CHAPTER 10

Cardiac Muscle

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CHAPTER OUTLINE

KEY CONCEPTS

1. Cardiac muscle is a striated muscle, with a sarcomere structure much like that of skeletal muscle. It has small cells (as in smooth muscle), firmly connected end-to-end at the intercalated disks.
2. The action potential in cardiac muscle is long lasting compared to the duration of the contraction, preventing a tetanic contraction.
3. Under normal circumstances, cardiac muscle operates at lengths somewhat less than the optimal length for peak force production, facilitating length-dependent regulation of the muscle activity.
4. A typical cardiac muscle contraction produces less than maximal force, allowing physiologically regulated changes in contractility to adjust the force of the muscle contraction to the body's current needs.
5. As in skeletal muscle, the speed of shortening of cardiac muscle is inversely related to the force being exerted, as expressed in the force-velocity curve.
6. The contractility of cardiac muscle is changed by inotropic interventions that include changes in the heart rate, the presence of circulating epinephrine, or sympathetic nerve stimulation.
7. Most changes in cardiac muscle contractility are associated with changes in the amount of calcium available to activate the contractile system.
8. Calcium enters a cardiac muscle cell during the plateau of the action potential. This entry promotes the release of internal calcium stores, which are located mainly in the sarcoplasmic reticulum (SR). Primary and secondary active transport systems remove calcium from the cytoplasm.
9. Cardiac muscle derives its energy primarily from the oxidative metabolism of lactic acid and free fatty acids. It has very little capacity for anaerobic metabolism.

The muscle mass of the heart, the **myocardium**, shares characteristics of both smooth muscle and skeletal muscle. The tissue is striated in appearance, as in skeletal muscle, and the structural characteristics of the sarcomeres and myofilaments are much like those of skeletal muscle. The regulation of contraction, involving calcium control of an actin-linked troponin-tropomyosin complex, is also quite like that of skeletal muscle. However, cardiac muscle is composed of many small cells, as is smooth muscle, and electrical and mechanical cell-to-cell communication is an essential feature of cardiac muscle structure and function. The mechanical properties of cardiac muscle relate more closely to those of skeletal muscle, although the mechanical performance is considerably more complex and subtle.

ANATOMIC SPECIALIZATIONS OF CARDIAC MUSCLE

The heart is composed of several varieties of cardiac muscle tissue. The **atrial myocardium** and **ventricular myocardium**, so named for their location, are similar structurally, although the electrical properties of these two areas differ significantly. The **conducting tissues** (e.g., Purkinje fibers) of the heart have a communicating function similar to nerve tissue, but they actually consist of muscle tissue that is highly adapted for the rapid and efficient conduction of action potentials, and their contractile ability is greatly reduced. Finally, there are the highly specialized tissues of the **sinoatrial** and **atrioventricular nodes**, muscle tissue that is greatly modified into structures concerned with the

initiation and conduction of the heartbeat. The discussions that follow refer primarily to the ventricular myocardium, the tissue that makes up the greatest bulk of the muscle of the heart.

Cardiac Muscle Cells Are Structurally Distinct From Skeletal Muscle Cells

The small size of cardiac muscle cells is one of the critical aspects in determining the function of heart muscle. The cells are approximately 10 to 15 μm in diameter and about 50 μm long. Cardiac muscle tissue is a branching network of cells, also called **cardiac myocytes**, joined together at intercalated disks (Fig. 10.1). This arrangement aids in the spread of electrical activity. Cardiac myocytes have a single, centrally located nucleus, although many cells may contain two nuclei. The cell membrane and associated fine connective tissue structures form the sarcolemma, as in skeletal muscle. The sarcolemma of cardiac muscle supports the resting and action potentials and is the location of ion pumps and ion exchange mechanisms vital to cell function. Just inside the sarcolemma are components of the SR where significant amounts of calcium ions may be bound and kept from general access to the cytoplasm. This bound calcium can exchange rapidly with the extracellular space and can be rapidly freed from its binding sites by the passage of an action potential.

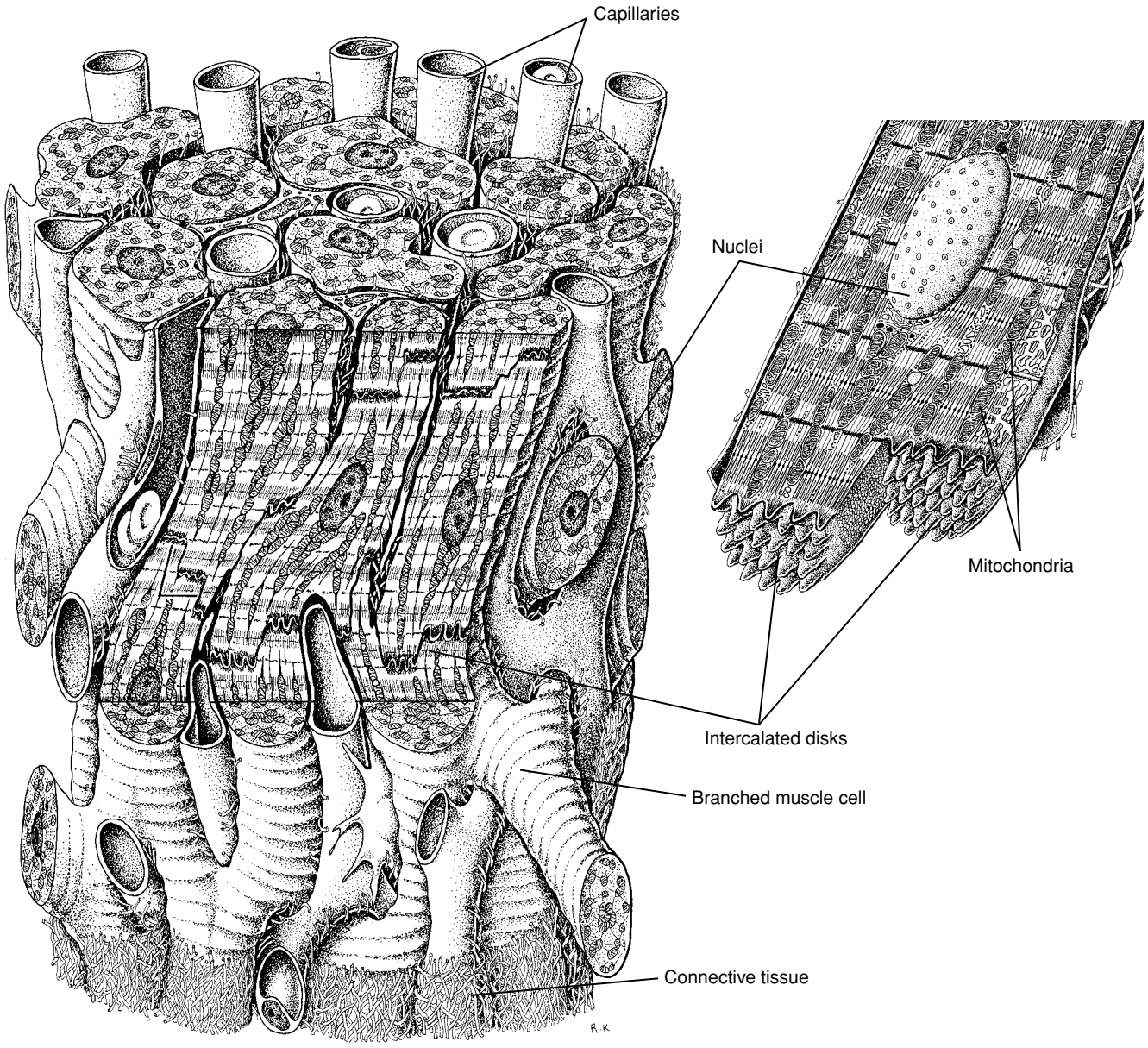

FIGURE 10.1 **The structure of cardiac muscle tissue.** Left: A small tissue sample in longitudinal and cross section. Note the branching nature of the cells and the large number of capillaries. Right: Two cardiac myocytes, showing the striated structure of the contractile filaments, the many mitochondria, and the three-dimensional structure of the intercalated disks. (Adapted from Krstic RV. General Histology of the Mammal. New York: Springer-Verlag, 1984.)

