CHAPTER

23

The Cardiac Pump

It is nearly impossible to contemplate the pumping action of the heart without being struck by its simplicity of design, its wide range of activity and functional capacity, and the staggering amount of work it performs over an individual's lifetime. A useful way to understand how the heart accomplishes its important task is to consider the relationships between the structure and function of its components.

■ *Structure of the Heart in Relation to Function*

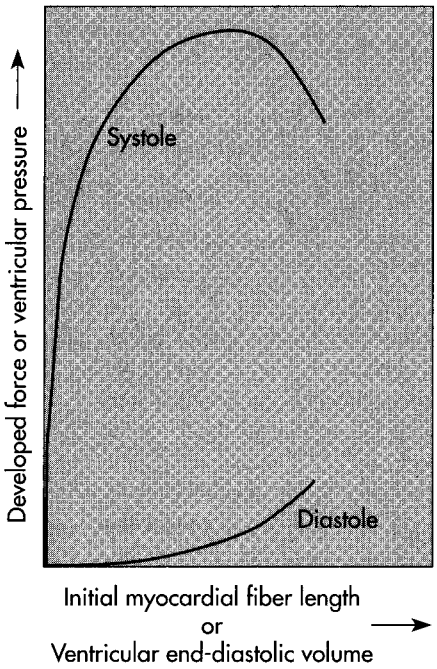
■ *The Myocardial Cell*

A number of important morphologic and functional differences exist between myocardial and skeletal muscle cells. Despite these differences, the contractile elements within the two types of cells are actually quite similar. Each skeletal and cardiac muscle cell is composed of **sarcomeres** (from Z line to Z line) containing thick filaments and thin filaments. Thick filaments are composed of myosin (in the band), while thin filaments contain actin. The thin filaments extend from the point at which they are anchored to the Z line (through the I band) to interdigitate with the thick filaments. As in skeletal muscle, shortening of cardiac muscle filaments occurs by the sliding filament mechanism. Actin filaments slide along adjacent myosin filaments by cycling of the intervening cross-bridges and thereby bring the Z lines closer together (see Chapter 17).

Skeletal and cardiac muscle also show similar length-force relationships. The developed force is maximal when the muscle begins its contractions at resting sarcomere lengths of 2 to 2.4 μm. At this resting length, there is optimal overlap of thick and thin filaments, and the number of cross-bridge attachments is maximal. Stretch of the myocardium and increases in load enhance the affinity of troponin C for Ca^{++}. It is still not known how an increase in sarcomere length increases the sensitivity of the myofilaments to calcium. One explanation is that the thick and thin filaments are brought closer to each other as the diameter of the muscle fiber narrows during stretch. When sarcomeres are stretched beyond the optimal length, the developed force of cardiac muscle drops to less than maximal value owing to less overlap of the filaments and hence less cycling of the cross-bridges. At resting sarcomere lengths shorter than optimal value, the thin filaments overlap, which diminishes contractile force.

In general, the fiber length-force relationship for the papillary muscle also holds true for fibers in the intact heart. This relationship may be expressed graphically, as in Fig. 23-1, by substituting ventricular systolic pressure for force, and end-diastolic ventricular volume for myocardial resting fiber (and hence sarcomere) length. The lower curve in Fig. 23-1 represents the increment in pressure produced by each increment in volume when the heart is in diastole. The upper curve represents the peak pressure developed by the ventricle during systole at each degree of filling, and illustrates the **Frank-Starling relationship** (also called *Starling's law of the heart*) of initial myocardial fiber length (or initial volume) to force (or pressure) development by the ventricle.

Note that the pressure-volume curve in diastole is initially quite flat, which indicates that large increases in volume can be accommodated with only small increases in pressure. In contrast, systolic pressure development is considerable at the lower filling pressures. However, the ventricle becomes much less distensible with greater filling, as evidenced by the sharp rise of the diastolic curve at large intraventricular volumes. In the normal intact heart, peak force may be attained at a filling pressure of about 12 mm Hg. At this intraventricular diastolic pressure, which is about the upper limit observed in the normal heart, the sarcomere length is 2.2 μm. However, developed force peaks at filling pressures as high as 30 mm Hg in the isolated heart. At even higher diastolic pressures (>50 mm Hg), the sarcomere length is not greater than 2.6 μm. This ability to resist stretch of the myocardium at high filling pressures probably resides in the noncontractile constituents of the heart tissue (connective tissue) and may serve as a safety factor against overloading of the heart in diastole. Usually, ventricular diastolic pressure is about 0 to 7 mm Hg, and the average



■ **Fig. 23-1** Relationship of myocardial resting fiber length (sarcomere length) or end-diastolic volume to developed force or peak systolic ventricular pressure during ventricular contraction in the intact dog heart. (Redrawn from Patterson SW, Piper H, Starling EH: *J Physiol* 48:465, 1914.)

diastolic sarcomere length is about 2.2 μm. Thus, *the normal heart operates on the ascending portion of the Frank-Starling curve* depicted in Fig. 23-1.

If the heart becomes greatly distended with blood during diastole, as may occur in **cardiac failure,** it functions less efficiently. More energy is required (greater wall tension) for the distended heart to eject the same volume of blood per beat than for the normal undilated heart. The less efficient pumping of the distended heart is an example of Laplace's law (see p 431), which states that the tension in the wall of a vessel (in this case the ventricles) equals the transmural pressure (pressure across the wall, or distending pressure) times the radius of the vessel or chamber. The Laplace relationship applies to infinitely thin-walled vessels but can be applied to the heart if correction is made for wall thickness. The equation is $\tau = Pr/w$ where τ = wall stress, P = transmural pressure, r = radius, and w = wall thickness.

■ *The Cardiac Pump*

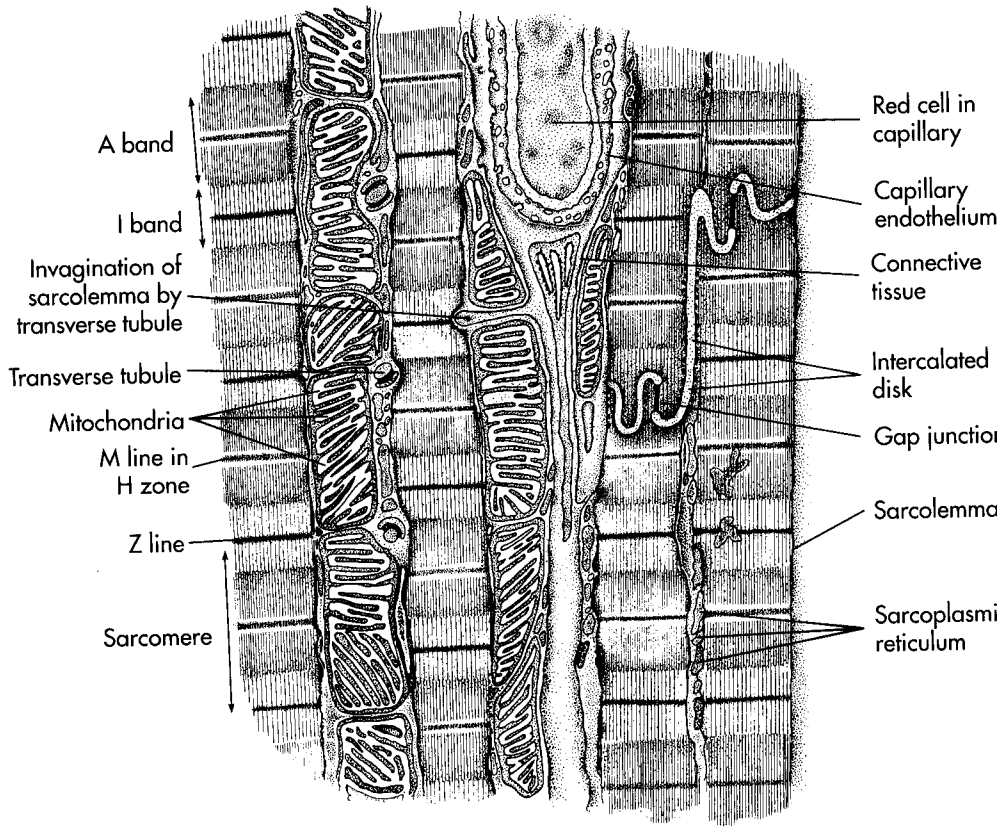
Functional anatomy of cardiac muscle. A striking difference between the appearance of the cardiac and skeletal muscle is the presence of what appears to be a syncytium in cardiac muscle with branching interconnecting fibers (Figs. 23-2 and 23-3). A syncytium is a multinucleated, protoplasmic mass of cells. However, the myocardium is not a true anatomic syncytium because the myocardial fibers are indeed separated from each other. Laterally, the myocardial fibers are separated from adjacent fibers by their respective sarcolemmas, and the end of each fiber is separated from its neighbor by dense structures, **intercalated disks,** that are continuous with the sarcolemma (Figs. 23-2 to 23-4). Nevertheless, *cardiac muscle functions as a syncytium;* that is, a stimulus applied to any one part of the cardiac muscle results in the contraction of the entire muscle. A wave of depolarization followed by contraction of the entire myocardium (an *all-or-none response*) occurs when a suprathreshold stimulus is applied to any one focus.

As the wave of excitation approaches the end of a cardiac cell, the spread of excitation to the next cell depends on the level of the electrical conductance of the boundary between the two cells. **Gap junctions (nexi)** with high conductances are present in the intercalated disks between adjacent cells (Figs. 23-2 to 23-4). These gap junctions, which facilitate the conduction of the cardiac impulse from one cell to the next, are made up of **connexons,** hexagonal structures that connect the cytosol of adjacent cells. Each connexon consists of six polypeptides that surround a core channel approximately 1.6 to 2.0 mm wide. Each channel thus serves as a low-resistance pathway for cell-to-cell conductance (see Chapter 4).

Impulse conduction in cardiac tissues progresses more rapidly in a direction parallel to the long axes of the constituent fibers than in a direction perpendicular to the long axes of those fibers. Gap junctions exist in the borders between myocardial fibers that are in contact with each other longitudinally; they are sparse or absent in the borders between myocardial fibers that lie side by side.

Another difference between cardiac and fast skeletal muscle fibers is in the number of mitochondria (**sarcosomes**) in the two tissues. Fast skeletal muscle is called on for relatively short periods of repetitive or sustained contraction, and can metabolize anaerobically and build up a substantial oxygen debt. Fast skeletal muscle fibers contain relatively few mitochondria. In contrast, cardiac muscle contracts repetitively for a lifetime and requires a continuous supply of oxygen. Cardiac muscle is therefore very rich in mitochondria (Figs. 23-2 to 23-4). The large number of mitochondria—which contain the enzymes necessary for oxidative phosphorylation—allows for the rapid oxidation of substrates with the synthesis of adenosine triphosphate (ATP) that sustains the myocardial energy requirements.

