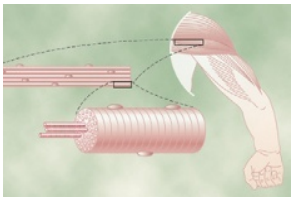
CHAPTER 6

Contraction of Skeletal Muscle



About 40 percent of the body is skeletal muscle, and perhaps another 10 percent is smooth and cardiac muscle. Some of the same basic principles of contraction apply to all three different types of muscle. In this chapter, function of skeletal muscle is considered mainly; the specialized functions of smooth muscle are discussed in Chapter 8, and cardiac muscle is discussed in Chapter 9.

Physiologic Anatomy of Skeletal Muscle

Skeletal Muscle Fiber

Figure 6-1 shows the organization of skeletal muscle, demonstrating that all skeletal muscles are composed of numerous fibers ranging from 10 to 80 micrometers in diameter. Each of these fibers is made up of successively smaller subunits, also shown in Figure 6-1 and described in subsequent paragraphs.

In most skeletal muscles, each fiber extends the entire length of the muscle. Except for about 2 percent of the fibers, each fiber is usually innervated by only one nerve ending, located near the middle of the fiber.

The Sarcolemma Is a Thin Membrane Enclosing a Skeletal Muscle Fiber. The sarcolemma consists of a true cell membrane, called the *plasma membrane,* and an outer coat made up of a thin layer of polysaccharide material that contains numerous thin collagen fibrils. At each end of the muscle fiber, this surface layer of the sarcolemma fuses with a tendon fiber. The tendon fibers in turn collect into bundles to form the muscle tendons that then insert into the bones.

Myofibrils Are Composed of Actin and Myosin Filaments. Each muscle fiber contains several hundred to several thousand *myofibrils,* which are demonstrated by the many small open dots in the cross-sectional view of Figure 6-1*C.* Each myofibril (Figure 6-1*D* and *E*) is composed of about 1500 adjacent *myosin filaments* and 3000 *actin filaments,* which are large polymerized protein molecules that are responsible for the actual muscle contraction. These can be seen in longitudinal view in the electron micrograph of Figure 6-2 and are represented diagrammatically in Figure 6-1, parts *E* through *L.* The thick filaments in the diagrams are *myosin,* and the thin filaments are *actin.*

Note in Figure 6-1*E* that the myosin and actin filaments partially interdigitate and thus cause the myofibrils to have alternate light and dark bands, as illustrated in Figure 6-2. The light bands contain only actin filaments and are called *I bands* because they are *isotropic* to polarized light. The dark bands contain myosin filaments, as well as the ends of the actin filaments where they overlap the myosin, and are called *A bands* because they are *anisotropic* to polarized light. Note also the small projections from the sides of the myosin filaments in Figure 6-1*E* and *L.* These are *cross-bridges.* It is the interaction between these cross-bridges and the actin filaments that causes contraction.

Figure 6-1*E* also shows that the ends of the actin filaments are attached to a so-called *Z disc.* From this disc, these filaments extend in both directions to interdigitate with the myosin filaments. The Z disc, which itself is composed of filamentous proteins different from the actin and myosin filaments, passes crosswise across the myofibril and also crosswise from myofibril to myofibril, attaching the myofibrils to one another all the way across the muscle fiber. Therefore, the entire muscle fiber has light and dark bands, as do the individual myofibrils. These bands give skeletal and cardiac muscle their striated appearance.

The portion of the myofibril (or of the whole muscle fiber) that lies between two successive Z discs is called a *sarcomere.* When the muscle fiber is contracted, as shown at the bottom of Figure 6-5, the length of the sarcomere is about 2 micrometers. At this length, the actin filaments completely overlap the myosin filaments, and the tips of the actin filaments are just beginning to overlap one another. As discussed later, at this length the muscle is capable of generating its greatest force of contraction.