As in skeletal muscle, there is a system of transverse (T) tubules, but both it and the SR are not as extensive in cardiac muscle, together constituting less than 2% of the cell volume. This correlates with the small cell size and consequent reduction in diffusion distances between the cell surface membrane and contractile proteins. In cardiac muscle cells, the T tubules enter the cells at the level of the Z lines. In many cases, the link between a T tubule and the SR is not a triad, as in skeletal muscle, but rather a **dyad,** composed of the T tubule and the terminal cisterna of the SR of only one sarcomere. The small size of the SR also limits its calcium storage capacity, and the other source of calcium entry and exit, the sarcolemma, has an important role in the excitation-contraction coupling process in cardiac muscle.

The sarcomeres appear essentially like those of skeletal muscle, with similar A bands and I bands, Z lines, and M lines. Myofilaments make up almost half the cell volume and are bathed in the cytosol. Numerous mitochondria comprise another 30 to 40% of the cell volume, reflecting the highly aerobic nature of cardiac muscle function. The rest of the cell volume, about 15%, consists of cytosol, containing numerous enzymes and metabolic products and substrates.

Cardiac Muscle Cells Are Linked in a Functional Syncytium

Electron microscopy reveals that in the region of the intercalated disk, each cardiac myocyte sends processes deep into its neighboring cell to form an interdigitating junction with a large surface area. Gap junctions in the intercalated disks function like those of smooth muscle, allowing close electrical communication between cells. Also plentiful in the intercalated disk region are desmosomes, areas where there is a firm mechanical connection between cells. This mode of attachment, rather than an extensive extracellular connective tissue matrix as in smooth muscle, allows the transmission of force from cell to cell. The intercalated disk, therefore, allows cardiac muscle to form a **functional syncytium,** with cells acting in concert both mechanically and electrically.

The stimulus for cardiac muscle contraction arises entirely within the heart and is not dependent on its nerve supply (see Chapter 13). The conduction of action potentials is solely a function of the muscle tissue. Impulse propagation is aided by the branched nature of the cells, the intercalated disks, and specialized conducting tissue, such as **Purkinje fibers**—strands of myocytes, nerve-like in outward appearance, that are specialized for electrical conduction. Their contractile protein is only about 20% of the cell volume, and their large size optimizes their electrical characteristics for rapid action potential conduction. Innervation of cardiac muscle comes from both branches of the autonomic nervous system, allowing for external regulation of the heart rate and strength of contraction, as well as providing some degree of sensory feedback.

Cell and Tissue Structure Allow and Require Unique Adaptations

As a result of the small size of cardiac muscle cells, the communication system described above (and in Chapter 13) is necessary for organized function. The small cell size also makes each cell more critically dependent on the external environment, and cardiac function may be greatly altered by electrolyte and metabolic imbalances arising elsewhere in the body. Hormonal messengers, such as norepinephrine, also have quick access to cardiac muscle cells.

From a mechanical standpoint, the lack of skeletal attachments means cardiac muscle can function over a wide range of lengths. While the length-tension property is not of major importance in the functioning of many skeletal muscles, in cardiac muscle, it is the basis of the remarkable capacity of the heart to adjust to a wide range of physiological conditions and requirements.

PHYSIOLOGICAL SPECIALIZATIONS OF CARDIAC MUSCLE

Cardiac muscle is a striated muscle, but it functions rather differently from skeletal muscle. The lack of skeletal attachments provides a wider range of lengths over which it can operate. Special features of the excitation-contraction coupling process allow a subtle degree of control at the level of the muscle that is largely independent of the central nervous system (CNS).

Specialized Electrical and Metabolic Properties Control Cardiac Muscle Contraction

A more detailed treatment of the electrical properties of cardiac muscle is given in Chapter 13. The discussion here focuses on the electrical properties most closely related to controlling the mechanical function of cardiac ventricular muscle.

The Cardiac Action Potential. As in other types of muscle and in nerve, the muscle cells of the heart have an excitable and selectively permeable cell membrane that is responsible for both resting potentials and action potentials. These electrical phenomena are the result of ionic concentration differences and several ion-selective membrane channels, some of which are voltage- and time-dependent. In cardiac muscle, however, the membrane events are more diverse and complex than in skeletal muscles and are much more closely linked to the actual form of the mechanical contraction. The closer association of electrical and mechanical events is one key to the inherent properties of cardiac muscle that suit it to its role in an organ that is largely self-regulating.

Figure 10.2 illustrates some features of the cardiac muscle action potential that pertain directly to myocardial function. Note that the duration of the action potential is quite long; in fact, it lasts nearly as long as the muscle contraction. One consequence is that the absolute and relative refractory periods are likewise extended, and the muscle cannot be restimulated during any but the latest part of the contraction. During the repolarization phase of the action potential, there is a brief period in which the muscle actually shows an increased sensitivity to stimulation. This period of **supranormal excitability** is due to a lowered potassium conductance that persists late in the action potential (see Chapter 13). If the muscle is accidentally stimulated

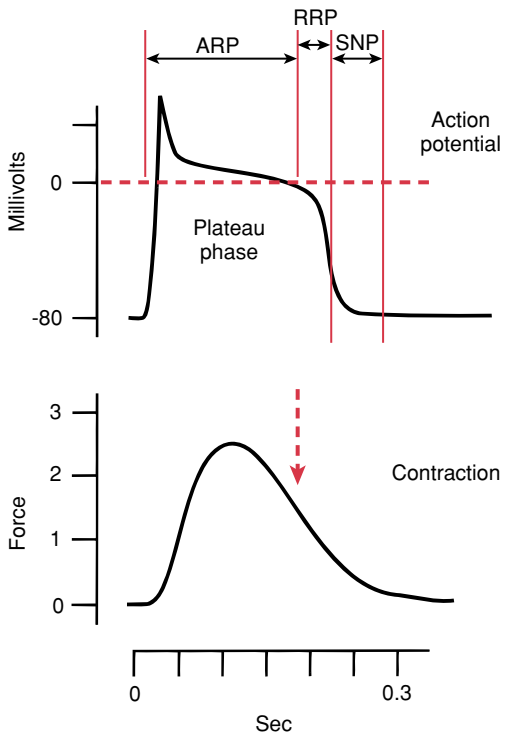

FIGURE 10.2 **A cardiac muscle action potential and isometric twitch.** Because of the duration of the action potential, an effective tetanic contraction cannot be produced, although a partial contraction can be elicited late in the twitch. ARP, absolute refractory period; RRP, relative refractory period; SNP, period of supranormal excitability.

during this period, the action potentials that are produced have reduced amplitude and duration and give rise to only small contractions. This period of supranormal excitability can lead to unwanted and untimely propagation of action potentials that can seriously interfere with the normal rhythm of the heart.

The long-lasting refractoriness of the cell membrane effectively prevents the development of a tetanic contraction (see Fig. 10.2); any failure of cardiac muscle to relax fully after every stimulus would make it quite unsuitable to function as a pump. When cardiac muscle is stimulated to contract more frequently (equivalent to an increase in the heart rate), the durations of the action potential and the contraction become less, and consecutive twitches remain separate contraction-and-relaxation events.

It must be emphasized that contraction in cardiac muscle is not the result of stimulation by motor nerves. Cells in some critical areas of the heart generate automatic and rhythmic action potentials that are conducted throughout the bulk of the tissue. These specialized cells are called **pacemaker cells** (see Chapter 13).