To provide adequate oxygen and substrate for its metabolic machinery, the myocardium is also endowed with a rich capillary supply, about one capillary per fiber. Thus, diffusion distances are short, and oxygen, carbon dioxide, substrates, and waste material can move rapidly between the myocardial cell and capillary. A structure called the **transverse (T) tubular system** within



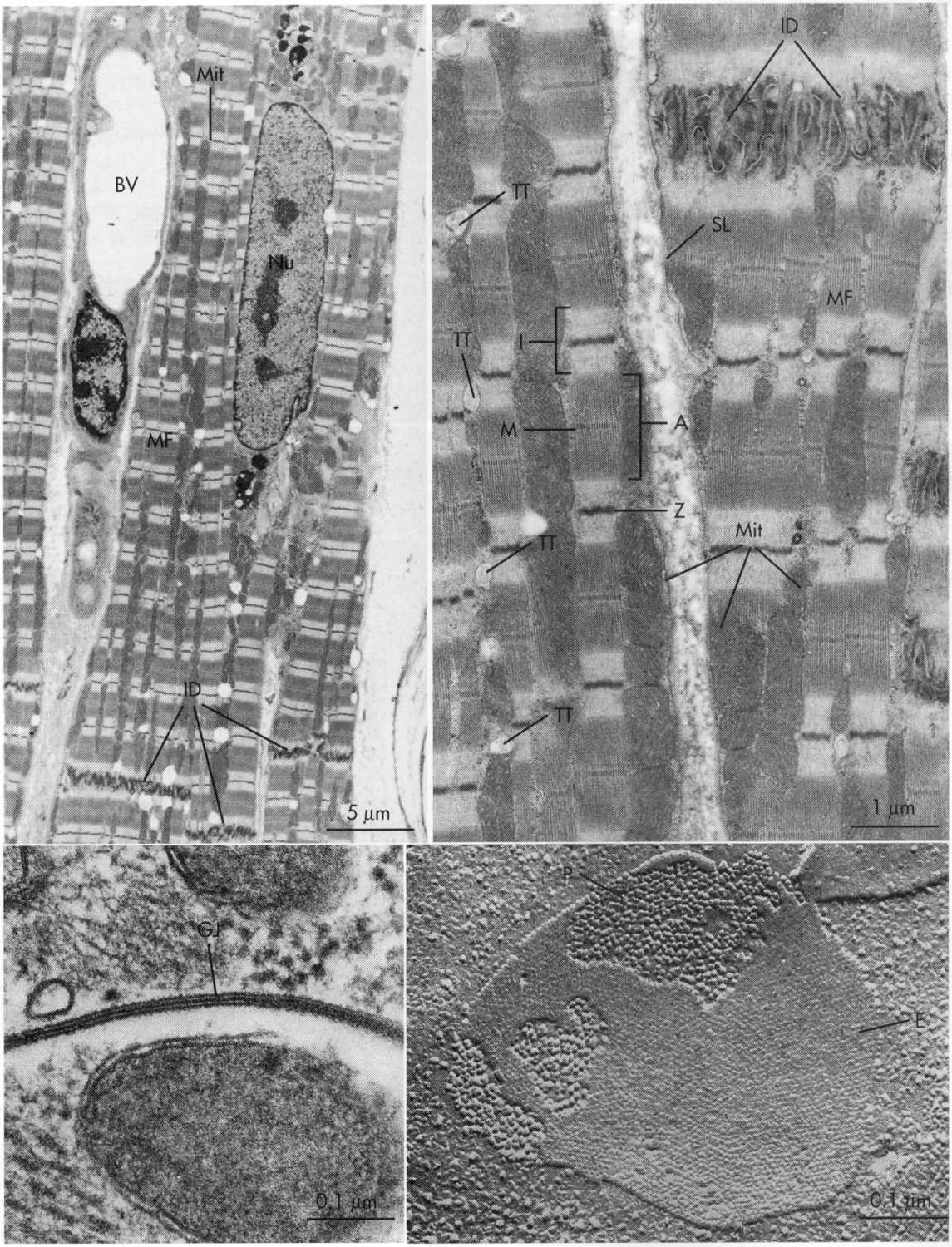
■ **Fig. 23-2** Diagram of an electron micrograph of cardiac muscle showing large numbers of mitochondria and the intercalated disks with nexi (gap junction), transverse tubules, and longitudinal tubules.

myocardial cells participates in this exchange of substances between the capillary blood and the myocardial cells. In electron micrographs of myocardium, the T-tubular system appears as deep invaginations of the sarcolemma into the fiber at the Z lines (Figs. 23-2 to 23-4). The lumina of these T tubules are continuous with the bulk interstitial fluid, and they play a key role in excitation-contraction coupling.

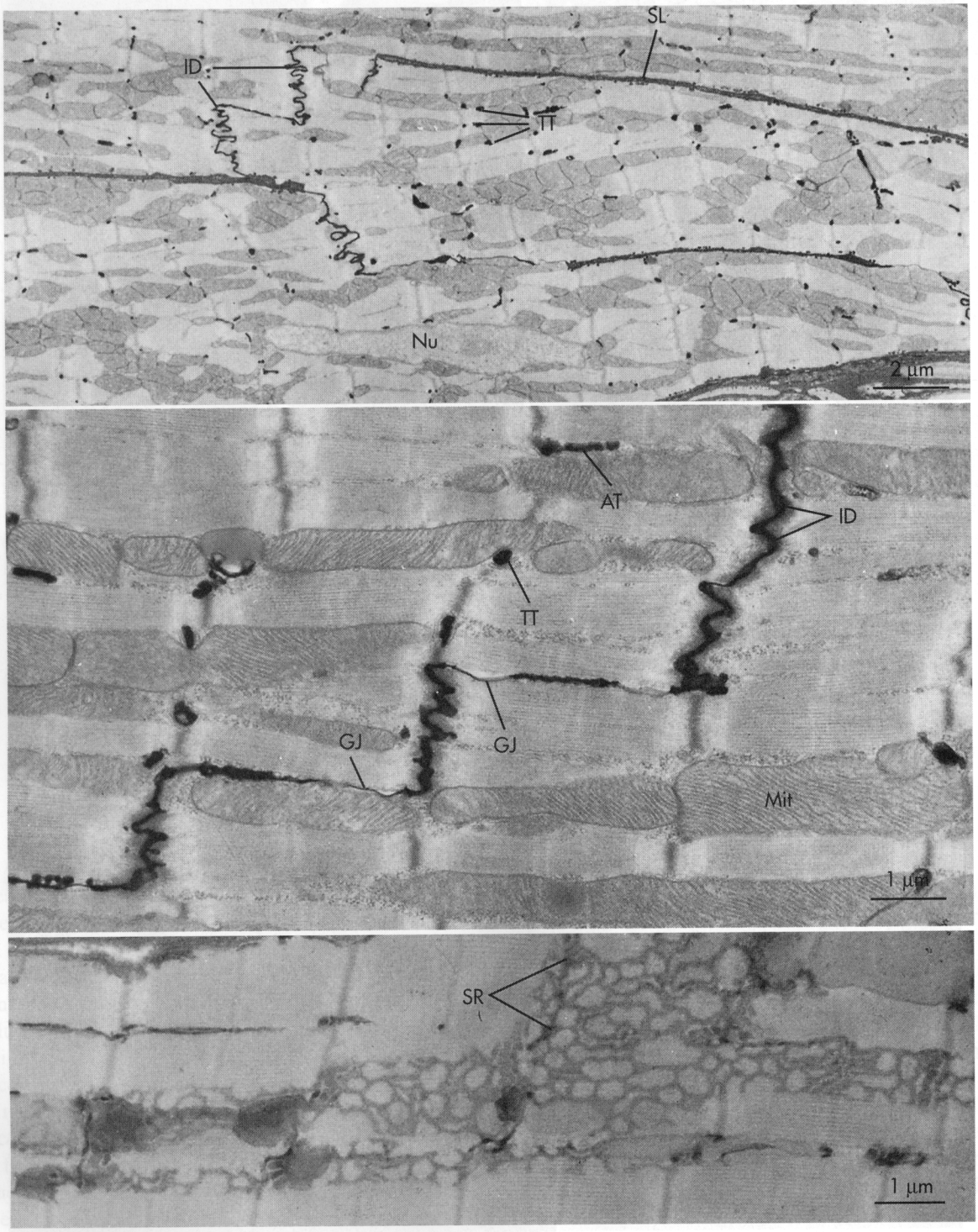
In mammalian ventricular cells, adjacent T tubules are interconnected by longitudinally running or axial tubules, thus forming an extensively interconnected lattice of "intracellular" tubules (Fig. 23-4). This T-tubule system is open to the interstitial fluid, is lined with a basement membrane continuous with that of the surface sarcolemma, and contains micropinocytotic vesicles. Thus, in ventricular cells, the T-tubular system provides the myofibrils and mitochondria with ready access to the interstitial fluid. The T-tubular system is absent or poorly developed in atrial cells of many mammalian hearts.

A network of **sarcoplasmic reticulum** (Fig. 23-4), consisting of small-diameter sarcotubules, is also present surrounding the myofibrils. These sarcotubules are believed to be "closed," because colloidal tracer particles (2 to 10 nm in diameter) do not enter them. They do not contain basement membrane. Flattened elements of the sarcoplasmic reticulum are often found in close proximity to the T-tubular system, as well as to the surface sarcolemma, forming **diads.**

Excitation-contraction coupling. The earliest studies on isolated hearts perfused with isotonic saline solutions indicated that optimal concentrations of Na^+, K^+, and Ca^{++} are necessary for cardiac muscle contraction. Without Na^+, the heart is not excitable and will not beat, because the action potential depends on extracellular Na ions. In contrast, the resting membrane potential is independent of the Na ion gradient across the membrane (see Fig. 22-5). Under normal conditions, the extracellular K^+ concentration is about 4 mM. A reduction in extracellular K^+ has little effect on myocardial excitation and contraction. However, increases in extracellular K^+, if great enough, produce depolarization, loss of excitability of the myocardial cells, and cardiac arrest in diastole. *Ca^{++} is also essential for cardiac contraction.* Removal of Ca^{++} from the extracellular fluid results in decreased contractile force and eventual arrest in diastole. Conversely, an increase in extracellular Ca^{++} enhances contractile force, and very high Ca^{++} concentrations induce cardiac arrest in systole (rigor). *The free intracellular Ca^{++} is the agent responsible for the contractile state of the myocardium.*



■ **Fig. 23-3** **A,** Low-magnification electron micrograph of a monkey heart (ventricle). Typical features of myocardial cells include the elongated nucleus *(Nu)*, striated myofibrils *(MF)* with columns of mitochondria *(Mit)* between the myofibrils, and intercellular junctions (intercalated disks, *ID*). A blood vessel *(BV)* is located between two myocardial cells. **B,** Medium-magnification electron micrograph of monkey ventricular cells showing details of the ultrastructure. The sarcolemma *(SL)* is the boundary of the muscle cells and is thrown into multiple folds where the cells meet at the intercalated disk region *(ID)*. The prominent myofibrils *(MF)* show distinct banding patterns, including the A band *(A),* dark Z lines *(Z),* I band regions *(I),* and M lines *(M)* at the center of each sarcomere unit. Mitochondria *(Mit)* occur either in rows between myofibrils or in masses just underneath the sarcolemma. Regularly spaced transverse tubules *(TT)* appear at the Z-line levels of the myofibrils. **C,** High-magnification electron micrograph of a specialized intercellular junction between two myocardial cells of the mouse. Called a gap junction *(GJ)* or nexus, this attachment consists of very close apposition of the sarcolemmal membranes of the two cells and appears in thin section to consist of seven layers. **D,** Freeze-fracture replica of mouse myocardial gap junction, showing distinct arrays of characteristic intramembranous particles. Large particles *(P)* belong to the inner half of the sarcolemma of one myocardial cell, whereas the "pitted" membrane face *(E)* is formed by the outer half of the sarcolemma of the cell above.