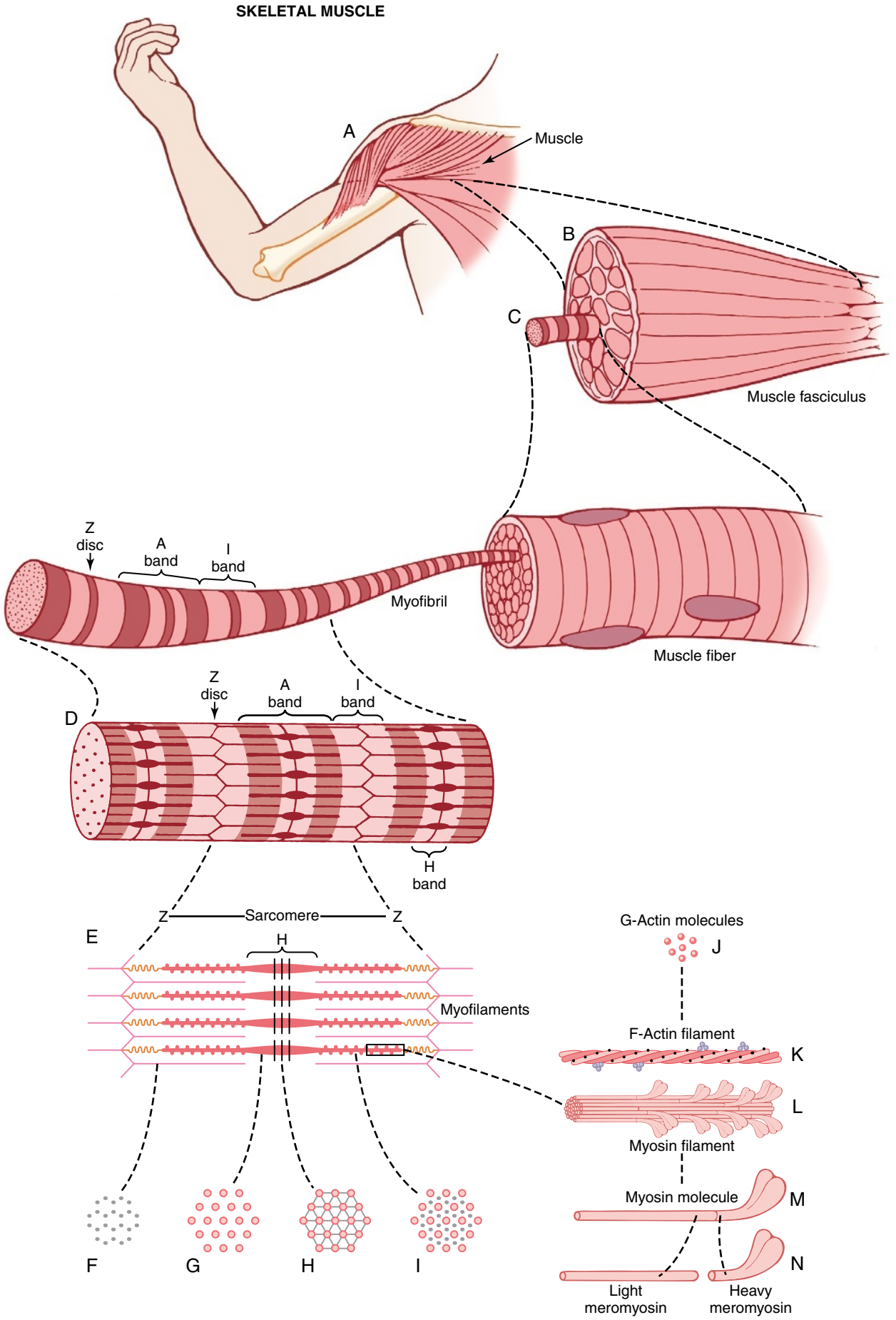


Figure 6-1 Organization of skeletal muscle, from the gross to the molecular level. *F, G, H,* and *I* are cross sections at the levels indicated.