Excitation-Contraction Coupling in Cardiac Muscle. The rapid depolarization associated with the upstroke of the action potential is conducted down the T tubule system of the ventricular myocardium, where it causes the release of intracellular calcium ions from the SR. In cardiac muscle, a large part of the calcium released during rapid depolarization is from additional SR just inside the cell membrane. As in skeletal muscle, the principal role of the SR is in the rapid release, active uptake, storage, and buffering of cytosolic calcium. The action of calcium ions on the **troponin-tropomyosin complex** of the thin filaments is similar to that in skeletal muscle, but cardiac muscle differs in its cellular handling of the activator, calcium.

Along with the calcium ions released from the SR, a significant amount of calcium enters the cell from outside during the upstroke and **plateau phase** of the action potential (see Fig. 10.2). The principal cause of the sustained depolarization of the plateau phase is the presence of a population of voltage-gated membrane channels permeable to calcium ions. These channels open relatively slowly; while open, there is a net influx of calcium ions, called the **slow inward current**, moving down an electrochemical gradient. Although the calcium entering during an action potential does not directly affect that specific contraction, it can affect the *next* contraction, and it does increase the cellular calcium content over time because of the repeated nature of the cardiac muscle contraction.

In addition, even a small amount of Ca^{2+} entering through the sarcolemma causes the release of significant additional Ca^{2+} from the SR, a phenomenon known as **calcium-induced calcium release** (similar to that in smooth muscle). This constant influx of calcium requires that there be a cellular system that can rid the cell of excess calcium. Regulation of cellular calcium content has important consequences for cardiac muscle function, because of the close relationship between calcium and contractile activity.

Mechanical Properties of Cardiac Muscle Adapt It to Changing Physiological Requirements

The mechanical function of cardiac muscle differs somewhat from that of skeletal muscle contraction. Cardiac muscle, in its natural location, does not exist as separate strips of tissue with skeletal attachments at the ends. Instead, it is present as interwoven bundles of fibers in the heart walls, arranged so that shortening results in a reduction of the volume of the heart chamber, and its force or tension results in an increase in pressure in the chamber. Because of geometric complexities of the intact heart and the complex mechanical nature of the blood and aorta, shortening contractions of the intact heart muscle are more nearly auxotonic than truly isotonic (see Chapter 9).

The experimental basis for the present understanding of cardiac muscle mechanics comes largely from studies done on isolated **papillary muscles** from the ventricles of experimental animals. A papillary muscle is a relatively long, slender muscle that can serve as a representative of the whole myocardium. It can be arranged to function under the same sort of conditions as a skeletal muscle. Analysis of research results is aided by using simple afterloads to produce isotonic contractions. Despite the limitations these simplifications impose, many of the unique properties of the intact heart can be understood on the basis of studies of isolated muscle. As the various phenomena are explained here, substitute *volume changes* for *length changes* and *pressure* for *force*. You will then be able to relate the function of the

heart as a pump to the properties of the muscle responsible for its operation (see Chapter 14).

The Length-Tension Curve. Some aspects of the cardiac muscle **length-tension curve** are associated with its specialized construction and physiological role (Fig. 10.3). Over the range of lengths that represent physiological ventricular volumes, there is an appreciable resting force that increases with length; at the length at which active force production is optimal, this can amount to 10 to 15% of the total force. Because this resting force exists before contraction occurs, it is known as **preload.** In the intact heart, the preload sets the resting fiber length according to the intracardiac blood pressure existing prior to contraction. The passive tension rises steeply beyond the optimal length and prevents overextension of the muscle (or overfilling of the heart). Note that the resting force curve is associated with the **diastolic (relaxed) phase** of the heart cycle, while the active force curve is associated with the **systolic (contraction) phase.**

The length-tension curve in Figure 10.3 describes isometric behavior; since the working heart never undergoes completely isometric contractions (see Chapter 14), other aspects of length-dependent behavior must be responsible for determining the effect length has on cardiac muscle function. One such aspect is the rate at which isometric force develops during a twitch. Notice the series of twitches shown in Figure 9.10; because of the constancy of the time required to reach peak force, the rate of rise of force also varies with muscle length. Other length-dependent aspects of contraction are encountered when we examine the complete contraction cycle of cardiac muscle.

The Contraction Cycle of Cardiac Muscle. A typical isotonic contraction of skeletal muscle (see Fig. 9.8) can be divided into four distinct phases:

1. **Isometric contraction**: the muscle force builds up to reach the afterload.
2. **Isotonic shortening**: the afterload is lifted.
3. **Isotonic lengthening**: the load stretches the muscle back to its starting length.
4. **Isometric relaxation**: the force dies away.

The isometric contraction and isotonic shortening phases of a typical cardiac muscle contraction are like those of skeletal muscle. However, in the intact heart at the peak of the shortening, the afterload is removed because of the closing of the aortic and pulmonary valves at the end of the cardiac ejection phase (see Chapter 14). Since the muscle is not allowed to lengthen (the inflow valves are still closed), it undergoes isometric relaxation at the shorter length. Some time later, the muscle is stretched back to its original length by an external force (the returning blood), producing an isotonic lengthening (isotonic relaxation) phase. Because the muscle has relaxed, only a small force is required for the reextension. In the intact heart, this force is supplied by the returning blood.

The principal difference between these two cycles is significant: in skeletal muscle, the work done on the afterload (by lifting it) is returned to the muscle. In cardiac muscle, the work done on the load is *not* returned to the muscle but is imparted to the afterload. The heart muscle is constrained by its anatomy and functional arrangements to follow different pathways during contraction and relaxation.

This pattern is seen clearly when the phases of the contraction-relaxation cycle are displayed on a length-tension curve. In Figure 10.4, at the beginning of the contraction (A), force increases without any change in length (isometric conditions); when the afterload is lifted (B), the muscle shortens at a constant force (isotonic conditions) to the shortest length possible for that afterload. The afterload is removed at the maximal extent of shortening, and the muscle relaxes (C) without any change in length (isometric conditions again, but at a reduced length). With sufficient force applied to the resting muscle by some external means (D), the mus-

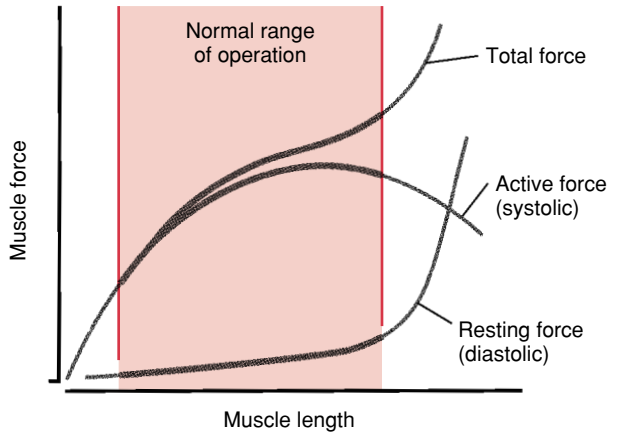

FIGURE 10.3 **The isometric length-tension curve for isolated cardiac muscle.** The total force at all physiologically significant lengths includes a resting force component.

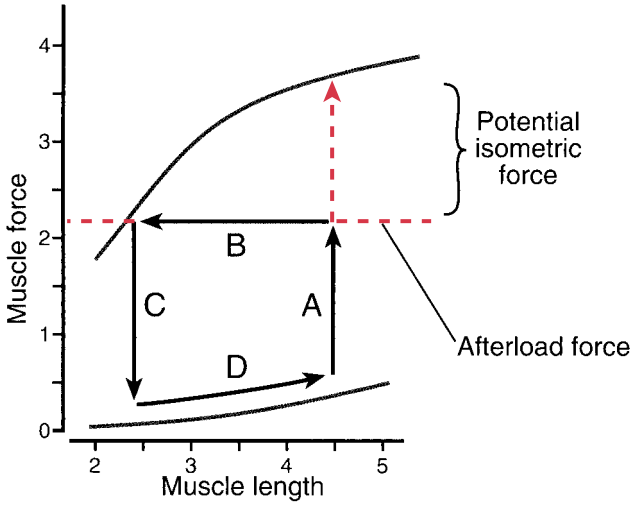

FIGURE 10.4 **An afterloaded contraction of cardiac muscle, plotted in terms of the length-tension curve.** The limit to force is provided by the afterload; the limit to shortening by the length-tension curve. A, isometric contraction phase; B, isotonic shortening phase; C, isometric relaxation phase; D, relengthening. (See text for details.)

cle is elongated back to its starting length. Because the muscle is unstimulated and its resting force rises somewhat during elongation, this phase is not strictly isotonic.