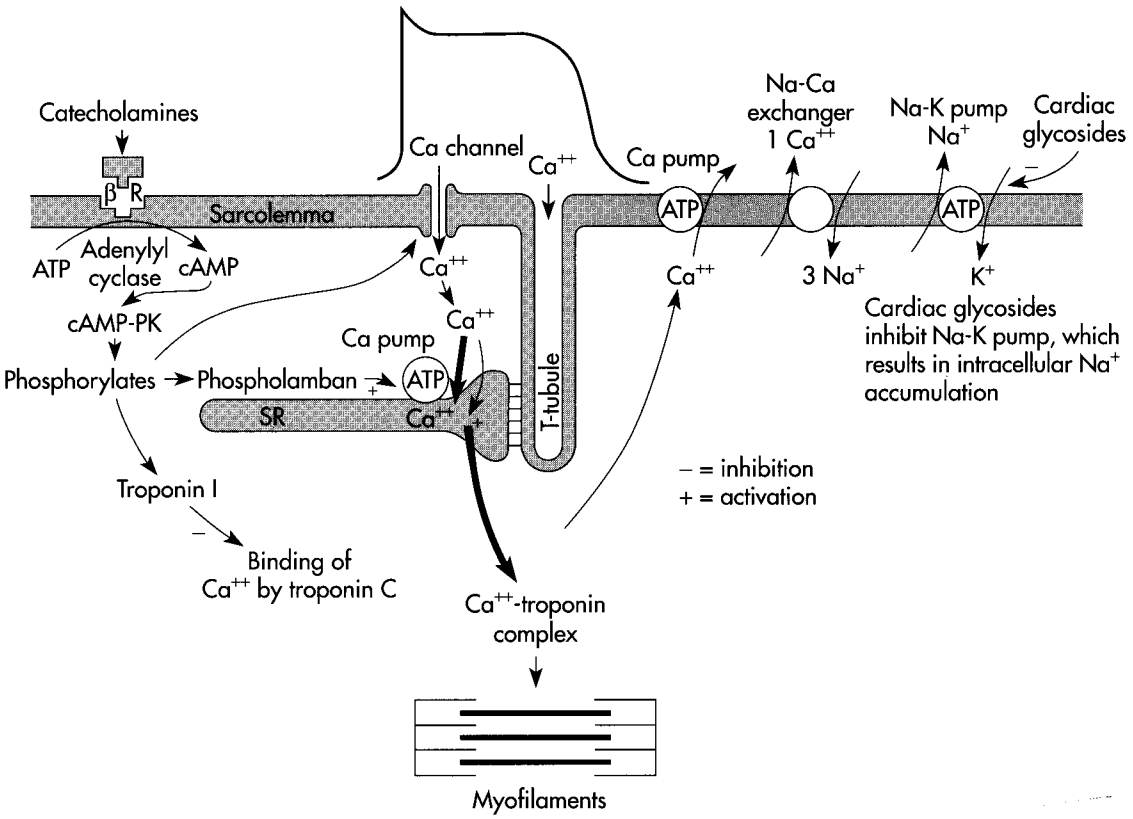


■ **Fig. 23-4** **A,** Low-magnification electron micrograph of the right ventricular wall of a mouse heart. Tissue was fixed in a phosphate-buffered glutaraldehyde solution and postfixed in ferrocyanide-reduced osmium tetroxide. This procedure has resulted in the deposition of electron-opaque precipitate in the extracellular space, thus outlining the sarcolemmal borders *(SL)* of the muscle cells and delineating the intercalated disks *(ID)* and transverse tubules *(TT)*. *Nu,* Nucleus of the myocardial cell. **B,** Mouse cardiac muscle in longitudinal section, treated as in **A.** The path of the extracellular space is traced through the intercalated disk region *(ID),* and sarcolemmal invaginations that are oriented transverse to the cell axis (transverse tubules, *TT*) or parallel to it (axial tubules, *AT*) are clearly identified. Gap junctions *(GJ)* are associated with the intercalated disk. Mitochondria are large and elongated and lie between the myofibrils. **C,** Mouse cardiac muscle. Tissue was treated with ferrocyanide-reduced osmium tetroxide to identify the internal membrane system (sarcoplasmic reticulum, *SR*). Specific staining of the SR reveals its architecture as a complex network of small-diameter tubules that are closely associated with the myofibrils and mitochondria.

Excitation of cardiac muscle starts when a wave of excitation spreads rapidly along the myocardial sarcolemma from cell to cell via gap junctions. Excitation also spreads into the interior of the cells via the T tubules (Figs. 23-2 to 23-4), which invaginate the cardiac fibers at the Z lines. Electrical stimulation at the Z line or the application of ionized Ca to the Z lines in the skinned (sarcolemma removed) cardiac fiber elicits a localized contraction of adjacent myofibrils. During the plateau (phase 2) of the action potential, Ca^{++} permeability of the sarcolemma increases. Ca^{++} flows down its electrochemical gradient and enters the cell through Ca^{++} channels in the sarcolemma and in the invaginations of the sarcolemma, the T tubules (see also Chapters 18 and 22).

Opening of the Ca^{++} channels is believed to be caused by phosphorylation of the channel proteins by a cyclic adenosine monophosphate (cAMP)–dependent protein kinase. The primary source of extracellular Ca^{++} is the interstitial fluid (10^{-3} M Ca^{++}). Some Ca^{++} may also be bound to the sarcolemma and to the **glycocalyx,** a mucopolysaccharide that covers the sarcolemma. The amount of calcium that enters the cell interior from the extracellular space is not sufficient to induce contraction of the myofibrils. Instead, it acts as a trigger (**trigger Ca^{++}**) to release Ca^{++} from the sarcoplasmic reticulum (where the intracellular Ca^{++} is stored) (Fig. 23-5). The concentration of free Ca^{++} in the cytoplasm increases from a resting level of about 10^{-7} M to levels of 10^{-6} to 10^{-5} M during excitation. This Ca^{++} then binds to the protein troponin C. The Ca^{++} -troponin complex interacts with tropomyosin to unblock active sites between the actin and myosin filaments. This unblocking action allows cross-bridge cycling and hence contraction of the myofibrils (see Chapter 18).

Mechanisms that raise the cytosolic Ca^{++} concentration increase the developed force, and those that lower the cystolic Ca^{++} concentration decrease the developed force. For example, catecholamines increase the movement of Ca^{++} into the cell by phosphorylation of the channels via a cAMP-dependent protein kinase (see also Chapters 18 and 22). In addition, catecholamines, like other agonists, enhance myocardial contractile force by increasing the sensitivity of the contractile machinery to Ca^{++}. Increasing the extracellular concentration of Ca^{++} or decreasing the Na^+ gradient across the sarcolemma also results in an increase in the cytosolic concentration of Ca^{++}.



■ **Fig. 23-5** Schematic diagram of the movements of calcium in excitation-contraction coupling in cardiac muscle. The influx of Ca^{++} from the interstitial fluid during excitation triggers the release of Ca^{++} from the saroplasmic reticulum *(SR).* The free cytosolic Ca^{++} activates contraction of the myofilaments (systole). Relaxation (diastole) occurs as a result of uptake of Ca^{++} by the sarcoplasmic reticulum, by extrusion of intracellular Ca^{++} by Na^+-Ca^{++} exchange, and to a limited degree by the Ca pump. *βR,* Beta-adrenergic receptor; *cAMP,* cyclic adenosine monophosphate; *cAMP-PK,* cyclic AMP–dependent protein kinase.

The sodium gradient can be reduced by increasing the intracellular concentration of Na^+ or decreasing the extracellular concentration of Na^+. Cardiac glycosides increase intracellular Na^+ concentration by "poisoning" the Na^+, K^+-ATPase, which results in an accumulation of Na^+ in the cells. The elevated cytosolic Na^+ reverses the direction of the Na,Ca exchanger so that less Ca^{++} is removed from the cell. A lowered extracellular Na^+ concentration causes less Na^+ to enter the cell, and hence less exchange of Na^+ for Ca^{++} (Fig. 23-5).

Developed tension is diminished by a reduction in extracellular Ca^{++} concentration, by an increase in the Na^+ gradient across the sarcolemma, or by administration of a Ca^{++} channel antagonist (channel blocker) that prevents Ca^{++} from entering the myocardial cell (see Fig. 22-11).

A patient in **heart failure** with a dilated heart, low cardiac output, fluid retention, high venous pressure, an enlarged liver, and peripheral edema is often treated with digitalis and a diuretic. The digitalis increases cardiomyocyte intracellular calcium, thereby enhancing contractile force. The diuretic reduces extracellular fluid volume, thereby lessening the volume load (preload) on the heart and reducing venous pressure, liver congestion, and edema.

At the end of systole, the Ca^{++} influx stops, and the sarcoplasmic reticulum is no longer stimulated to release Ca^{++}. In fact, the sarcoplasmic reticulum avidly takes up Ca^{++} by means of an ATP-energized calcium pump. This pump is stimulated by **phospholamban** after the phospholamban is phosphorylated by cAMP-dependent protein kinase. In addition, phosphorylation of troponin I inhibits the Ca^{++} binding to troponin C. This process permits tropomyosin to again block the sites for interaction between the actin and myosin filaments, and relaxation (diastole) occurs (see also Chapters 17 and 18).

Cardiac contraction and relaxation are both accelerated by catecholamines and adenylyl cyclase activation. The resultant increase in cAMP activates the cAMP-dependent protein kinase, which phosphorylates the Ca channel in the sarcolemma. These events cause more Ca^{++} to move into the cell, thereby accelerating contraction. However, these events also accelerate *relaxation* by phosphorylating phospholamban, which enhances Ca^{++} uptake by the sarcoplasmic reticulum, and by phosphorylating troponin I, which inhibits the Ca^{++} binding of troponin C. Thus, the phosphorylations by cAMP-dependent protein kinase serve to increase both the speed of contraction *and* the speed of relaxation.

Mitochondria also take up and release Ca^{++}, but the process is too slow to have an impact on normal excitation-contraction coupling. Only at very high intracellular Ca^{++} levels (pathological states) do the mitochondria take up a significant amount of Ca^{++}.