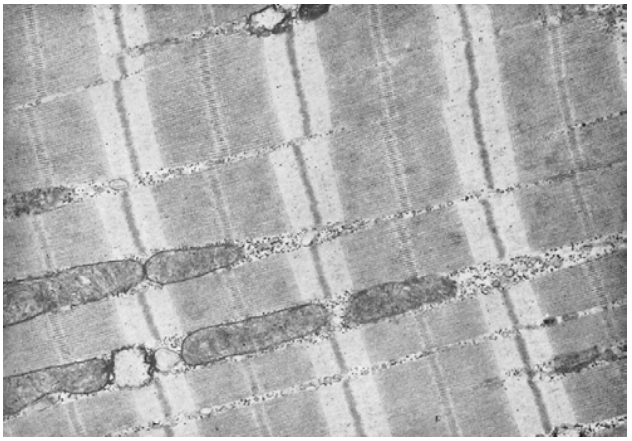


Figure 6-2 Electron micrograph of muscle myofibrils showing the detailed organization of actin and myosin filaments. Note the mitochondria lying between the myofibrils. (From Fawcett DW: The Cell. Philadelphia: WB Saunders, 1981.)

Titin Filamentous Molecules Keep the Myosin and Actin Filaments in Place. The side-by-side relationship between the myosin and actin filaments is difficult to maintain. This is achieved by a large number of filamentous molecules of a protein called *titin* (Figure 6-3). Each titin molecule has a molecular weight of about 3 million, which makes it one of the largest protein molecules in the body. Also, because it is filamentous, it is *very springy.* These springy titin molecules act as a framework that holds the myosin and actin filaments in place so that the contractile machinery of the sarcomere will work. One end of the titin molecule is elastic and is attached to the Z disk, acting as a spring and changing length as the sarcomere contracts and relaxes. The other part of the titin molecule tethers it to the myosin thick filament. The titin molecule itself also appears to act as a template for initial formation of portions of the contractile filaments of the sarcomere, especially the myosin filaments.

Sarcoplasm Is the Intracellular Fluid Between Myofibrils. The many myofibrils of each muscle fiber are suspended side by side in the muscle fiber. The spaces between the myofibrils are filled with intracellular fluid called *sarcoplasm,* containing large quantities of potassium, magnesium, and phosphate, plus multiple protein enzymes. Also present are tremendous numbers of *mitochondria* that lie parallel to the myofibrils. These supply the contracting myofibrils with large amounts of energy in the form of adenosine triphosphate (ATP) formed by the mitochondria.

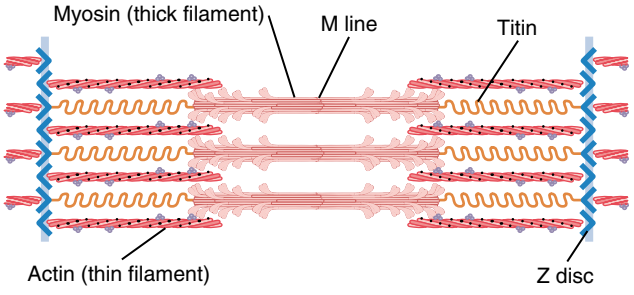


Figure 6-3 Organization of proteins in a sarcomere. Each titin molecule extends from the *Z disc* to the *M line*. Part of the titin molecule is closely associated with the myosin thick filament, whereas the rest of the molecule is springy and changes length as the sarcomere contracts and relaxes.

Sarcoplasmic Reticulum Is a Specialized Endoplasmic Reticulum of Skeletal Muscle. Also in the sarcoplasm surrounding the myofibrils of each muscle fiber is an extensive reticulum (Figure 6-4), called the *sarcoplasmic reticulum.* This reticulum has a special organization that is extremely important in controlling muscle contraction, as discussed in Chapter 7. The rapidly contracting types of muscle fibers have especially extensive sarcoplasmic reticula.

General Mechanism of Muscle Contraction

The initiation and execution of muscle contraction occur in the following sequential steps.