In physical terms, the area enclosed by this pathway represents work done by the muscle on the external load. If the afterload or the starting length (or both) is changed, then a different pathway will be traced (Fig. 10.5, left). The area enclosed will differ with changes in the conditions of contraction, reflecting differing amounts of external work delivered to the load. In a typical skeletal muscle contraction, as shown in Fig. 10.5 (right), steps A and B are reversed during relaxation. Such a contraction does no net external work, and no area is enclosed by the pathway.

Cardiac Muscle Self-Regulation. Each case in Figure 10.5 (center and left) demonstrates that the active portion of the length-tension curve provides the limit to shortening and, thus, interacts with the particular afterload chosen. With smaller afterloads, the muscle will shorten further than it would with a larger afterload. It is important to realize that during isotonic shortening, the muscle force is limited by the magnitude of the afterload and *not* by the length-tension capability of the muscle. It is the *extent of shortening* at a given afterload that is limited by the length-tension property of the muscle; this is a very important consideration when measuring cardiac performance under conditions of changing blood pressure and filling of the heart (see Chapter 14). This length- and force-dependent behavior is the key to **autoregulation** (self-regulation) by cardiac muscle and is the functional basis of **Starling's law of the heart** (see Chapter 14); when the muscle is set to a longer length at rest, the active contraction results in a greater shortening that is also more rapid and is preceded by a more rapid isometric phase. This allows the heart to adjust

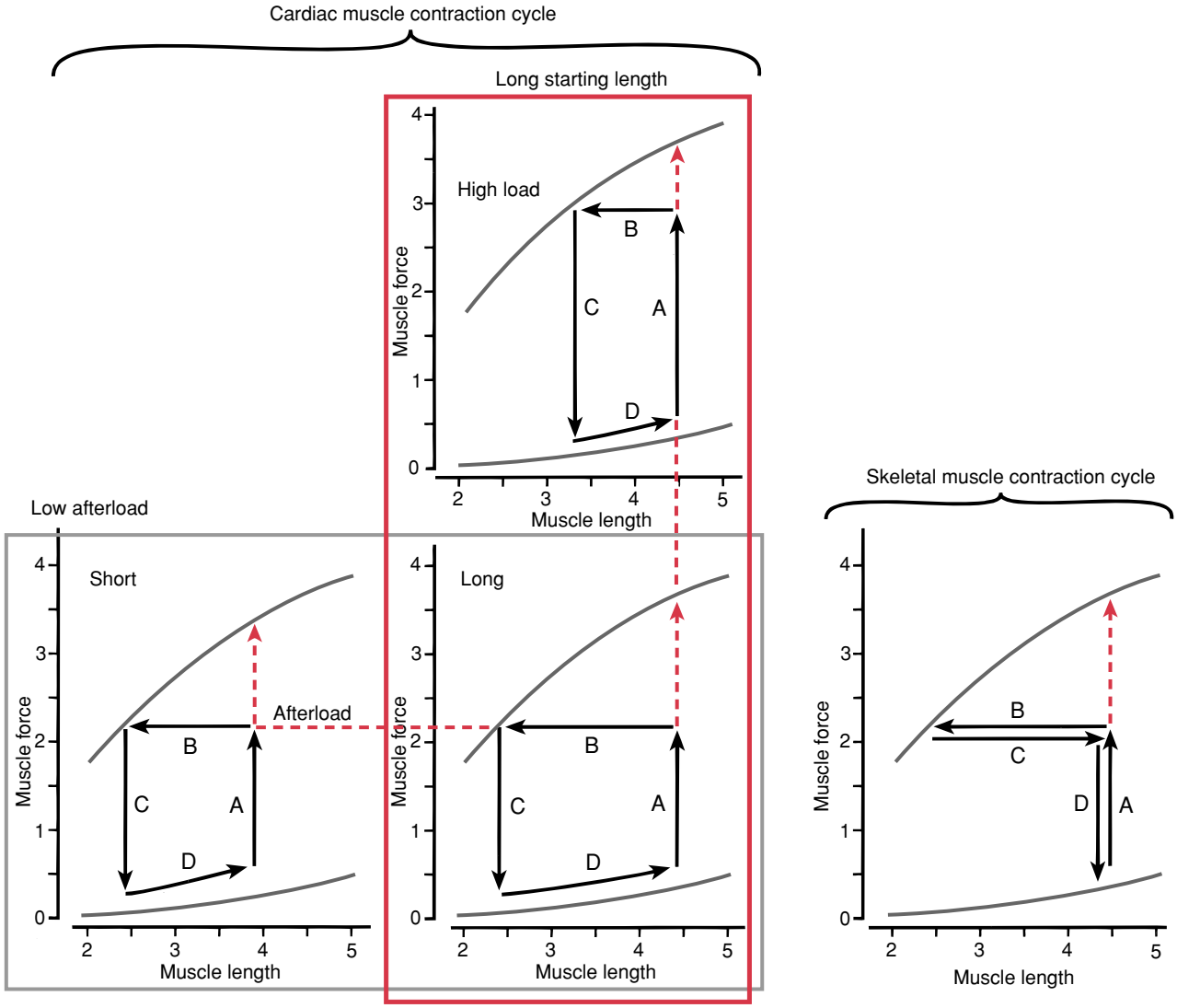

FIGURE 10.5 Afterloaded contractions under a variety of conditions. Left: Cardiac muscle contraction cycles. The horizontal box shows the effect of starting at two different initial lengths at the same afterload. The vertical box shows the effect of two different afterloads on shortening that begins at the same initial length. Increasing the afterload reduces the amount of shortening possible, as does decreasing the starting length; in both cases, the limit to shortening is determined by the length-tension curve. Right: The contraction cycle of skeletal muscle. Contraction and relaxation pathways are the same.

its pumping to exactly the amount required to keep the circulatory system in balance.

Variable Contractility Facilitates Essential Physiological Adjustments

Under a wide range of conditions, the contractile behavior of skeletal muscle is fixed and repeatable. The peak force and shortening velocity depend primarily on muscle length and afterload, and unless the muscle is worked to fatigue, these properties will not change from contraction to contraction. For this reason, skeletal muscle is said to possess **fixed contractility. Contractility** or the contractile state of muscle may be defined as a certain level of functional capability (as measured by a quantity such as isometric force, shortening velocity, etc.) when measured at a constant muscle length. (Length must be held constant to preclude the effects of the length-tension curve properties already discussed.) The regulation of skeletal muscle contraction to produce useful activity is primarily the task of the CNS, using the mechanisms of motor unit summation and partially fused tetani (see Chapter 9). Cardiac muscle has no motor innervation, but has a capacity for adjustment that is not solely accomplished by changes in afterload and starting length.

The **variable contractility** of cardiac muscle enables it to make adjustments to the varying demands of the circulatory system. Certain chemical and pharmacological agents, as well as physiological circumstances, affect cardiac contractility. The collective term for the influence of such agents is **inotropy**. Contractility is altered by **inotropic interventions,** agents or processes that change the functional state of cardiac muscle. **Positive inotropes** are inotropic interventions that increase contractility and include the action of adrenergic (sympathetic nervous system) stimulation, bloodborne catecholamine hormones, drugs such as the digitalis derivatives, and an increase in the rate of stimulation (i.e., increased heart rate). **Negative inotropes** include a decrease in heart rate, disease processes such as myocarditis or coronary artery disease, and certain drugs. Chronically reduced contractility can lead to the condition known as heart failure (see Clinical Focus Box 10.1).

Effects of Inotropic Interventions.