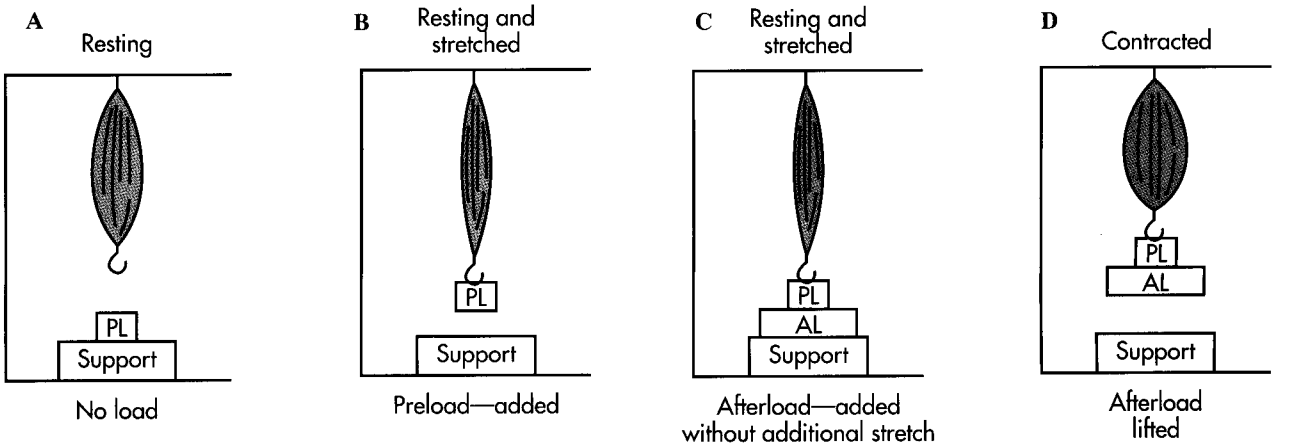
The Ca^{++} that enters the cell to initiate contraction must be removed during diastole. The removal is primarily accomplished by the exchange of 3 Na^+ for 1 Ca^{++} (Fig. 23-5). Ca^{++} is also removed from the cell by an electrogenic pump that uses ATP to transport Ca^{++} across the sarcolemma (Fig. 23-5).

Myocardial contractile machinery and contractility. The sequence of events that occur during the contraction of a preloaded and afterloaded papillary muscle is shown in Fig. 23-6. In Fig. 23-6, *A,* the muscle is relaxed and bears no weight. For the intact left ventricle,* this situation is analogous to the point in the cardiac cycle when the ventricle has relaxed after ejection, the aortic valve is closed, and the mitral valve is about to open (the end of isovolumic relaxation—see p 373 and Fig. 23-10). In Fig. 23-6, *B,* the resting muscle is stretched by a preload, which in the intact heart represents the end of filling of the left ventricle during ventricular diastole (in other words, it represents the **end-diastolic volume**). In Fig. 23-6, *C,* the resting muscle is still stretched by the preload, but a supported afterload has been added without allowing the muscle to be stretched further. In the intact heart, this situation is analogous to the point in the cardiac cycle when ventricular contraction has started and the mitral valve has closed, but the aortic valve has not yet opened because the ventricle has not developed enough intraventricular pressure to open it (isovolumic contraction phase—see p 372 and Fig. 23-10). In Fig. 23-6, *D,* the ventricle has contracted and lifted the afterload. In the intact heart, this situation represents left ventricular ejection into the aorta. During ejection, the afterload is represented by aortic and intraventricular pressures, which are virtually equal to each other.

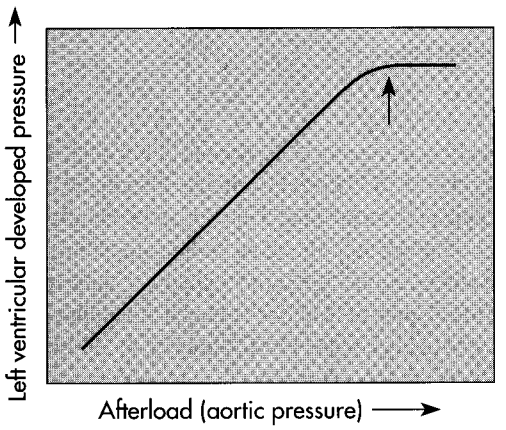
The preload can be increased by greater filling of the left ventricle during diastole (Fig. 23-1). At lower end-diastolic volumes, incremental increases in filling pressure during diastole elicit a greater systolic pressure during the subsequent contraction. Systolic pressure increases until a maximal systolic pressure is reached at the optimal preload (Fig. 23-1). If diastolic filling continues beyond this point, no further increase in developed pressure will occur. At very high filling pressures, peak pressure development in systole is reduced.

At a constant preload, a higher systolic pressure can be reached during ventricular contractions by raising the afterload (e.g., increasing aortic pressure by restricting the runoff of blood to the periphery during diastole). Incremental increases in afterload produce progressively higher peak systolic pressures (Fig. 23-7). If the afterload increases continue, the afterload becomes so great that the ventricle can no longer generate enough force to open the aortic valve (Fig. 23-7). At this point, ventricular sys-

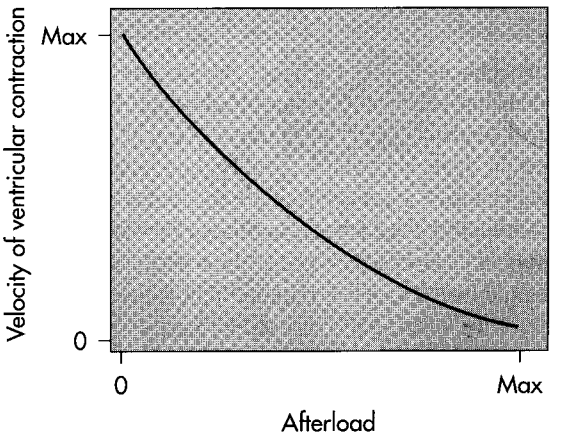
*The left ventricle has been chosen because it supplies the entire body except the lungs, and thus faces the larger afterload. However, the principles of preload and afterload apply equally well to the right ventricle.



■ **Fig. 23-6** Preload and afterload in a papillary muscle. **A,** Resting stage—in the intact heart just before opening of the AV valves. **B,** Preload—in the intact heart at the end of ventricular filling. **C,** Supported preload plus afterload—in the intact heart just before opening of the aortic valve. **D,** Lifting preload plus afterload—in the intact heart ventricular ejection with a decrease in ventricular volume. *PL,* Preload; *AL,* afterload; *PL + AL* = total load.



■ **Fig. 23-7** Effect of increasing afterload on developed pressure at constant preload. At the arrow, maximal developed pressure is reached. Further increments in afterload prevent opening of the aortic valve.



■ **Fig. 23-8** Effect of increasing afterload on the velocity of contraction at constant preload.

tole is totally isometric; there is no ejection of blood, and thus no change in volume of the ventricle during systole. The maximal pressure developed by the left ventricle under these conditions is the maximal isometric force the ventricle is capable of generating at a given preload. At preloads below the optimal filling volume, an increase in preload can yield a greater maximal isometric force (Fig. 23-1).

Force and velocity are functions of the intracellular concentration of free calcium ions. At a constant velocity, force equals the afterload during shortening of the muscle with contraction. *Force and velocity are inversely related. With no load, the velocity of the muscle contraction is maximal, whereas with a maximal load (when contraction can no longer shorten the muscle), velocity is zero* (Fig. 23-8).

Preloads and afterloads depend on certain characteristics of the vascular system and the behavior of the heart. With respect to the vasculature, the degree of venomotor tone and peripheral resistance influence preload and afterload. With respect to the heart, a change in rate or stroke volume can also alter preload and afterload. Hence, cardiac and vascular factors interact to produce effects on preload and afterload (see Chapter 29 for a full explanation).

In contrast to the normal heart, strips of papillary muscle from the terminally failing human heart show no increase in developed force with increases in preload.

If the phospholamban gene is ablated in mice, myocardial contractility is enhanced, as evidenced by increased

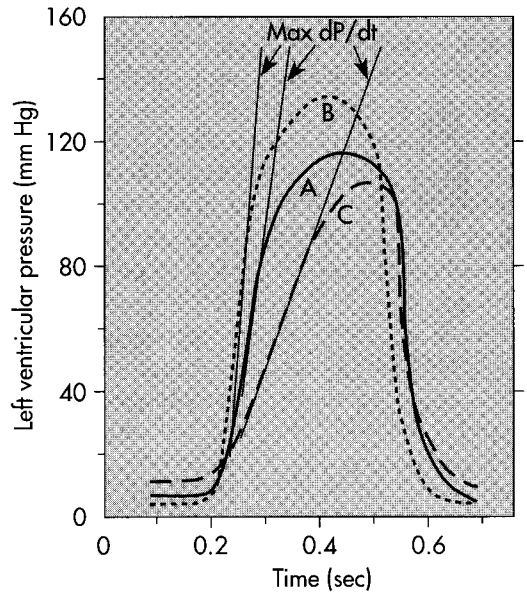
work at a given preload, afterload, and heart rate, and by a greater dP/dt (see below).

Contractility represents the performance of the heart at a given preload and afterload. Contractility is defined as *the change in peak isometric force (isovolumic pressure) at a given initial fiber length (end-diastolic volume).* Contractility can be augmented with certain drugs, such as norepinephrine or digitalis, and with an increase in contraction frequency **(tachycardia).** The increase in contractility **(positive inotropic effect)** produced by any of these interventions is reflected by incremental increases in developed force and velocity of contraction.

In rare instances, patients have accidentally received excessive doses of epinephrine subcutaneously for severe asthmatic attacks. The patients develop marked tachycardia and increases in myocardial contractility, cardiac output, and total peripheral resistance. The result is dangerously high blood pressure. Treatment consists of a tourniquet on the injected limb, with intermittent brief releases of the tourniquet, and the use of adrenergic blocking drugs.

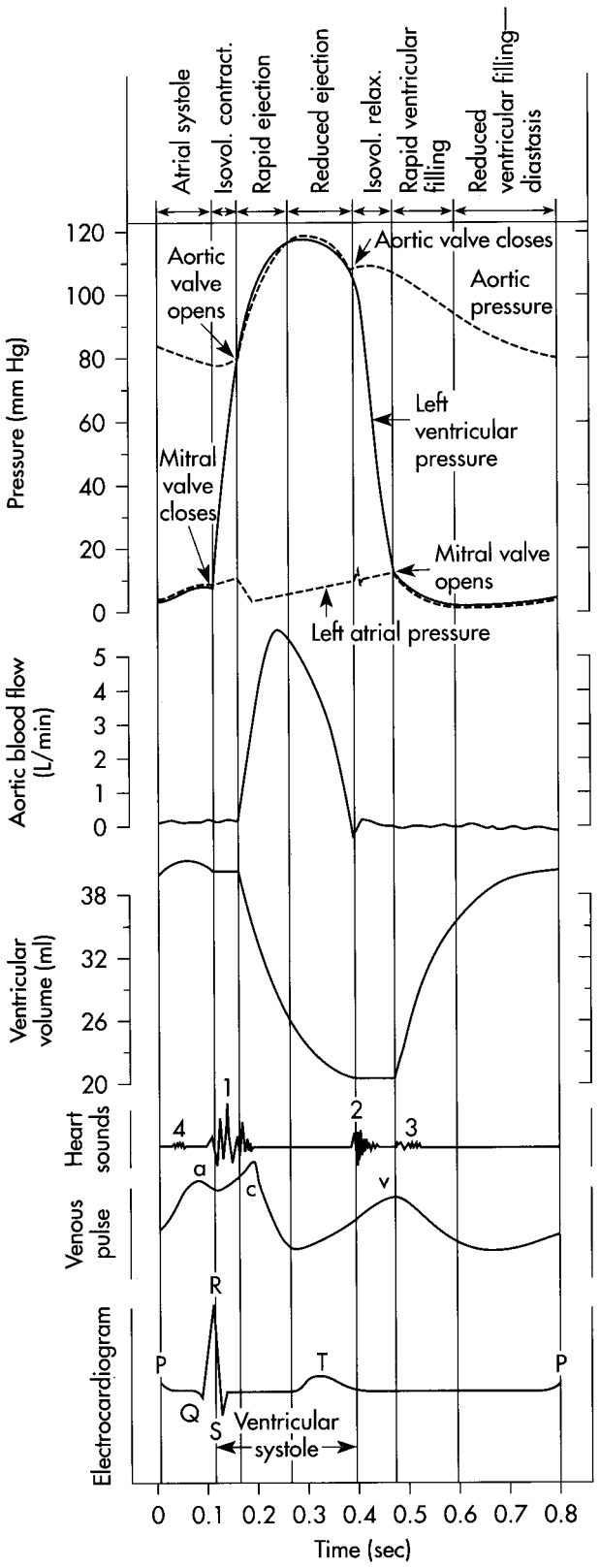
Indices of contractility. A reasonable index of myocardial contractility can be obtained from the contour of ventricular pressure curves (Fig. 23-9). A hypodynamic heart is characterized by an elevated end-diastolic pressure, a slowly rising ventricular pressure, and a somewhat reduced ejection phase (curve *C,* Fig. 23-9). A hyperdynamic heart (such as a heart stimulated by norepinephrine) shows reduced end-diastolic pressure, fast-rising ventricular pressure, and a brief ejection phase (curve *B,* Fig. 23-9). The slope of the ascending limb of the ventricular pressure curve indicates the maximal rate of force development by the ventricle (maximal rate of change in pressure with time—maximal dP/dt, as illustrated by the tangents to the steepest portion of the ascending limbs of the ventricular pressure curves in Fig. 23-9). The slope is maximal during the isovolumic phase of systole (Fig. 23-10). At any given degree of ventricular filling, the slope provides an index of the initial contraction velocity, and hence of contractility.