1. An action potential travels along a motor nerve to its endings on muscle fibers.
2. At each ending, the nerve secretes a small amount of the neurotransmitter substance *acetylcholine.*
3. The acetylcholine acts on a local area of the muscle fiber membrane to open multiple "acetylcholine-gated" cation channels through protein molecules floating in the membrane.
4. Opening of the acetylcholine-gated channels allows large quantities of sodium ions to diffuse to the interior of the muscle fiber membrane. This causes a local depolarization that in turn leads to opening of

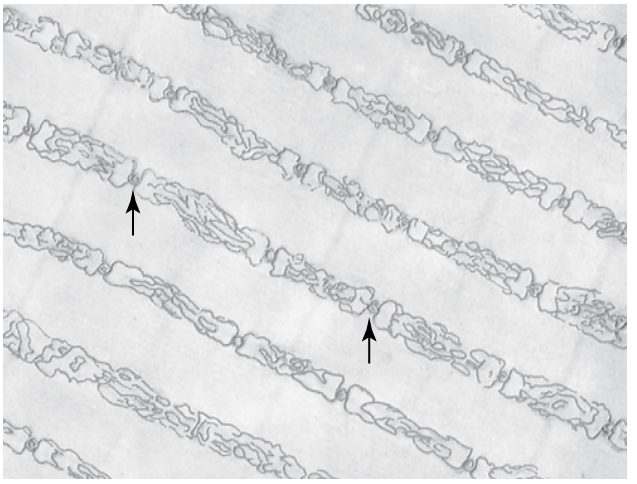


Figure 6-4 Sarcoplasmic reticulum in the extracellular spaces between the myofibrils, showing a longitudinal system paralleling the myofibrils. Also shown in cross section are T tubules (*arrows*) that lead to the exterior of the fiber membrane and are important for conducting the electrical signal into the center of the muscle fiber. (From Fawcett DW: The Cell. Philadelphia: WB Saunders, 1981.)

voltage-gated sodium channels. This initiates an action potential at the membrane.

5. The action potential travels along the muscle fiber membrane in the same way that action potentials travel along nerve fiber membranes.
6. The action potential depolarizes the muscle membrane, and much of the action potential electricity flows through the center of the muscle fiber. Here it causes the sarcoplasmic reticulum to release large quantities of calcium ions that have been stored within this reticulum.
7. The calcium ions initiate attractive forces between the actin and myosin filaments, causing them to slide alongside each other, which is the contractile process.
8. After a fraction of a second, the calcium ions are pumped back into the sarcoplasmic reticulum by a Ca^{++} membrane pump and remain stored in the reticulum until a new muscle action potential comes along; this removal of calcium ions from the myofibrils causes the muscle contraction to cease.

We now describe the molecular machinery of the muscle contractile process.

Molecular Mechanism of Muscle Contraction

Sliding Filament Mechanism of Muscle Contraction. Figure 6-5 demonstrates the basic mechanism of muscle contraction. It shows the relaxed state of a sarcomere (top) and the contracted state (bottom). In the relaxed state, the ends of the actin filaments extending from two successive Z discs barely begin to overlap one another. Conversely, in the contracted state, these actin filaments have been pulled inward among the myosin filaments, so their ends overlap one another to their maximum extent. Also, the Z discs have been pulled by the actin filaments up to the ends of the myosin filaments. Thus, muscle contraction occurs by a *sliding filament mechanism.*

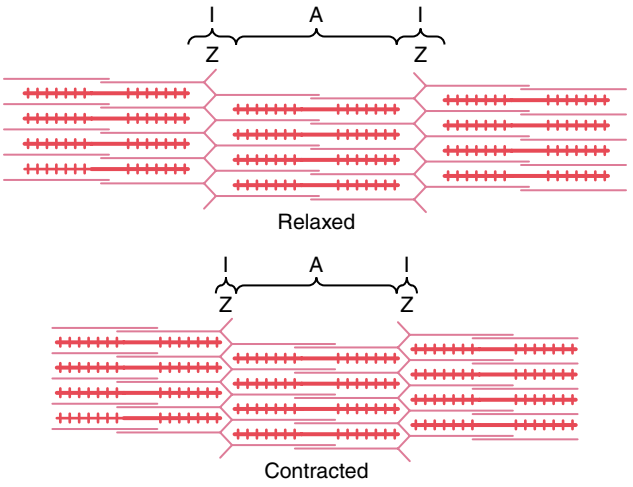


Figure 6-5 Relaxed and contracted states of a myofibril showing (*top*) sliding of the actin filaments (*pink*) into the spaces between the myosin filaments (*red*) and (*bottom*) pulling of the Z membranes toward each other.