Figure 10.6 shows an increase in contractility plotted on a length-tension graph. It has the effect of shifting the active length-tension curve upward and to the left; relaxation and the passive curve are minimally affected. Careful experiments have shown that one effect of short muscle length on muscle contraction is actually a reduction in contractility as a result of inefficiencies in the excitation-contraction coupling mechanism at these lengths. Such effects cannot be separated from other length-related effects on cardiac muscle functions, and they are usually included without mention in the more familiar length-dependent changes in muscle performance.

An example of the similarities and differences between changes in resting length and changes in contractility is shown in the force-velocity curves in Figure 10.7. The set of curves in Figure 10.7A represents the isotonic behavior of muscle at a constant level of contractility at three different muscle lengths. The maximum force point on each curve shows the isometric length-tension effect. When a particular afterload is chosen (in this case, 0.5 units), the initial shortening velocity varies with the starting length, although the curves do tend to converge at the lowest forces. The curves in Figure 10.7B represent contractions made at the same starting length but with the muscle operating at different levels of contractility. Again there is a difference in shortening velocity at a constant afterload, but there is no tendency for the curves to converge at the low forces. These examples show only one aspect of the effects of changing contractility; those not illustrated include changes in the rate of rise of isometric force and changes in the time required to reach peak force in a twitch.

Ultimately, any change in the muscle contraction will result in a change in the overall performance of the heart, but cardiac performance can change drastically even without changes in contractility because of length-tension effects. The need to distinguish such effects from changes in contractility (to guide treatment and therapy) has led to a search for aspects of muscle performance that are dependent on the state of contractility but independent of muscle length. The results of these studies (based on the properties of isolated muscle) are questionable because the complicated structure and function of the intact heart do not permit a reliable extrapolation of findings. Instead, several empirical measures have been developed from studies of the intact heart, some of which provide a reasonable and useful index of contractility (see Chapter 14).

The Cellular Basis of Contractility Changes.

The basic determinant of the variable contractility of cardiac muscle is the calcium content in the myocardial cell. Under normal conditions, the contractile filaments of cardiac muscle are only partly activated. This is because, unlike with skeletal muscle, not enough calcium is released to occupy all of the troponin molecules, and not all potentially available crossbridges can attach and cycle. An increase in the availability of calcium would increase the number of crossbridges activated; thus, contractility would be increased. To understand the mechanisms of contractility change, it is necessary to consider the factors affecting cellular calcium handling.

The processes linking membrane excitation to contraction via calcium ions are illustrated in Figure 10.8. Since this involves many possible movements and locations of calcium, the processes are considered in the order in which they would be encountered during a single contraction.

The initial event is an action potential (1) traveling along the cell surface. As in skeletal muscle, the action potential enters a T tubule (2), where it can communicate with the SR (3) to cause calcium release. This mechanism for release of calcium in cardiac muscle is much less than in skeletal muscle and is insufficient to cause adequate activation of the contraction. To some extent, activation is aided by a calcium-induced calcium release mechanism (4) triggered by a rise in the cytoplasmic calcium concentration. The action potential (5) on the cell surface (sarcolemma) also causes the opening of calcium channels, through which strong inward calcium current flows. These calcium ions accumulate just inside the sarcolemma (6), although some probably diffuse rapidly into the cell interior. Calcium induces the rapid release of calcium from the subsarcolemmal SR, and the calcium then diffuses the short distance to the

CLINICAL FOCUS BOX 10.1

Heart Failure and Muscle Mechanics

Heart failure is evident when the heart is unable to maintain sufficient output to meet the body's normal metabolic needs. It is usually a progressively worsening condition. The condition is due to either deterioration of the heart muscle or worsening of the contributing factors external to the heart. The term *congestive heart failure* refers to fluid congestion of the lungs that often accompanies heart failure.

Patients suffering from heart failure may be unable to perform simple everyday tasks without fatigue or shortness of breath. In later stages, there may be significant distress even while resting. While many intrinsic and extrinsic factors contribute to the condition, this discussion will focus on those closely related to the mechanical properties of the heart muscle.

Much of poor cardiac function can be understood in terms of the mechanics of the heart muscle as it interacts with several external factors that determine the resting muscle length (or preload) or the load against which it must contract (the afterload). The most important aspects of the mechanical behavior are described by the length-tension and force-velocity curves, which, together with knowledge of the current state of contractility, can provide a complete picture of the muscle function.

Some heart failure is of the systolic type. If the heart has been damaged by a myocardial infarction (heart attack) or ischemia (impaired blood supply to the heart muscle) or by chronic overload (as with untreated high blood pressure), the muscle may become weakened and have reduced contractility. In this case, the load presented to the heart by the blood pressure is too high (relative to the weakened condition of the muscle), and (as the force-velocity curve describes) the rate of shortening (velocity) of the muscle will be reduced. The length-tension curve indicates that the larger the load, the less the shortening (see Fig. 10.5). Therefore, less blood will be pumped with each beat. Therapy for this type of failure involves improving the contractility of the muscle and/or reducing the load on the heart.

Heart failure can also be of the diastolic type (and may occur along with systolic failure). Here the relaxation is impaired, and the muscle is resistant to the stretch that must take place during its filling with blood. Some types of hypertrophy or connective tissue fibrosis also may contribute to diastolic failure. Because the muscle cannot be sufficiently lengthened during its rest period (diastole), it begins its contraction at too short a length. As the length-tension curve would predict, the muscle is unable to shorten sufficiently to pump an adequate volume of blood with each beat. Because the force-velocity curve is also length-dependent, the speed at which the muscle can shorten is also reduced.

Treatment of heart failure involves approaches that affect several areas of muscle mechanics. Drugs that increase the contractility of cardiac muscle, such as digitalis and its derivatives, may be used to cause more effective contraction and allow the muscle to operate along an improved force-velocity curve. Most contractility-increasing drugs work by increasing the amount of intracellular calcium available to the myofilaments, thereby increasing the number of crossbridges participating in the contractions. Care must be taken, however, that the increased contractility does not create a metabolic demand that would further weaken the muscle. Drugs that blunt the response of the heart to the excitatory action of the sympathetic nervous system (which affects both heart rate and muscle contractility) can protect against an increased workload. Drugs that lower blood pressure by their effects on the arterial muscle will reduce the load against which the heart muscle must contract, and the muscle can operate on a more efficient portion of the force-velocity curve. Drugs or dietary regimens that reduce blood volume (via increased renal excretion of salt and water) can also lower the load against which the muscle must contract; the same is true of drugs that cause relaxation of the muscle in the walls of the venous system. Lowering the blood volume also acts to decrease the over-distension of the heart during diastole. While it would seem that an increase in the resting muscle length would have a beneficial effect on the strength of contraction, geometric factors in the intact heart place the overstretched muscle at a mechanical disadvantage that the length-tension curve cannot adequately overcome.

Heart failure involves numerous interacting organ systems. The mechanical behavior of the heart muscle, as understood in the context of the length-tension and force-velocity curves, is only a part of the problem. Effective therapy must also consider factors external to the heart muscle itself.

myofilaments (7) and activates them. The amount of calcium in the cytoplasm, the **cytosolic calcium pool**, determines the magnitude of the myofilament activation and, hence, the level of contractility.