A similar indication of the contractile state of the myocardium can be obtained from the velocity of blood flow that initially occurs in the ascending aorta during the cardiac cycle (the initial slope of the aortic flow curve) (Fig. 23-10). Also, the **ejection fraction,** which is the ratio of the volume of blood ejected from the left ventricle per beat **(stroke volume)** to the volume of blood in the left ventricle at the end of diastole (end-diastolic volume), is widely used clinically as an index of contractility. Other measurements (or combinations of measurements) that reflect the magnitude or velocity of the ventricular contraction have been used to assess the contractile state of the cardiac muscle. No index is entirely satisfactory at present, which undoubtedly accounts for the several indices currently in use.

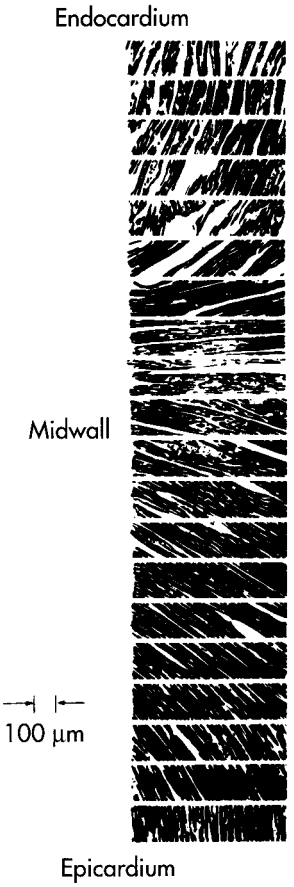


■ **Fig. 23-9** Left ventricular pressure curves with tangents drawn to the steepest portions of the ascending limbs to indicate maximal dP/dt values. *A,* Control; *B,* hyperdynamic heart, as with norepinephrine administration; C, hypodynamic heart, as in cardiac failure.

Cardiac chambers. The atria are thin-walled, low-pressure chambers that function more as large-reservoir conduits of blood for their respective ventricles than as important pumps for the forward propulsion of blood. The ventricles were once thought to be composed of bands of muscle. However, it now appears that they are formed by a continuum of muscle fibers that originate from the fibrous skeleton at the base of the heart (chiefly around the aortic orifice). These fibers sweep toward the heart apex at the epicardial surface. They pass toward the endocardium and gradually undergo a 180-degree change in direction to lie parallel to the epicardial fibers and form the endocardium and papillary muscles (Fig. 23-11). At the apex of the heart, the fibers twist and turn inward to form papillary muscles. At the base of the heart and around the valve orifices, they form a thick, powerful muscle that not only decreases ventricular circumference for ejection of blood, but also narrows the atrioventricular (AV) valve orifices as an aid to valve closure. Ventricular ejection is also accomplished by a decrease in the longitudinal axis as the heart begins to narrow toward the base. The earlier contraction of the apical part of the ventricles, coupled with approximation of the ventricular walls, propels the blood toward the outflow tracts. The right ventricle, which develops a mean pressure about one seventh of that developed by the left ventricle, is considerably thinner than the left.



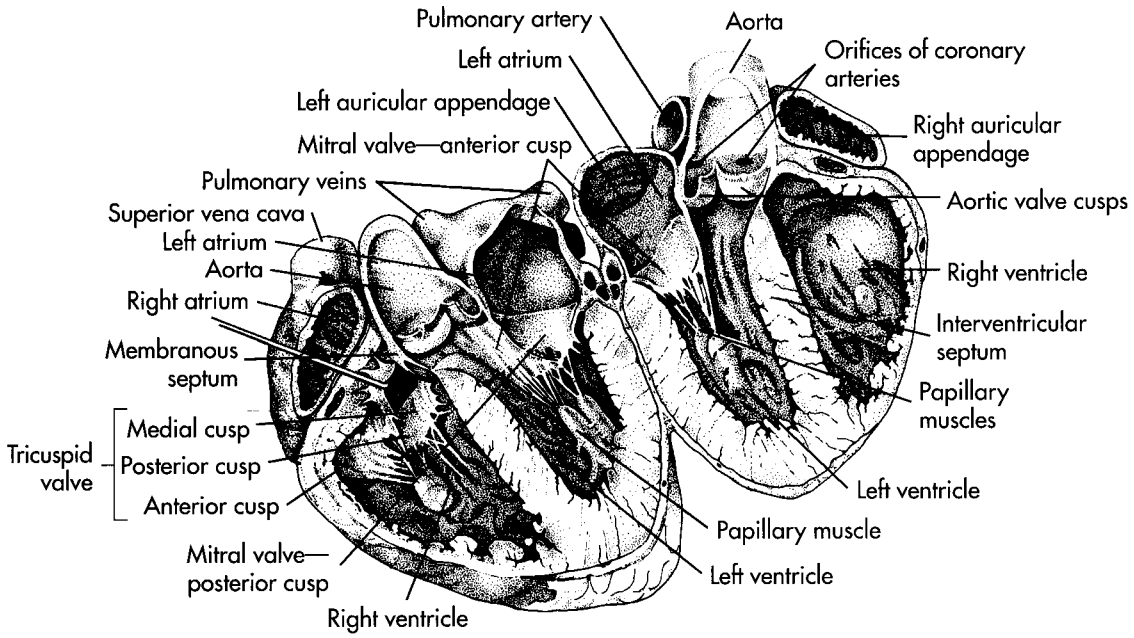
■ **Fig. 23-10** Left atrial, aortic, and left ventricular pressure pulses correlated in time with aortic flow, ventricular volume, heart sounds, venous pulse, and the electrocardiogram for a complete cardiac cycle in the dog.



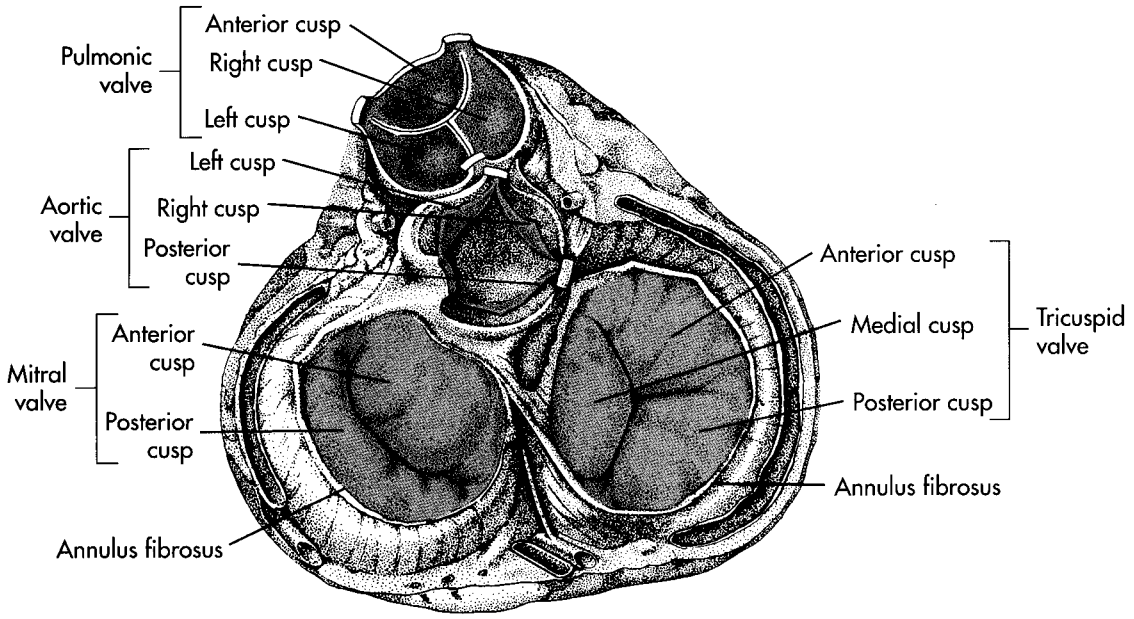
■ **Fig. 23-11** Sequence of photomicrographs showing fiber angles in successive sections taken from the middle of the free wall of the left ventricle from a heart in systole. The sections are parallel to the epicardial plane. The fiber angle is 90 degrees at the endocardium, running through 0 degrees at the midwall to −90 degrees at the epicardium. (From Streeter DD Jr et al: *Circ Res* 24:339, 1969, with permission of the American Heart Association.)

Cardiac valves. The cardiac valves consist of thin flaps of flexible, tough, endothelium-covered fibrous tissue (valve leaflets) that is firmly attached at the base to the fibrous valve rings. Movements of the valve leaflets are essentially passive, and the orientation of the cardiac valves is responsible for unidirectional flow of blood through the heart. There are two types of valves in the heart: the **atrioventricular** and the **semilunar valves** (Figs. 23-12 and 23-13).

Atrioventricular valves. The AV valve located between the right atrium and the right ventricle is made up of three cusps **(tricuspid valve),** whereas that between the left atrium and the left ventricle has two cusps **(mitral valve).** The total area of the cusps of each AV valve is approximately twice that of the respective AV orifice, so that considerable overlap of the leaflets occurs in the closed position (Figs. 23-12 and 23-13). Attached to the free edges of these valves are fine, strong ligaments **(chordae**



■ **Fig. 23-12** Drawing of a heart split perpendicular to the interventricular septum to illustrate the anatomic relationships of the leaflets of the atrioventricular and aortic valves.

