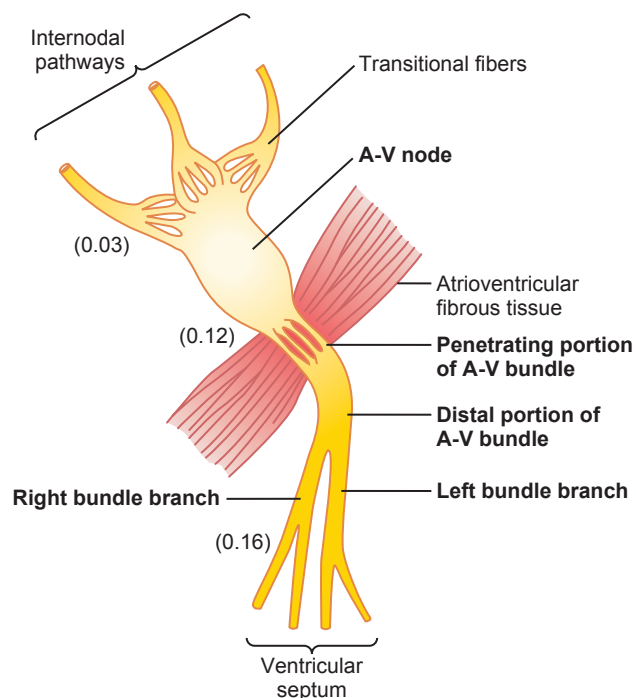

Figure 10-3. Organization of the atrioventricular (A-V) node. The numbers represent the interval of time from the origin of the impulse in the sinus node. The values have been extrapolated to human beings.

THE ATRIOVENTRICULAR NODE DELAYS IMPULSE CONDUCTION FROM THE ATRIA TO THE VENTRICLES

The atrial conductive system is organized so that the cardiac impulse does not travel from the atria into the ventricles too rapidly; this delay allows time for the atria to empty their blood into the ventricles before ventricular contraction begins. It is primarily the A-V node and its adjacent conductive fibers that delay this transmission into the ventricles.

The A-V node is located in the posterior wall of the right atrium immediately behind the tricuspid valve, as shown in **Figure 10-1**. **Figure 10-3** shows diagrammatically the different parts of this node, plus its connections with the entering atrial internodal pathway fibers and the exiting A-V bundle. This figure also shows the approximate intervals of time in fractions of a second between the initial onset of the cardiac impulse in the sinus node and its subsequent appearance in the A-V nodal system. Note that the impulse, after traveling through the internodal pathways, reaches the A-V node about 0.03 second after its origin in the sinus node. Then there is a delay of another 0.09 second in the A-V node itself before the impulse enters the penetrating portion of the A-V bundle, where it passes into the ventricles. A final delay of another 0.04 second occurs mainly in this penetrating A-V bundle, which is composed of multiple small fascicles passing through the fibrous tissue separating the atria from the ventricles.

Thus, the total delay in the A-V nodal and A-V bundle system is about 0.13 second. This delay, in addition to the initial conduction delay of 0.03 second from the sinus node to the A-V node, makes a total delay of 0.16 second before the excitatory signal finally reaches the contracting muscle of the ventricles.

Cause of the Slow Conduction. The slow conduction in the transitional, nodal, and penetrating A-V bundle fibers is caused mainly by diminished numbers of gap junctions between successive cells in the conducting pathways, so there is great resistance to conduction of excitatory ions from one conducting fiber to the next. Therefore, it is easy to see why each succeeding cell is slow to be excited.

RAPID TRANSMISSION IN THE VENTRICULAR PURKINJE SYSTEM

Special Purkinje fibers lead from the A-V node through the A-V bundle into the ventricles. Except for the initial portion of these fibers where they penetrate the A-V fibrous barrier, they have functional characteristics that are quite the opposite of those of the A-V nodal fibers. They are very large fibers, even larger than the normal ventricular muscle fibers, and they transmit action potentials at a velocity of 1.5 to 4.0 m/sec, a velocity about six

times that in the usual ventricular muscle and 150 times that in some of the A-V nodal fibers. This velocity allows almost instantaneous transmission of the cardiac impulse throughout the entire remainder of the ventricular muscle.