During relaxation, the cytoplasmic calcium concentration is rapidly lowered through several pathways. The SR membrane contains a vigorous Ca^{2+}-ATPase (8) that runs continuously and is further activated, through a protein phosphorylation mechanism, by high levels of cytoplasmic calcium. At the level of the sarcolemma, two additional mechanisms work to rid the cell of the calcium that entered via previous action potentials. A membrane Ca^{2+}-ATPase (9) actively extrudes calcium, ejecting one calcium ion for each ATP molecule consumed. Additional calcium is removed by a Na^+/Ca^{2+} exchange mechanism (10), also located in the cell membrane. This mechanism is part of a coupled transport system in which three sodium ions, entering the cell down their electrochemical gradient, are exchanged for the ejection of one calcium ion. Proper function of this exchange mechanism requires a steep sodium concentration gradient, maintained by the membrane Na^+/K^+-ATPase (11) located in the sarcolemma. Because the Na^+/Ca^{2+} exchange mechanism derives its energy from the sodium gradient, any reduction in the pumping action of the Na^+/K^+-ATPase leads to reduced calcium extrusion. Under normal conditions, these mechanisms can maintain a 10,000-fold Ca^{2+} concentration difference between the inside and outside of the cell. Since a cardiac cell contracts repeatedly many times per minute with each beat being accompanied by an influx of calcium, the extrusion mechanisms must also work continuously to balance the incoming calcium. The mito-

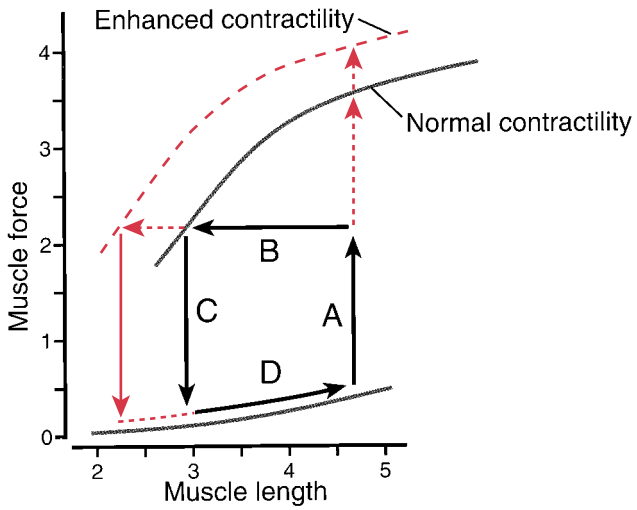

FIGURE 10.6 **Effect of enhanced contractility on the contraction cycle of cardiac muscle.** When contractility is increased, the rate of rise of force is increased, the time to afterload force is decreased, and potential force is increased. The muscle shortens faster and further (A) while isometric relaxation (B) and relengthening (C) are minimally affected (D).

chondria of cardiac muscle (12) are also capable of accumulating and releasing calcium, although this system does not appear to play a role in the normal functioning of the cell.

Calcium and the Function of Inotropic Agents. Inotropic agents usually work through changes in the internal calcium content of the cell. An increase in the heart rate, for instance, allows more separate influxes of calcium per minute, and the amount of releasable calcium in the subsarcolemmal space and SR increases. More crossbridges are activated, and the force of isometric contraction (and other indicators of contractility) increases. This is the basis of the **force-frequency relationship**, one of the principal means of changing myocardial contractility.

Cardiac glycosides are an important class of therapeutic agents used to increase the contractility of failing hearts. The drug **digitalis**, used for centuries for its effects on the circulation, is typical of these agents. While some details of its action are obscure, the drug has been shown to work by inhibiting the membrane Na^+/K^+-ATPase. This allows the cell to gain sodium and reduces the steepness of the sodium gradient. This makes the Na^+/Ca^{2+} exchange mechanism less effective, and the cell gains calcium. Since more calcium is available to activate the myofilaments, contractility increases. These effects, however, can lead to **digitalis toxicity** when the cell gains so much calcium that the capacity of the sarcoplasmic and sarcolemmal binding sites is exceeded. At this point, the mitochondria begin to take up the excess calcium; however, too much mitochondrial calcium interferes with ATP production. The cell, with its ATP needs already increased by enhanced contractility, is less able to pump out accumulated calcium, and the final result is a lowering of metabolic energy stores and a reduction in contractility. Some changes in the contractility of cardiac muscle may be permanent and life threatening. Many of these changes are due to disease or factors external to the heart and may be described by the general term **cardiomyopathy** (see Clinical Focus Box 10.2).

Sources of Energy for Cardiac Muscle Function

In contrast to skeletal muscle, cardiac muscle does not have the opportunity to rest from a period of intense activity to "pay back" an oxygen debt. As a result, the metabolism of cardiac muscle is almost entirely aerobic under basal conditions and uses free fatty acids and lactate as its primary substrates. This correlates with the high con-

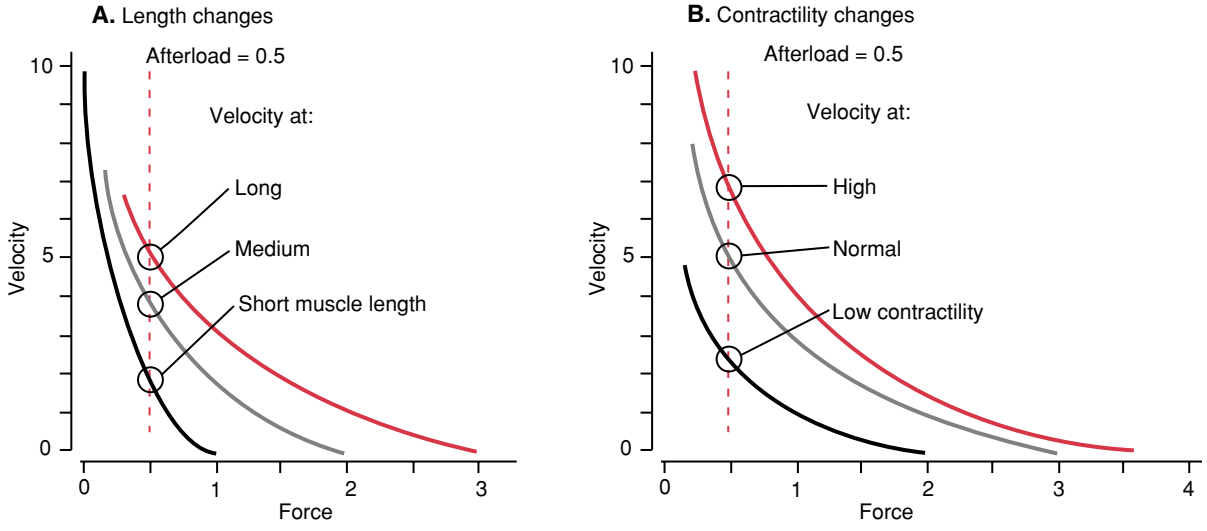

FIGURE 10.7 **Effect of length and contractility changes on the force-velocity curves of cardiac muscle.** A, Decreased starting length (with constant contractility) produces lower velocities of shortening at a given afterload. Because of the presence of resting force (characteristic of heart muscle), it is impossible to make a direct measure of a zero-force contraction at each length. There is a tendency for the curves to converge at the lower forces. B, Increased contractility produces increased velocity of shortening at a constant muscle length, but there is no tendency for the curves to converge at the low forces.

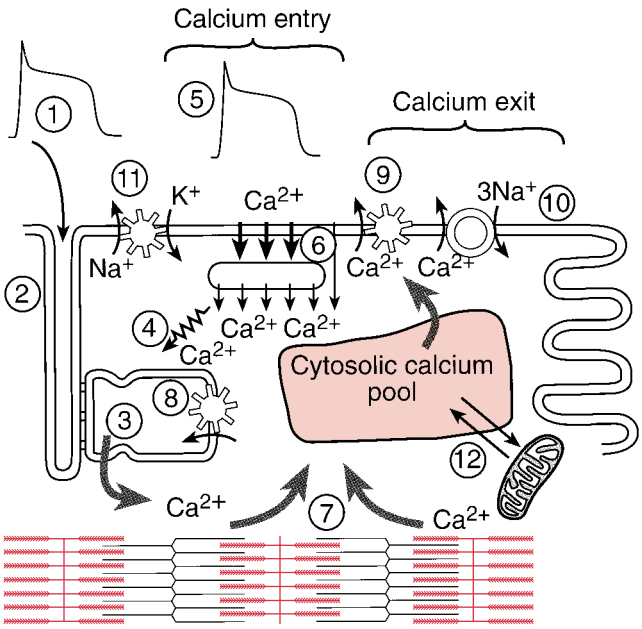

FIGURE 10.8 The paths of calcium in and out of the cardiac muscle cell and its role in the regulation of contraction. (See text for details.)

tent of mitochondria in the cells and with the high cellular content of myoglobin. Under conditions of **hypoxia** (lack of oxygen), the anaerobic component of the metabolism may approach 10% of the total, but beyond that limit, the supply of metabolic energy is insufficient to sustain adequate function.