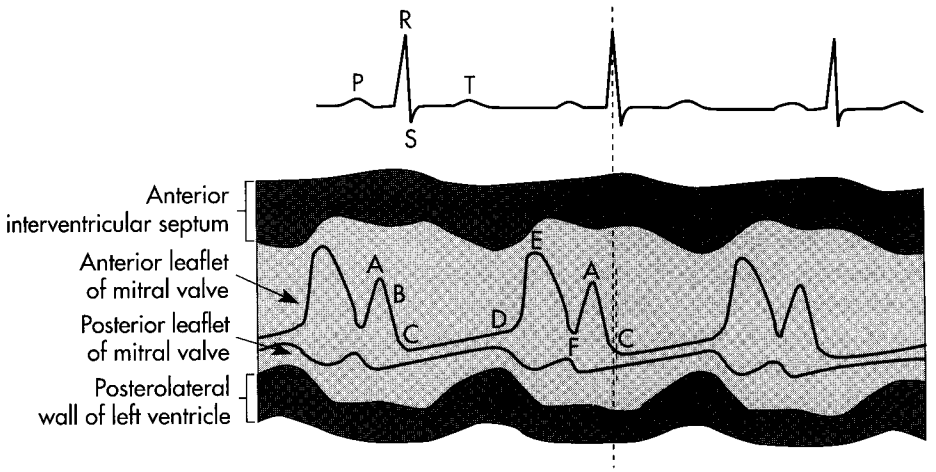


■ **Fig. 23-13** Four cardiac valves as viewed from the base of the heart. Note how the leaflets overlap in the closed valves.

tendineae), which arise from the powerful papillary muscles of the respective ventricles and prevent the valves from becoming everted during ventricular systole.

In the normal heart, the valve leaflets remain relatively close together during ventricular filling and thus provide a funnel for the transfer of blood from atrium to ventricle. The partial approximation of the valve surfaces during diastole is caused by eddy currents behind the leaflets and also by some tension on the free edges of the valves. This tension is exerted by the chordae tendineae and papillary muscles that are stretched by the filling ventricle.

Movements of the mitral valve leaflets throughout the cardiac cycle are shown in an **echocardiogram** (Fig. 23-14). Echocardiography consists of sending short pulses of high-frequency sound waves (ultrasound) through the chest tissues and the heart and recording the echoes reflected from the various structures. The timing and pattern of the reflected waves provide such information as



■ **Fig. 23-14** Drawing made from an echocardiogram showing movements of the mitral valve leaflets (particularly the anterior leaflet) and the changes in the diameter of the left ventricular cavity and the thickness of the left ventricular walls during cardiac cycles in a normal person. *D* to *C*, Ventricular diastole; *C* to *D*, ventricular systole; *D* to *E*, rapid filling; *E* to *F*, reduced filling (diastasis); *F* to *A*, atrial contraction. The mitral valve closes at *C* and opens at *D*. Simultaneously recorded electrocardiogram at top.

the diameter of the heart, the ventricular wall thickness, and the magnitude and direction of the movements of various components of the heart.

In Fig. 23-14, the echocardiogram is positioned to depict movement of the anterior leaflet of the mitral valve. The posterior leaflet moves in a pattern that is a mirror image of the anterior leaflet, but in the projection shown in Fig. 23-14 its movements appear to be much smaller. At point *D*, the mitral valve opens, and during rapid filling *(D* to *E)* the anterior leaflet moves toward the ventricular septum. During the reduced filling phase *(E* to *F)*, the valve leaflets float toward each other, but the valve does not close. The ventricular filling contributed by atrial contraction *(F* to *A)* forces the leaflets apart, followed by a second approximation of the leaflets *(A* to *C)*. At point *C* the valve is closed by ventricular contraction. The valve leaflets, which bulge toward the atrium, stay pressed together during ventricular systole *(C* to *D)*.

Semilunar valves. The semilunar valves located between the right ventricle and the pulmonary artery and between the left ventricle and the aorta consist of three cuplike cusps attached to the valve rings (Figs. 23-12 and 23-13). At the end of the reduced ejection phase of ventricular systole, blood flow briefly reverses toward the ventricles (shown as a negative flow in the phasic aortic flow curve in Fig. 23-10). This reversal of blood flow snaps the cusps together and prevents regurgitation of blood into the ventricles. During ventricular systole, the cusps do not lie back against the walls of the pulmonary artery and aorta, but instead float in the bloodstream at a point approximately midway between the vessel walls and their closed position. Behind the semilunar valves are small outpocketings of the pulmonary artery and aorta **(sinuses of Valsalva),** where eddy currents develop that tend to keep the valve cusps away from the vessel walls. In addition, the orifices of the right and left coronary arteries are behind the right and the left cusps, respectively, of the aortic valve. Were it not for the presence of the sinuses of Valsalva and the eddy currents developed therein, the coronary ostia could be blocked by the valve cusps.

The pericardium. The pericardium is an epithelialized fibrous sac. It closely invests the entire heart and the cardiac portion of the great vessels and is reflected onto the cardiac surface as the epicardium. The sac normally contains a small amount of fluid, which provides lubrication for the continuous movement of the enclosed heart. The distensibility of the pericardium is small, so that it strongly resists a large, rapid increase in cardiac size. Because of this characteristic, the pericardium plays a role in preventing sudden overdistention of the chambers of the heart. However, in congenital absence of the pericardium or after its surgical removal, cardiac function still remains within physiological limits. Nevertheless, with the pericardium intact, an increase in diastolic pressure in one ventricle increases the pressure and decreases the compliance of the other ventricle.

Heart sounds. Four sounds are usually produced by the heart, but only two are ordinarily audible through a stethoscope. With electronic amplification, the less intense sounds can be detected and recorded graphically as a **phonocardiogram.** This means of registering faint heart sounds helps to delineate the precise timing of the heart sounds relative to other events in the cardiac cycle.

The first heart sound is initiated at the onset of ventricular systole (Fig. 23-10) and consists of a series of vibrations of mixed, unrelated, low frequencies (a noise). It is the loudest and longest of the heart sounds, has a crescendo-decrescendo quality, and is heard best over the apical region of the heart. The tricuspid valve sounds are heard best in the fifth intercostal space just to the left of the sternum; the mitral sounds are heard best in the fifth intercostal space at the cardiac apex.

The first heart sound is chiefly caused by oscillation of blood in the ventricular chambers and vibration of the chamber walls. The vibrations are engendered in part by the abrupt rise of ventricular pressure with acceleration

of blood back toward the atria. However, the main cause of the first heart sound is the sudden tension and recoil of the AV valves and adjacent structures with deceleration of the blood as the AV valves close. The vibrations of the ventricles and the contained blood are transmitted through surrounding tissues and reach the chest wall (where they may be heard or recorded). The intensity of the first sound is a function of the force of ventricular contraction and of the distance between the valve leaflets. The first sound is loudest when the leaflets are farthest apart, as occurs when the interval between atrial and ventricular systoles is prolonged (AV valve leaflets float apart) or when ventricular systole immediately follows atrial systole.

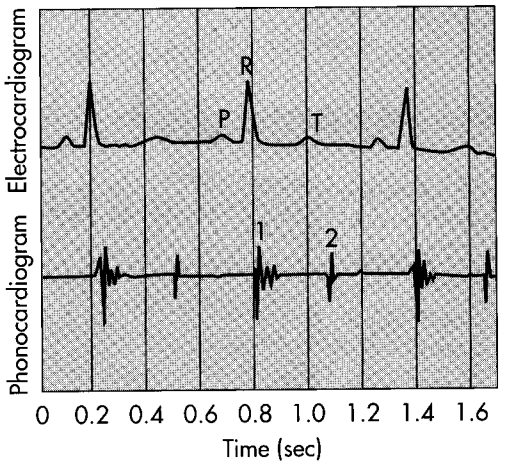
The second heart sound, which occurs with the abrupt closure of the semilunar valves (Fig. 23-10), is composed of higher-frequency vibrations (higher pitch), is of shorter duration and lower intensity, and has a more snapping quality than the first heart sound. Semilunar valve closure initiates oscillations of the columns of blood and the tensed vessel walls by the stretch and recoil of the closed valve. The portion of the second sound caused by closure of the pulmonic valve is heard best in the second thoracic interspace just to the left of the sternum, whereas that caused by closure of the aortic valve is heard best in the same intercostal space but to the right of the sternum. Conditions that cause the semilunar valves to close more rapidly than usual, such as increases in pulmonary artery or aortic pressure (e.g., pulmonary or systemic hypertension), increase the intensity of the second heart sound. The aortic valve sound is usually louder than the pulmonic, but in cases of pulmonary hypertension the reverse is true.

A normal phonocardiogram taken simultaneously with an electrocardiogram (ECG) is illustrated in Fig. 23-15. The first sound starts just beyond the peak of the R waves. Note that this sound is composed of irregular waves and is of greater intensity and duration than the second sound, which appears at the end of the T wave. A third and fourth heart sound do not appear on this record.

The third heart sound is sometimes heard in children with thin chest walls or in patients with left ventricular failure. It consists of a few low-intensity, low-frequency vibrations heard best in the region of the apex. The vibrations occur in early diastole and are caused by abrupt cessation of ventricular distention and deceleration of blood entering the ventricles.

In overloaded hearts, as in congestive heart failure, when the ventricular volume is very large and the ventricular walls are stretched to the point where distensibility abruptly decreases, a third heart sound may be heard. A third heart sound in patients with heart disease is usually a grave sign.

A fourth, or atrial, sound consists of a few low-frequency oscillations. This sound is occasionally heard in normal individuals. It is caused by oscillation of blood and cardiac chambers created by atrial contraction (Fig. 23-10).



■ **Fig. 23-15** Phonocardiogram illustrating the first and second heart sounds and their relationship to the P, R, and T waves of the electrocardiogram. Time lines = 0.04 second.

Because the onset and termination of right and left ventricular systoles are not precisely synchronous, differences in the time of vibration of the two AV valves or two semilunar valves can sometimes be detected with the stethoscope. Asynchrony of valve vibrations, which may sometimes indicate abnormal cardiac function, is heard as a **split sound** over the apex of the heart for the AV valves and over the base for the semilunar valves.

Mitral insufficiency and **mitral stenosis** produce, respectively, systolic and diastolic murmurs heard best at the cardiac apex. **Aortic insufficiency** and **aortic stenosis,** on the other hand, produce, respectively, diastolic and systolic murmurs heard best in the second intercostal space just to the right of the sternum. The characteristics of the murmur serve as an important guide in the diagnosis of valvular disease.

When the third and fourth (atrial) sounds are accentuated, as occurs in certain abnormal conditions, triplets of sounds may occur, resembling the sound of a galloping horse. These **gallop rhythms** are essentially of two types: **presystolic gallop** caused by accentuation of the atrial sound, and **protodiastolic gallop** caused by accentuation of the third heart sound.

■ *The Cardiac Cycle*

■ *Ventricular Systole*

Isovolumic contraction. The onset of ventricular contraction coincides with the peak of the R wave on an ECG and the initial vibration of the first heart sound. It is indicated on the ventricular pressure curve as the earliest rise in ventricular pressure after atrial contraction.

The time between the start of ventricular systole and the opening of the semilunar valves (when ventricular pressure rises abruptly) is called **isovolumic** (literally, "same volume") **contraction.** This term is appropriate because ventricular volume remains constant during this brief period (Fig. 23-10).

The increment in ventricular pressure during isovolumic contraction is transmitted across the closed valves. Isovolumic contraction has also been referred to as isometric contraction ("isometric" describes a contraction of a muscle that produces increased tension at a constant length). However, some cardiac muscle fibers shorten and others lengthen, as evidenced by changes in ventricular shape; it is therefore not a true isometric contraction.