The rapid transmission of action potentials by Purkinje fibers is believed to be caused by a very high level of permeability of the gap junctions at the intercalated discs between the successive cells that make up the Purkinje fibers. Therefore, ions are transmitted easily from one cell to the next, thus enhancing the velocity of transmission. The Purkinje fibers also have very few myofibrils, which means that they contract little or not at all during the course of impulse transmission.

One-Way Conduction Through the A-V Bundle. A special characteristic of the A-V bundle is the inability, except in abnormal states, of action potentials to travel backward from the ventricles to the atria. This characteristic prevents re-entry of cardiac impulses by this route from the ventricles to the atria, allowing only forward conduction from the atria to the ventricles.

Furthermore, it should be recalled that everywhere, except at the A-V bundle, the atrial muscle is separated from the ventricular muscle by a continuous fibrous barrier, a portion of which is shown in **Figure 10-3**. This barrier normally acts as an insulator to prevent passage of the cardiac impulse between atrial and ventricular muscle through any other route besides forward conduction through the A-V bundle. (In rare instances, an abnormal muscle bridge does penetrate the fibrous barrier elsewhere besides at the A-V bundle. Under such conditions, the cardiac impulse can re-enter the atria from the ventricles and cause serious cardiac arrhythmias.)

Distribution of the Purkinje Fibers in the Ventricles— The Left and Right Bundle Branches. After penetrating the fibrous tissue between the atrial and ventricular muscle, the distal portion of the A-V bundle passes downward in the ventricular septum for 5 to 15 millimeters toward the apex of the heart, as shown in **Figures 10-1** and **10-3**. Then the bundle divides into left and right bundle branches that lie beneath the endocardium on the two respective sides of the ventricular septum. Each branch spreads downward toward the apex of the ventricle, progressively dividing into smaller branches. These branches in turn course sidewise around each ventricular chamber and back toward the base of the heart. The ends of the Purkinje fibers penetrate about one third of the way into the muscle mass and finally become continuous with the cardiac muscle fibers.

The total elapsed time averages only 0.03 second from the time the cardiac impulse enters the bundle branches in the ventricular septum until it reaches the terminations of the Purkinje fibers. Therefore, once the cardiac impulse enters the ventricular Purkinje conductive system, it spreads almost immediately to the entire ventricular muscle mass.

TRANSMISSION OF THE CARDIAC IMPULSE IN THE VENTRICULAR MUSCLE

Once the impulse reaches the ends of the Purkinje fibers, it is transmitted through the ventricular muscle mass by the ventricular muscle fibers themselves. The velocity of transmission is now only 0.3 to 0.5 m/sec, one sixth that in the Purkinje fibers.

The cardiac muscle wraps around the heart in a double spiral, with fibrous septa between the spiraling layers; therefore, the cardiac impulse does not necessarily travel directly outward toward the surface of the heart but instead angulates toward the surface along the directions of the spirals. Because of this angulation, transmission from the endocardial surface to the epicardial surface of the ventricle requires as much as another 0.03 second, approximately equal to the time required for transmission through the entire ventricular portion of the Purkinje system. Thus, the total time for transmission of the cardiac impulse from the initial bundle branches to the last of the ventricular muscle fibers in the normal heart is about 0.06 second.

SUMMARY OF THE SPREAD OF THE CARDIAC IMPULSE THROUGH THE HEART

Figure 10-4 summarizes transmission of the cardiac impulse through the human heart. The numbers on the figure represent the intervals of time, in fractions of a second, that lapse between the origin of the cardiac impulse in the sinus node and its appearance at each respective point in the heart. Note that the impulse spreads at moderate velocity through the atria but is delayed more than 0.1 second in the A-V nodal region before appearing in the ventricular septal A-V bundle. Once it has entered this bundle, it spreads very rapidly through the Purkinje fibers to the entire endocardial surfaces of the ventricles. Then the impulse once again spreads slightly less rapidly through the ventricular muscle to the epicardial surfaces.

It is important that the student learn in detail the course of the cardiac impulse through the heart and the precise times of its appearance in each separate part of the heart; a thorough quantitative knowledge of this process is essential to the understanding of electrocardiography, which is discussed in Chapters 11 through 13.