The substrates that provide chemical energy input to the heart during periods of increased activity consist of carbohydrates (mostly in the form of lactic acid produced as a result of skeletal muscle exercise; see Chapters 8 and 9), fats (largely as free fatty acids), and, to a small degree, ketone body acids and amino acids. The relative amounts of the various metabolites vary according to the nutritional status of the body. Because of the highly aerobic nature of cardiac muscle metabolism, there is a strong correlation between the amount of work performed and the amount of oxygen consumed. Under most conditions, the contraction of cardiac muscle in the intact heart is approximately 20% efficient, with the remainder of the energy going to other cellular processes or wasted as heat. Regardless of the dietary or metabolic source of energy, ATP (as in all other muscle types) provides the immediate energy for contraction. As in skeletal muscle, cardiac muscle contains a "rechargeable" creatine phosphate buffering system that supplies the short-term ATP demands of the contractile system.

CLINICAL FOCUS BOX 10.2

Cardiomyopathies: Abnormalities of Heart Muscle

Heart disease takes many forms. While some of these are related to problems with the valves or the electrical conduction system (see Chapters 13 and 14), many are due to malfunctions of the cardiac muscle itself. These conditions, called **cardiomyopathy,** result in impaired heart function that may range from being essentially asymptomatic to malfunctions causing sudden death.

There are several types of cardiomyopathy, and they have several causes. In **hypertrophic cardiomyopathy,** an enlargement of the cardiac muscle fibers occurs because of a chronic overload, such as that caused by hypertension or a defective heart valve. Such muscle may fail because its high metabolic demands cannot be met, or fatal electrical arrhythmias may develop (see Chapter 13). **Congestive** or **dilated cardiomyopathy** refers to cardiac muscle so weakened that it cannot pump strongly enough to empty the heart properly with each beat. In **restrictive cardiomyopathy,** the muscle becomes so stiffened and inextensible that the heart cannot fill properly between beats. Chronic poisoning with heavy metals, such as cobalt or lead, can produce **toxic cardiomyopathy.** The skeletal muscle degeneration associated with **muscular dystrophy** is often accompanied by cardiomyopathy (see Chapter 8).

The cardiomyopathy arising from **viral myocarditis** is difficult to diagnose and may show no symptoms until death occurs. The action of some enteroviruses (e.g., coxsackievirus B) may cause an autoimmune response that does the actual damage to the muscle. This damage may occur at the subcellular level by interfering with energy metabolism while producing little apparent structural disruption. Such conditions, which can usually only be diagnosed by direct muscle biopsy, are difficult to treat effectively, although spontaneous recovery can occur. Excessive and chronic consumption of alcohol can also cause cardiomyopathy that is often reversible if total abstinence is maintained. In tropical regions, infection with a trypanosome **(Chagas' disease)** can produce chronic cardiomyopathy. The tick-borne spirochete infection called **Lyme disease** can cause heart muscle damage and lead to heart block, a conduction disturbance (see Chapter 13).

Another important kind of cardiomyopathy arises from ischemia, an inadequate oxygen (blood) supply to working cardiac muscle. An acute ischemic episode may be followed by a **stunned myocardium,** with reduced mechanical performance. Chronic ischemia can produce a **hibernating myocardium,** also with reduced mechanical performance. Ischemic tissue has impaired calcium handling, which can lead to destructively high levels of internal calcium. These conditions can be improved by reestablishing an adequate oxygen supply (e.g., following clot dissolution or coronary bypass surgery), but even this treatment is risky because rapidly restoring the blood flow to ischemic tissue can lead to the production of oxygen radicals that cause significant cellular damage. The use of calcium blockers and free radical scavengers, such as vitamin E, following ischemic episodes may limit this damage.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. Which of the following sets of attributes best characterizes cardiac muscle?
   (A) Large cells, electrically isolated, neurally stimulated
   (B) Small cells, electrically coupled, chemically stimulated
   (C) Small cells, electrically coupled, spontaneously active
   (D) Small cells, electrically isolated, spontaneously active
2. Cardiac muscle functions as both an electrical and a mechanical syncytium. The structural basis of this ability is the
   (A) T tubule system
   (B) Intercalated disks
   (C) Striated nature of the contractile system
   (D) Extensive SR
3. The regulation of contraction in cardiac muscle is
   (A) Most like that of smooth muscle (i.e., myosin-linked)
   (B) Most like that of skeletal muscle (i.e., actin-linked)
   (C) Independent of filament-related proteins
   (D) Dependent on autonomic neural stimulation
4. What prevents cardiac muscle from undergoing a tetanic contraction?
   (A) The rate of neural stimulation is limited by the CNS
   (B) The muscle fatigues so quickly that it must relax fully between contractions
   (C) The refractory period of the action potential lasts into the relaxation phase of the contraction
   (D) The electrical activity is conducted too slowly for tetanus to occur
5. The contraction cycle for cardiac muscle differs in significant ways from that of skeletal muscle. Which situation below is more typical of cardiac muscle?
   (A) The cycle involves only isometric contraction and relaxation
   (B) Isometric relaxation occurs at a shorter length than isometric contraction
   (C) The muscle relaxes along the same combination of lengths and forces that it took during contraction
   (D) The complete cycle in cardiac muscle is isotonic
6. What is the physiological role of the passive length-tension curve in cardiac muscle?
   (A) It ensures that force stays constant as the muscle is stretched
   (B) It allows the muscle to be extended without limit when it is at rest
   (C) It lets the resting muscle length to be set in proportion to the preload
   (D) It prevents a contraction from having an isometric phase at shorter lengths
7. Why does cardiac muscle shorten less at higher afterloads?
   (A) Higher loads cause a reduction in contractility and this limits the shortening
   (B) Higher loads cause rapid fatigue, which limits the shortening
   (C) Moving a heavy load causes premature relaxation
   (D) It encounters the limit set by the length-tension curve with less shortening
8. What factor provides the most important limit to force production in cardiac muscle?
   (A) The resting muscle length from which contraction begins
   (B) The size of the preload, which sets the initial length
   (C) The size of the afterload during isotonic shortening
   (D) The rate (velocity) at which the muscle shortens
9. The factor common to most changes in cardiac muscle contractility is the
   (A) Amplitude of the action potential
   (B) Availability of cellular ATP
   (C) Cytoplasmic calcium concentration
   (D) Rate of neural stimulation
10. At a given muscle length, the velocity of contraction depends on
    (A) Only the afterload
    (B) Only the contractility of the muscle
    (C) Both the contractility and the afterload
    (D) Only the preload because the contractility is constant

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CASE STUDIES FOR PART III • • •

Case Study for Chapter 8

Polymyositis in an Older Patient

A 67-year-old woman consulted her physician because of recent and progressive muscle weakness. She reported difficulty in rising out of a chair and had intermittent difficulty in swallowing. Physical examination reveals the presence of a light purple rash around her eyes and on her knuckles and elbows. Muscle weakness is noted in all four limbs, but the woman does not complain of muscular soreness. She is somewhat underweight, slightly short of breath, and speaks in a low voice. Laboratory tests show a moderately elevated creatine kinase level. There is no family history of muscle problems, and she is not currently taking any medication.

Because of the symptoms present, no muscle biopsy or electromyographic study is carried out. A tentative diagnosis of polymyositis/dermatomyositis was made. The

(continued)

woman is placed on high-dose prednisone, and arrangements are made for periodic tests for circulating muscle enzymes. Because of her age, she is referred to a cancer specialist to screen for a possible underlying malignancy, and physical therapy is strongly recommended.