Ejection. Opening of the semilunar valves marks the onset of the ventricular ejection phase, which may be subdivided into an earlier, shorter phase **(rapid ejection)** and a later, longer phase **(reduced ejection).** The rapid ejection phase is distinguished from the reduced ejection phase by three factors: (1) the sharp rise in ventricular and aortic pressures that terminates at the peak ventricular and aortic pressures, (2) a more abrupt decrease in ventricular volume, and (3) a greater aortic blood flow (Fig. 23-10). The sharp decrease in the left atrial pressure curve at the onset of ejection results from the descent of the base of the heart and stretch of the atria. During the reduced ejection period, runoff of blood from the aorta to the periphery exceeds ventricular output, and therefore aortic pressure declines. Throughout ventricular systole, the blood returning to the atria produces a progressive increase in atrial pressure.

Note that during the first third of the ejection period, left ventricular pressure slightly exceeds aortic pressure and blood flow into the aorta accelerates (continues to increase), whereas during the last two thirds of ventricular ejection the reverse holds true. This reversal of the ventricular-aortic pressure gradient in the presence of continued flow of blood from the left ventricle to the aorta (caused by the momentum of the forward blood flow) is the result of storage of potential energy in the stretched arterial walls. This stored potential energy decelerates blood flow into the aorta. The peak of the flow curve coincides with the point at which the left ventricular pressure curve intersects the aortic pressure curve during ejection. Thereafter, flow decelerates (continues to decrease) because the pressure gradient has been reversed.

In right ventricular ejection, a shortening of the free wall of the right ventricle (descent of the tricuspid valve ring) occurs in addition to lateral compression of the chamber. However, with left ventricular ejection, very little shortening of the base-to-apex axis occurs, and ejection is accomplished chiefly by compression of the left ventricular chamber.

The effect of ventricular systole on left ventricular diameter is shown in an echocardiogram (Fig. 23-14). During ventricular systole (Fig. 23-14, *C* to *D*), the septum and the free wall of the left ventricle become thicker and move closer to each other.

Fig. 23-10 shows a tracing of a venous pulse curve taken from a jugular vein. The *c* wave in this tracing is caused by the impact of the common carotid artery with the adjacent jugular vein and to some extent by the abrupt closure of the tricuspid valve in early ventricular systole. Note that except for the *c* wave, the venous pulse closely follows the atrial pressure curve.

At the end of ejection, a volume of blood approximately equal to that ejected during systole remains in the ventricular cavities. This **residual volume** is fairly constant in normal hearts. However, the residual volume is smaller with increased heart rate or reduced outflow resistance and larger when the opposite conditions prevail.

An increase in myocardial contractility, as produced by catecholamines or by digitalis in a patient with a depressed heart, may decrease residual volume and increase stroke volume and ejection fraction. With severely hypodynamic and dilated hearts, as in **heart failure,** the residual volume can become many times greater than the stroke volume.

In addition to serving as a small adjustable blood reservoir, the residual volume, to a limited degree, allows for transient disparities between the outputs of the two ventricles.

■ *Ventricular Diastole*

Isovolumic relaxation. Closure of the aortic valve produces the characteristic **incisura (notch)** on the descending limb of the aortic pressure curve and the second heart sound (with some vibrations evident on the atrial pressure curve), and it marks the end of ventricular systole. The period between closure of the semilunar valves and opening of the AV valves is termed **isovolumic relaxation.** It is characterized by a precipitous fall in ventricular pressure without a change in ventricular volume.

Rapid filling phase. The major part of ventricular filling occurs immediately on opening of the AV valves. At this point the blood that had returned to the atria during the previous ventricular systole is abruptly released into the relaxing ventricles. This period of ventricular filling is called the **rapid filling phase.** In Fig. 23-10 the onset of the rapid filling phase is indicated by the decrease in left ventricular pressure below left atrial pressure. This pressure reversal results in the opening of the mitral valve. The rapid flow of blood from atria to relaxing ventricles produces a decrease in atrial and ventricular pressures and a sharp increase in ventricular volume.

Elastic recoil of the previous ventricular contraction may help draw blood into the relaxing ventricle when residual volume is small, especially when ventricular

contractility is enhanced (such as when catecholamines are administered). However, this mechanism probably does not contribute to ventricular filling under most normal conditions.

Diastasis. The rapid filling phase is followed by a phase of slow filling called **diastasis.** During diastasis, blood returning from the periphery flows into the right ventricle, and blood from the lungs flows into the left ventricle. This small, slow addition to ventricular filling is indicated by a gradual rise in atrial, ventricular, and venous pressures and in ventricular volume (Fig. 23-10).

Atrial systole. The onset of atrial systole occurs soon after the beginning of the P wave of the ECG (curve of atrial depolarization). The transfer of blood from atrium to ventricle made by the peristalsis-like wave of atrial contraction completes the period of ventricular filling. Atrial systole is responsible for the small increases in atrial, ventricular, and venous pressures, as well as in ventricular volume shown in Fig. 23-10. Throughout ventricular diastole, atrial pressure barely exceeds ventricular pressure. This small pressure difference indicates that the pathway through the open AV valves during ventricular filling has low resistance.

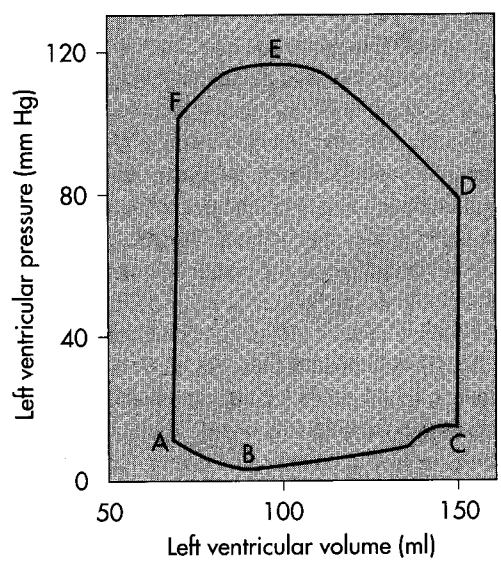
Because there are no valves at the junctions of the venae cavae and right atrium or of the pulmonary veins and left atrium, atrial contraction can force blood in both directions. Actually, little blood is pumped back into the venous tributaries during the brief atrial contraction, mainly because of the inertia of the inflowing blood.

Atrial contraction is not essential for ventricular filling, as can be observed in atrial fibrillation or complete heart block. In atrial fibrillation, the atrial myofibers contract in an uncoordinated fashion and therefore cannot pump blood into the ventricles. In complete heart block, the atria and ventricles beat independently of each other. However, ventricular filling can be normal with these two arrhythmias.

The contribution of atrial contraction to ventricular filling is governed to a great extent by the heart rate and position of the AV valves. At slow heart rates, filling practically ceases toward the end of diastasis, and atrial contraction contributes little additional filling. During tachycardia, however, diastasis is abbreviated and the atrial contribution can become substantial, especially if the atrial contraction occurs immediately after the rapid filling phase, when the AV pressure gradient is maximal. Should tachycardia become so great that the rapid filling phase is encroached on, atrial contraction assumes great importance in rapidly propelling blood into the ventricle during this brief period of the cardiac cycle. Of course, if the period of ventricular relaxation is so brief that filling is seriously impaired, even atrial contraction cannot provide adequate ventricular filling. The consequent reduction in cardiac output may result in syncope (fainting). Obviously, if atrial contraction occurs simultaneously with ventricular contraction, no atrial contribution to ventricular filling can occur.

Pressure-volume relationship. The changes in left ventricular pressure and volume throughout the cardiac cycle are summarized in Fig. 23-16. Time is not considered in this **pressure-volume loop.** Diastolic filling starts at *A* and terminates at *C*, when the mitral valve closes. The initial decrease in left ventricular pressure (*A* to *B*), despite the rapid inflow of blood from the atrium, is attributed to progressive ventricular relaxation and distensibility. During the remainder of diastole (*B* to *C*), the increase in ventricular pressure reflects ventricular filling and the passive elastic characteristics of the ventricle. Note that only a small increase in pressure occurs with the increase in ventricular volume during diastole (*B* to *C*). The small increase in pressure just to the left of *C* is caused by the contribution of atrial contraction to ventricular filling. With isovolumic contraction (*C* to *D*), pressure rises steeply, but no change occurs in ventricular volume. At *D*, the aortic valve opens, and during the first phase of ejection (rapid ejection, *D* to *E*), the large reduction in volume is associated with a steady increase in ventricular pressure that is less steep than the pressure increase that occurred during isovolumic contraction. This volume reduction is followed by reduced ejection (*E* to *F*) and a small decrease in ventricular pressure. The aortic valve closes at *F*, and this event is followed by isovolumic relaxation (*F* to *A*), which is characterized by a sharp drop in pressure and no change in volume. The mitral valve opens at A to complete one cardiac cycle.

In certain disease states, the AV valves may be markedly narrowed **(stenotic).** Under such conditions, atrial contraction plays a much more important role in ventricular filling than it does in the normal heart.



■ **Fig. 23-16** Pressure-volume loop of the left ventricle for a single cardiac cycle *(ABCDEF).*

■ *Measurement of Cardiac Output*

■ *Fick Principle*

In 1870 the German physiologist Adoph Fick contrived the first method for measuring cardiac output in intact animals and people. The basis for this method, called the **Fick principle,** is simply an application of the law of conservation of mass. It is derived from the fact that the quantity of oxygen (O_2) delivered to the pulmonary capillaries via the pulmonary artery, plus the quantity of O_2 that enters the pulmonary capillaries from the alveoli, must equal the quantity of O_2 that is carried away by the pulmonary veins.

The Fick principle is depicted schematically in Fig. 23-17. The rate, q_1, of O_2 delivery to the lungs equals the O_2 concentration in the pulmonary arterial blood, $[O_2]_{pa}$, times the pulmonary arterial blood flow, Q, which equals the cardiac output; that is

$$q_1 = Q[O_2]_{pa} \qquad (23\text{-}1)$$

Let q_2 be the net rate of O_2 uptake by the pulmonary capillaries from the alveoli. At equilibrium, q_2 equals the **O_2 consumption** of the body. The rate, q_3, at which O_2 is carried away by the pulmonary veins equals the O_2 concentration in the pulmonary venous blood, $[O_2]_{pv}$, times the total pulmonary venous flow, which is virtually equal to the pulmonary arterial blood flow, Q; that is,

$$q_3 = Q[O_2]_{pv} \qquad (23\text{-}2)$$

From conservation of mass,

$$q_1 + q_2 = q_3 \qquad (23\text{-}3)$$

Therefore,

$$Q[O_2]_{pa} + q_2 = Q[O_2]_{pv} \qquad (23\text{-}4)$$

Solving for cardiac output,

$$Q = q_2/([O_2]_{pv} - [O_2]_{pa}) \qquad (23\text{-}5)$$

Equation 23-5 is the statement of the Fick principle.