CONTROL OF EXCITATION AND CONDUCTION IN THE HEART

THE SINUS NODE IS THE NORMAL PACEMAKER OF THE HEART

In the discussion thus far of the genesis and transmission of the cardiac impulse through the heart, we have noted that the impulse normally arises in the sinus node. In some abnormal conditions, this is not the case. Other
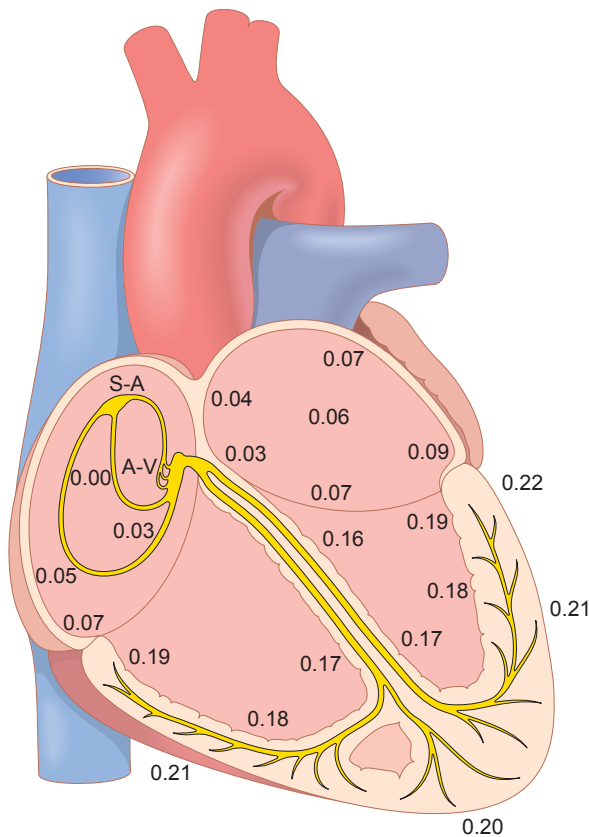
Figure 10-4. Transmission of the cardiac impulse through the heart, showing the time of appearance (in fractions of a second after initial appearance at the sinoatrial node) in different parts of the heart. A-V, atrioventricular; S-A, sinoatrial.

parts of the heart can also exhibit intrinsic rhythmical excitation in the same way that the sinus nodal fibers do; this capability is particularly true of the A-V nodal and Purkinje fibers.

The A-V nodal fibers, when not stimulated from some outside source, discharge at an intrinsic rhythmical rate of 40 to 60 times per minute, and the Purkinje fibers discharge at a rate somewhere between 15 and 40 times per minute. These rates are in contrast to the normal rate of the sinus node of 70 to 80 times per minute.

Why then does the sinus node rather than the A-V node or the Purkinje fibers control the heart's rhythmicity? The answer derives from the fact that the discharge rate of the sinus node is considerably faster than the natural self-excitatory discharge rate of either the A-V node or the Purkinje fibers. Each time the sinus node discharges, its impulse is conducted into both the A-V node and the Purkinje fibers, also discharging their excitable membranes. However, the sinus node discharges again before either the A-V node or the Purkinje fibers can reach their own thresholds for self-excitation. Therefore, the new impulse from the sinus node discharges both the A-V node and the Purkinje fibers before self-excitation can occur in either of these sites.

Thus, the sinus node controls the beat of the heart because its rate of rhythmical discharge is faster than that

of any other part of the heart. Therefore, the sinus node is almost always the pacemaker of the normal heart.

Abnormal Pacemakers—"Ectopic" Pacemaker. Occasionally some other part of the heart develops a rhythmical discharge rate that is more rapid than that of the sinus node. For instance, this development sometimes occurs in the A-V node or in the Purkinje fibers when one of these becomes abnormal. In either case, the pacemaker of the heart shifts from the sinus node to the A-V node or to the excited Purkinje fibers. Under rarer conditions, a place in the atrial or ventricular muscle develops excessive excitability and becomes the pacemaker.

A pacemaker elsewhere than the sinus node is called an *"ectopic" pacemaker*. An ectopic pacemaker causes an abnormal sequence of contraction of the different parts of the heart and can cause significant debility of heart pumping.

Another cause of shift of the pacemaker is blockage of transmission of the cardiac impulse from the sinus node to the other parts of the heart. The new pacemaker then occurs most frequently at the A-V node or in the penetrating portion of the A-V bundle on the way to the ventricles.