In follow-up visits, the woman shows gradual improvement in muscle strength, and her rash is much less apparent. No malignancy is detected. She maintains a regimen of physical therapy and is able to have the prednisone dosage progressively reduced over the course of the next year.

Questions

1. What was a likely cause for the patient's underweight condition?
2. Could the shortness of breath also have been a result of polymyositis?
3. Does the pattern of recovery suggest that the diagnosis was correct?
4. What was the underlying cause of her disease?

Answers to Case Study Questions for Chapter 8

1. Patients with polymyositis involving the pharyngeal and esophageal muscles have difficulty swallowing. This leads to reduced nutritional intake, to the point where it may be life threatening.
2. Although several things could contribute to shortness of breath, weakness of the respiratory muscles can lead to hypoventilation; this, too, can be life threatening.
3. The response to therapy was what one would expect for a person suffering from polymyositis. Conditions such as muscular dystrophy would not have responded as well to the prednisone therapy.
4. Because a malignancy was ruled out, this case must be considered, like most cases of polymyositis, to be of idiopathic origin.

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Case Study for Chapter 9

A Muscle-Pull Injury

A 35-year-old man visited his family physician early on a Monday morning. He walked into the waiting room with a pronounced limp, favoring his right leg, and was in obvious discomfort. When he arose from the waiting-room chair, it was with some difficulty and with considerable assistance from his arms and his left leg. He related that, during the weekend, he had been putting up a swing in a backyard tree for his children. At one point during the work, he jumped to the ground from a ladder leaning against the tree, a distance of about 4 feet. As he landed, he felt a sharp pain in the front of his right thigh, and he fell to his knees upon landing. He was immediately in considerable discomfort, and the pain did not lessen over the course of the weekend.

Physical examination reveals a somewhat swollen aspect to the lower part of the anterior surface of his right thigh. The area is tender to the touch, but the pain does not involve the knee joint. Using the left leg for comparison, he is considerably impaired in his ability to extend the lower portion of his right leg and doing so causes great discomfort.

After the physical examination, he is told that he has most likely experienced a strain (or "pull") of the rectus femoris muscle. He is given a few days' supply of a nonsteroidal drug to manage the pain and inflammation and is told to lessen the pain by applying ice packs to the affected region. He is advised to avoid stair climbing as much as possible during this time, but to begin walking as soon as he could do it without undue pain. On a follow-up visit 2 weeks later, he is experiencing little impairment in walking, although the strength of the leg is still less than normal and stair climbing is still somewhat of a problem. He is advised to return to regular activity, but to avoid any undue overloading of the affected leg for the foreseeable future.

Questions

1. What kind of contraction was the injured muscle undergoing at the time of the injury? Why does this kind of activity pose a special risk for injury?
2. What factors contributed to the occurrence and severity of this injury?
3. Why was the pain localized to the lower portion of the thigh?
4. What sort of activity would be most likely to reinjure the muscle?
5. What precautions should be taken to avoid reinjury?
6. Why was the patient given a limited supply of the pain medication?

Answers to Case Study Questions for Chapter 9

1. The muscle was undergoing an eccentric contraction; that is, the muscle was activated in order to break the fall upon landing, and the body weight extended it while it was active. Such a stretch can produce a force considerably in excess of the maximal isometric capability of a muscle.
2. The first factor was the sudden eccentric contraction (see above). Second, because the patient was not accustomed to the activity in question, the muscle was not conditioned to absorb the suddenly applied stretch. Third, the height from which the patient jumped could potentially generate a force considerably greater than the capability of the muscle.
3. The pain was localized in the general area of the myotendinous junction, the area where damage is most likely to occur.
4. Given the same conditions, a similar jump to the one causing the injury would be quite likely to result in reinjury. In general, any activity that would lead to an eccentric contraction of the muscle would put it at risk. This would explain the caution against stair climbing during the early stages of recovery.
5. There should be a gradual return to full activity, with adequate time for healing and repair, without any sudden increase in the use of the muscle. The initial precipitating behavior should be avoided.
6. The use of the anti-inflammatory medication should be limited because its continued use has been shown to delay the healing process, and it could also mask warning signs of reinjury.

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Case Study for Chapter 10

Heart Failure

A 50-year-old man consulted his family physician with the principal complaint of shortness of breath and fatigue upon rather mild exertion and a recent weight gain. He appears to be rather pale, moderately overweight, and somewhat short of breath from walking from his car

(continued)

to the office. A careful history yields several pieces of information: He has been a light smoker for most of his adult life, although he has tried to quit; he attributes his morning cough, which resolves after being up for a while, to the smoking habit. He reports that sometimes he awakens suddenly during the night with a feeling of suffocation; sitting upright for a while makes this feeling go away. He has been treated for chronic hypertension, but is no longer taking his prescribed medication. Minor chest pain that he associates with heavy exertion quickly ceases on resting.

Physical examination notes some swelling of his ankles and feet, and palpation reveals a somewhat enlarged and tender liver. Distinct basilar rales (abnormal sounds that indicate pulmonary congestion) are heard during auscultation of the chest. A chest X-ray shows moderate enlargement of the heart, and the same finding (cardiomegaly) was apparent in an ultrasound examination.

The patient is placed on a mild diuretic, along with a drug designed to relax the smooth muscle in the walls of both arteries and veins. He is advised to limit salt intake to less than 4 grams per day; other dietary restrictions include a reduction in the amount of saturated fat and red meat. He is advised that moderate exercise, such as walking, would be beneficial if it is tolerated well. He is referred to a support program to help him quit smoking.

During the next few weeks, significant improvement in exercise tolerance is noted, and both systolic and diastolic blood pressures are reduced. His weight has decreased somewhat. The abnormal lung sounds are absent, and he has been able to quit smoking.

Questions

1. The X-ray and ultrasound data show an increase in the amount of heart muscle. If this was the case, why did the patient suffer from the problems reported above?
2. What effect would lowering the systolic blood pressure have on the ability of the heart muscle to shorten. Why?
3. This patient was not treated with contractility-enhancing drugs. Would such medication have been helpful in this case?
4. Did the result of the diuretic therapy relate most directly to the properties of the muscle at rest or during contraction?
5. Was the patient's morning cough most likely a result of smoking?
6. Did the complaint of fatigue during exercise relate more strongly to problems of the muscle at rest or during contraction?
7. Did the beneficial effects of his therapy relate more to changes in contractility or to changes in the mechanical situation of the heart muscle?
8. What is the benefit of a drug that tends to relax both arterial and venous smooth muscle?

Answers to Case Study Questions for Chapter 10

1. Because of the continuous overload of the heart muscle, it had hypertrophied. At this stage of the patient's disease, however, even the added muscle strength was not sufficient to handle the demands of the body during exercise.
2. With a lowered systolic pressure, the afterload during shortening would be reduced. An examination of the length-tension curve shows that more shortening would be possible, and the force-velocity curve would predict that the contraction would also be more rapid.
3. The use of drugs such as digitalis could have relieved the patient's symptoms sooner, but the risks of such drugs (heart rhythm disturbances, systemic and cardiac toxicity, etc.) make it advisable, if at all possible, to let the inherent properties of the muscle, when properly aided, to correct the problem.
4. The diuretic therapy reduced the blood volume, which meant that the heart muscle was less distended at rest. A lowered arterial volume would have also lowered the afterload on the muscle. Thus, both aspects of the problem were addressed.
5. Because the cough went away soon after arising, it was more likely a result of fluid accumulation in the lungs. The increased heart rate and contractility of the muscle associated with waking activity would have at least partly overcome this problem as the day progressed.
6. The feeling of fatigue is related to the lack of blood circulation in the skeletal muscle. This was most directly related to the weakened state of the heart muscle during contraction, which would reduce the amount of blood that could be pumped with each beat.
7. Because the patient was not given drugs that directly addressed the contractility of the muscle, the beneficial changes must have come about principally through the reduction of the preload and afterload on the muscle.
8. Such drugs can address problems of both excessive afterload and preload at the same time.

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