The clinical determination of cardiac output requires three values: (1) O_2 consumption of the body, (2) the O_2 concentration in the pulmonary venous blood ($[O_2]_{pv}$), and (3) the O_2 concentration in the pulmonary arterial blood ($[O_2]_{pa}$). O_2 consumption is computed from measurements of the volume and O_2 content of expired air over a given interval of time. Because the O_2 concentration of peripheral arterial blood is essentially identical to that in the pulmonary veins, $[O_2]_{pv}$ is determined on a sample of peripheral arterial blood withdrawn by needle puncture. Pulmonary arterial blood, $[O_2]_{pa}$, actually represents mixed systemic venous blood. Samples for O_2 analysis are obtained from the pulmonary artery or right ventricle through a catheter. In the past, a relatively stiff catheter was used and it had to be introduced into the pulmonary artery under fluoroscopic guidance. Today, a very flexible catheter with a small balloon near the tip can be inserted into a peripheral vein. As the tube is advanced, it is carried by the flowing blood toward the heart. By following the pressure changes, the physician is able to advance the catheter tip into the pulmonary artery without the aid of fluoroscopy.

An example of the calculation of cardiac output in a normal, resting adult is illustrated in Fig. 23-17. With an O_2 consumption of 250 ml/min, an arterial (pulmonary venous) O_2 content of 0.20 ml O_2/ml blood, and a mixed venous (pulmonary arterial) O_2 content of 0.15 ml O_2/ml blood, the cardiac output equals $250/(0.20 - 0.15) = 5000$ ml/min.

The Fick principle is also used for estimating the O_2 consumption of organs when blood flow and the O_2 contents of the arterial and venous blood can be determined. Algebraic rearrangement reveals that O_2 consumption equals the blood flow times the arteriovenous O_2 concentration difference. For example, if the blood flow through one kidney is 700 ml/min, arterial O_2 content is 0.20 ml O_2/ml blood, and renal venous O_2 content is 0.18 ml O_2/ml blood, the rate of O_2 consumption by that kidney must be $700\ (0.2 \times 0.18) = 14$ ml O_2/min.

■ *Indicator Dilution Techniques*

The indicator dilution technique for measuring cardiac output is also based on the law of conservation of mass and is illustrated by the model in Fig. 23-18. In this model, a liquid flows through a tube at a rate of Q ml/sec, and q mg of dye is injected as a slug into the stream at point *A*. Mixing occurs at some point downstream. If a small sample of liquid is continually withdrawn from point *B* farther downstream and passed through a densitometer, a curve of the dye concentration, *c,* may be recorded as a function of time, *t,* as shown in the lower half of Fig. 23-18.

If no dye is lost between points *A* and *B,* the amount of dye, *q*, passing point *B* between times t_1 and t_2 will be

$$q = \bar{c}\,Q(t_1 - t_2) \qquad (23\text{-}6)$$

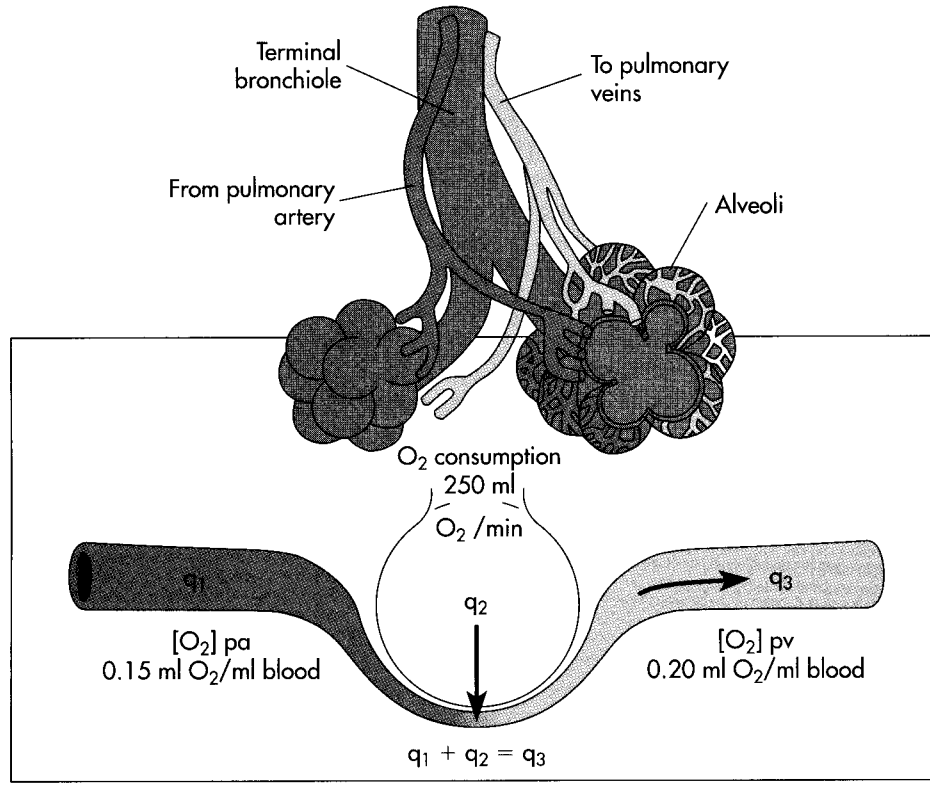
where $\bar{c}$ is the mean concentration of dye. The value of $\bar{c}$ may be computed by dividing the area of the dye concentration by the duration $(t_2 - t_1)$ of the curve; that is

$$\bar{c} = \int_{t_1}^{t_2} c\,dt/(t_2 - t_1) \qquad (23\text{-}7)$$

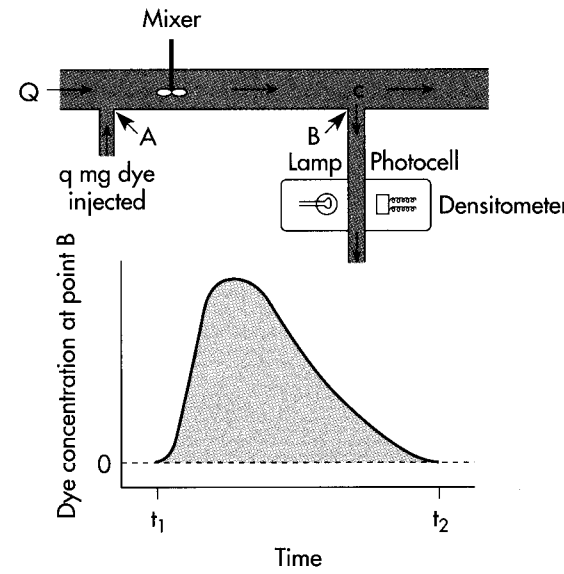
Substituting this value of $\bar{c}$ into equation 23-6 and solving for Q yields

$$Q = \frac{q}{\int_{t_1}^{t_2} c\,dt} \qquad (23\text{-}8)$$

Thus, flow may be measured by dividing the amount of indicator (the dye) injected upstream by the area under the downstream concentration curve.



■ **Fig. 23-17** Schema illustrating the Fick principle for measuring cardiac output. The change in color from pulmonary artery to pulmonary vein represents the change in color of the blood as venous blood becomes fully oxygenated.



■ **Fig. 23-18** Indicator dilution technique for measuring cardiac output. In this model, in which there is no recirculation, q mg of dye are injected instantaneously at point *A* into a stream flowing at Q ml/min. A mixed sample of the fluid flowing past point *B* is withdrawn at a constant rate through a densitometer; *C* is concentration of dye in the fluid. The resultant dye concentration curve at point *B* has the configuration shown in the lower section of the figure.

This technique has been widely used to estimate cardiac output in humans. A measured quantity of some indicator (a dye or isotope that remains within the circulation) is injected rapidly into a large central vein or into the right side of the heart through a catheter. Arterial blood is continuously drawn through a detector (densitometer or isotope rate counter), and a curve of indicator concentration is recorded as a function of time.

Currently, the most popular indicator dilution technique is **thermodilution.** The indicator used in this method is cold saline. The temperature and volume of the saline are measured accurately before injection. A flexible catheter is introduced into a peripheral vein and advanced so that the tip lies in the pulmonary artery. A small thermistor at the catheter tip records the changes in temperature. The opening in the catheter lies a few inches proximal to the tip. When the tip is in the pulmonary artery, the opening lies in or near the right atrium. The cold saline is injected rapidly into the right atrium through the catheter and flows out through the opening in the catheter. The change in temperature downstream is recorded by the thermistor in the pulmonary artery.

The thermodilution technique has the following advantages: (1) an arterial puncture is not necessary; (2) the small volumes of saline used in each determination are innocuous, and thus repeated determinations can be made; and (3) recirculation is negligible. Temperature equilibration takes place as the cooled blood flows through the pulmonary and systemic capillary beds, before it flows by the thermistor in the pulmonary artery the second time.

Summary

1. An increase in myocardial fiber length, as occurs with augmented ventricular filling (preload) during diastole, produces a more forceful ventricular contraction. This relation between fiber length and strength of contraction is known as the Frank-Starling relationship or Starling's law of the heart.

2. Although the myocardium is made up of individual cells with discrete membrane boundaries, the cardiac myocytes that make up the ventricles contract almost in unison, as do those of the atria. The myocardium functions as a syncytium with an all-or-none response to excitation. Cell-to-cell conduction occurs through gap junctions that connect the cytosol of adjacent cells.

3. On excitation, voltage-gated calcium channels open to admit extracellular Ca^{++} into the cell. The influx of Ca^{++} triggers the release of Ca^{++} from the sarcoplasmic reticulum. The elevated intracellular [Ca^{++}] produces contraction of the myofilaments. Relaxation is accomplished via restoration of the resting cytosolic Ca^{++} level by pumping it back into the sarcoplasmic reticulum and exchanging it for extracellular Na^{+} across the sarcolemma.

4. Velocity and force of contraction are functions of the intracellular concentration of free calcium ions. Force and velocity are inversely related, so that with no load, velocity is maximal. In an isovolumic contraction, where no external shortening occurs, total load is maximal and velocity is zero.

5. In ventricular contraction, the preload is the stretch of the fibers by the blood during ventricular filling. The afterload is the aortic pressure against which the left ventricle ejects the blood.

6. Contractility is an expression of cardiac performance at a given preload and afterload.

7. Simultaneous recording of left atrial, left ventricular, and aortic pressures; ventricular volume; heart sounds; and the electrocardiogram graphically portray the sequential and related electrical and cardiodynamic events throughout a cardiac cycle.

8. The first heart sound is caused mainly by abrupt closure of the AV valve; the second heart sound is caused by abrupt closure of the semilunar valves.

9. Cardiac output can be determined, according to the Fick principle, by measuring the oxygen consumption of the body (q_2) and the oxygen content of arterial $[O_2]_a$ and mixed venous $[O_2]_v$ blood. Cardiac output = $q_2 / ([O_2]_a - [O_2]_v)$. It can also be measured by dye dilution or thermodilution techniques. The greater the cardiac output, the greater is the dilution of the injected dye or cold saline by the arterial blood.

Self-Study Problems

1. Increase of force in skeletal muscle is accomplished by recruitment of muscle fibers via motor nerve activity. How does the heart increase its contractile force?
2. What are cardiac preload and afterload, and how do they affect developed pressure and velocity of contraction?
3. How is myocardial contractility evaluated?
4. What is the function of the pericardium, and how can it affect cardiac filling and performance?
5. In a patient with severe mitral stenosis, where precisely in the cardiac cycle does the murmur occur?
6. If the arterial blood oxygen content is 19 ml/dl, the mixed venous oxygen content 12 ml/dl, and the oxygen consumption 280 ml/min, what is the cardiac output? In the same person, if the coronary sinus blood oxygen content is 5 ml/dl and the coronary sinus blood flow 150 ml/min, what is the oxygen consumption of the myocardium drained via the coronary sinus?

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