When A-V block occurs—that is, when the cardiac impulse fails to pass from the atria into the ventricles through the A-V nodal and bundle system—the atria continue to beat at the normal rate of rhythm of the sinus node, while a new pacemaker usually develops in the Purkinje system of the ventricles and drives the ventricular muscle at a new rate somewhere between 15 and 40 beats per minute. After sudden A-V bundle block, the Purkinje system does not begin to emit its intrinsic rhythmical impulses until 5 to 20 seconds later because, before the blockage, the Purkinje fibers had been "overdriven" by the rapid sinus impulses and, consequently, are in a suppressed state. During these 5 to 20 seconds, the ventricles fail to pump blood, and the person faints after the first 4 to 5 seconds because of lack of blood flow to the brain. This delayed pickup of the heartbeat is called *Stokes-Adams syndrome*. If the delay period is too long, it can lead to death.

ROLE OF THE PURKINJE SYSTEM IN CAUSING SYNCHRONOUS CONTRACTION OF THE VENTRICULAR MUSCLE

The rapid conduction of the Purkinje system normally permits the cardiac impulse to arrive at almost all portions of the ventricles within a narrow span of time, exciting the first ventricular muscle fiber only 0.03 to 0.06 second ahead of excitation of the last ventricular muscle fiber. This timing causes all portions of the ventricular muscle in both ventricles to begin contracting at almost the same time and then to continue contracting for about another 0.3 second.

Effective pumping by the two ventricular chambers requires this synchronous type of contraction. If the cardiac impulse should travel through the ventricles slowly, much of the ventricular mass would contract before contraction of the remainder, in which case the overall pumping effect would be greatly depressed. Indeed, in some types of cardiac debilities, several of which are discussed in Chapters 12 and 13, slow transmission does occur, and the pumping effectiveness of the ventricles is decreased as much as 20 to 30 percent.

SYMPATHETIC AND PARASYMPATHETIC NERVES CONTROL HEART RHYTHMICITY AND IMPULSE CONDUCTION BY THE CARDIAC NERVES

The heart is supplied with both sympathetic and parasympathetic nerves, as shown in **Figure 9-13** of Chapter 9. The parasympathetic nerves (the vagi) are distributed mainly to the S-A and A-V nodes, to a lesser extent to the muscle of the two atria, and very little directly to the ventricular muscle. The sympathetic nerves, conversely, are distributed to all parts of the heart, with strong representation to the ventricular muscle, as well as to all the other areas.

Parasympathetic (Vagal) Stimulation Slows the Cardiac Rhythm and Conduction. Stimulation of the parasympathetic nerves to the heart (the vagi) causes the hormone *acetylcholine* to be released at the vagal endings. This hormone has two major effects on the heart. First, it decreases the rate of rhythm of the sinus node, and second, it decreases the excitability of the A-V junctional fibers between the atrial musculature and the A-V node, thereby slowing transmission of the cardiac impulse into the ventricles.

Weak to moderate vagal stimulation slows the rate of heart pumping, often to as little as one-half normal. Furthermore, strong stimulation of the vagi can stop completely the rhythmical excitation by the sinus node or block completely transmission of the cardiac impulse from the atria into the ventricles through the A-V node. In either case, rhythmical excitatory signals are no longer transmitted into the ventricles. The ventricles may stop beating for 5 to 20 seconds, but then some small area in the Purkinje fibers, usually in the ventricular septal portion of the A-V bundle, develops a rhythm of its own and causes ventricular contraction at a rate of 15 to 40 beats per minute. This phenomenon is called *ventricular escape.*

Mechanism of the Vagal Effects. The acetylcholine released at the vagal nerve endings greatly increases the permeability of the fiber membranes to potassium ions, which allows rapid leakage of potassium out of the conductive fibers. This process causes increased negativity inside the fibers, an effect called *hyperpolarization,* which makes this excitable tissue much less excitable, as explained in Chapter 5.

In the sinus node, the state of hyperpolarization makes the "resting" membrane potential of the sinus nodal fibers considerably more negative than usual, that is, −65 to −75 millivolts rather than the normal level of −55 to −60 millivolts. Therefore, the initial rise of the sinus nodal membrane potential caused by inward sodium and calcium leakage requires much longer to reach the threshold potential for excitation. This requirement greatly slows the rate of rhythmicity of these nodal fibers. If the vagal stimulation is strong enough, it is possible to stop entirely the rhythmical self-excitation of this node.