But what causes the actin filaments to slide inward among the myosin filaments? This is caused by forces generated by interaction of the cross-bridges from the myosin filaments with the actin filaments. Under resting conditions, these forces are inactive. But when an action potential travels along the muscle fiber, this causes the sarcoplasmic reticulum to release large quantities of calcium ions that rapidly surround the myofibrils. The calcium ions in turn activate the forces between the myosin and actin filaments, and contraction begins. But energy is needed for the contractile process to proceed. This energy comes from high-energy bonds in the ATP molecule, which is degraded to adenosine diphosphate (ADP) to liberate the energy. In the next few sections, we describe what is known about the details of these molecular processes of contraction.

Molecular Characteristics of the Contractile Filaments

Myosin Filaments Are Composed of Multiple Myosin Molecules. Each of the myosin molecules, shown in Figure 6-6*A*, has a molecular weight of about 480,000. Figure 6-6*B* shows the organization of many molecules to form a myosin filament, as well as interaction of this filament on one side with the ends of two actin filaments.

The *myosin molecule* (see Figure 6-6*A*) is composed of six polypeptide chains—two *heavy chains,* each with a molecular weight of about 200,000, and four *light chains* with molecular weights of about 20,000 each. The two heavy chains wrap spirally around each other to form a double

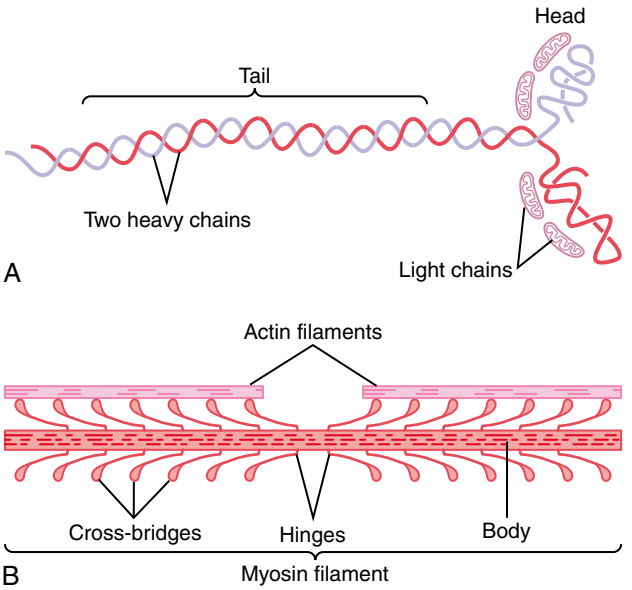


Figure 6-6 *A,* Myosin molecule. *B,* Combination of many myosin molecules to form a myosin filament. Also shown are thousands of myosin *cross-bridges* and interaction between the *heads* of the cross-bridges with adjacent actin filaments.

helix, which is called the *tail* of the myosin molecule. One end of each of these chains is folded bilaterally into a globular polypeptide structure called a myosin *head.* Thus, there are two free heads at one end of the double-helix myosin molecule. The four light chains are also part of the myosin head, two to each head. These light chains help control the function of the head during muscle contraction.

The *myosin filament* is made up of 200 or more individual myosin molecules. The central portion of one of these filaments is shown in Figure 6-6*B,* displaying the tails of the myosin molecules bundled together to form the *body* of the filament, while many heads of the molecules hang outward to the sides of the body. Also, part of the body of each myosin molecule hangs to the side along with the head, thus providing an *arm* that extends the head outward from the body, as shown in the figure. The protruding arms and heads together are called *cross-bridges.* Each cross-bridge is flexible at two points called *hinges*—one where the arm leaves the body of the myosin filament, and the other where the head attaches to the arm. The hinged arms allow the heads to be either extended far outward from the body of the myosin filament or brought close to the body. The hinged heads in turn participate in the actual contraction process, as discussed in the following sections.

The total length of each myosin filament is uniform, almost exactly 1.6 micrometers. Note, however, that there are no cross-bridge heads in the center of the myosin filament for a distance of about 0.2 micrometer because the hinged arms extend away from the center.

Now, to complete the picture, the myosin filament itself is twisted so that each successive pair of cross-bridges is axially displaced from the previous pair by 120 degrees. This ensures that the cross-bridges extend in all directions around the filament.