In the A-V node, a state of hyperpolarization caused by vagal stimulation makes it difficult for the small atrial fibers entering the node to generate enough electricity to excite the nodal fibers. Therefore, the safety factor for transmission of the cardiac impulse through the transitional fibers into the A-V nodal fibers decreases. A moderate decrease simply delays conduction of the impulse, but a large decrease blocks conduction entirely.

Sympathetic Stimulation Increases the Cardiac Rhythm and Conduction. Sympathetic stimulation causes essentially the opposite effects on the heart to those caused by vagal stimulation, as follows: First, it increases the rate of sinus nodal discharge. Second, it increases the rate of conduction, as well as the level of excitability in all portions of the heart. Third, it increases greatly the force of contraction of all the cardiac musculature, both atrial and ventricular, as discussed in Chapter 9.

In short, sympathetic stimulation increases the overall activity of the heart. Maximal stimulation can almost triple the heartbeat frequency and can increase the strength of heart contraction as much as twofold.

Mechanism of the Sympathetic Effect. Stimulation of the sympathetic nerves releases the hormone *norepinephrine* at the sympathetic nerve endings. Norepinephrine in turn stimulates *beta-1 adrenergic receptors*, which mediate the effects on heart rate. The precise mechanism by which beta-1 adrenergic stimulation acts on cardiac muscle fibers is somewhat unclear, but the belief is that it increases the permeability of the fiber membrane to sodium and calcium ions. In the sinus node, an increase of sodium-calcium permeability causes a more positive resting potential and also causes an increased rate of upward drift of the diastolic membrane potential toward the threshold level for self-excitation, thus accelerating self-excitation and, therefore, increasing the heart rate.

In the A-V node and A-V bundles, increased sodium-calcium permeability makes it easier for the action potential to excite each succeeding portion of the conducting

fiber bundles, thereby decreasing the conduction time from the atria to the ventricles.

The increase in permeability to calcium ions is at least partially responsible for the increase in contractile strength of the cardiac muscle under the influence of sympathetic stimulation, because calcium ions play a powerful role in exciting the contractile process of the myofibrils.

Bibliography

Anderson RH, Boyett MR, Dobrzynski H, Moorman AF: The anatomy of the conduction system: implications for the clinical cardiologist. J Cardiovasc Transl Res 6:187, 2013.

Barbuti A, DiFrancesco D: Control of cardiac rate by "funny" channels in health and disease. Ann N Y Acad Sci 1123:213, 2008.

DiFrancesco D: The role of the funny current in pacemaker activity. Circ Res 106:434, 2010.

Dobrzynski H, Boyett MR, Anderson RH: New insights into pacemaker activity: promoting understanding of sick sinus syndrome. Circulation 115:1921, 2007.

Fedorov VV, Glukhov AV, Chang R: Conduction barriers and pathways of the sinoatrial pacemaker complex: their role in normal rhythm and atrial arrhythmias. Am J Physiol Heart Circ Physiol 302:H1773, 2012.

Kléber AG, Rudy Y: Basic mechanisms of cardiac impulse propagation and associated arrhythmias. Physiol Rev 84:431, 2004.

Leclercq C, Hare JM: Ventricular resynchronization: current state of the art. Circulation 109:296, 2004.

Mangoni ME, Nargeot J: Genesis and regulation of the heart automaticity. Physiol Rev 88:919, 2008.

Monfredi O, Maltsev VA, Lakatta EG: Modern concepts concerning the origin of the heartbeat. Physiology (Bethesda) 28:74, 2013.

Munshi NV: Gene regulatory networks in cardiac conduction system development. Circ Res 110:1525, 2012.

Roubille F, Tardif JC: New therapeutic targets in cardiology: heart failure and arrhythmia: HCN channels. Circulation 127:1986, 2013.

Smaill BH, Zhao J, Trew ML: Three-dimensional impulse propagation in myocardium: arrhythmogenic mechanisms at the tissue level. Circ Res 112:834, 2013.

Wickramasinghe SR, Patel VV: Local innervation and atrial fibrillation. Circulation 128:1566, 2013.