ATPase Activity of the Myosin Head. Another feature of the myosin head that is essential for muscle contraction is that it functions as an *ATPase enzyme.* As explained later, this property allows the head to cleave ATP and use the energy derived from the ATP's high-energy phosphate bond to energize the contraction process.

Actin Filaments Are Composed of Actin, Tropomyosin, and Troponin. The backbone of the actin filament is a double-stranded *F-actin protein molecule,* represented by the two lighter-colored strands in Figure 6-7. The two strands are wound in a helix in the same manner as the myosin molecule.

Each strand of the double F-actin helix is composed of polymerized *G-actin molecules,* each having a molecular weight of about 42,000. Attached to each one of the G-actin molecules is one molecule of ADP. It is believed that these ADP molecules are the active sites on the actin filaments with which the cross-bridges of the myosin filaments interact to cause muscle contraction. The active sites on the two F-actin strands of the double helix are staggered, giving one active site on the overall actin filament about every 2.7 nanometers.

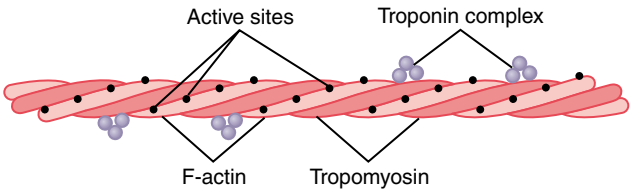


Figure 6-7 Actin filament, composed of two helical strands of ***F-actin*** molecules and two strands of ***tropomyosin*** molecules that fit in the grooves between the actin strands. Attached to one end of each tropomyosin molecule is a ***troponin*** complex that initiates contraction.

Each actin filament is about 1 micrometer long. The bases of the actin filaments are inserted strongly into the Z discs; the ends of the filaments protrude in both directions to lie in the spaces between the myosin molecules, as shown in Figure 6-5.

Tropomyosin Molecules. The actin filament also contains another protein, *tropomyosin.* Each molecule of tropomyosin has a molecular weight of 70,000 and a length of 40 nanometers. These molecules are wrapped spirally around the sides of the F-actin helix. In the resting state, the tropomyosin molecules lie on top of the active sites of the actin strands so that attraction cannot occur between the actin and myosin filaments to cause contraction.

Troponin and Its Role in Muscle Contraction. Attached intermittently along the sides of the tropomyosin molecules are still other protein molecules called *troponin.* These are actually complexes of three loosely bound protein subunits, each of which plays a specific role in controlling muscle contraction. One of the subunits (troponin I) has a strong affinity for actin, another (troponin T) for tropomyosin, and a third (troponin C) for calcium ions. This complex is believed to attach the tropomyosin to the actin. The strong affinity of the troponin for calcium ions is believed to initiate the contraction process, as explained in the next section.

Interaction of One Myosin Filament, Two Actin Filaments, and Calcium Ions to Cause Contraction

Inhibition of the Actin Filament by the Troponin-Tropomyosin Complex; Activation by Calcium Ions. A pure actin filament without the presence of the troponin-tropomyosin complex (but in the presence of magnesium ions and ATP) binds instantly and strongly with the heads of the myosin molecules. Then, if the troponin-tropomyosin complex is added to the actin filament, the binding between myosin and actin does not take place. Therefore, it is believed that the active sites on the normal actin filament of the relaxed muscle are inhibited or physically covered by the troponin-tropomyosin complex. Consequently, the sites cannot attach to the heads of the myosin filaments to cause contraction. Before contraction can take place, the inhibitory effect of the troponin-tropomyosin complex must itself be inhibited.

This brings us to the role of the calcium ions. In the presence of large amounts of calcium ions, the inhibitory effect of the troponin-tropomyosin on the actin filaments is itself inhibited. The mechanism of this is not known, but one suggestion is the following: When calcium ions combine with troponin C, each molecule of which can bind strongly with up to four calcium ions, the troponin complex supposedly undergoes a conformational change that in some way tugs on the tropomyosin molecule and moves it deeper into the groove between the two actin strands. This "uncovers" the active sites of the actin, thus allowing these to attract the myosin cross-bridge heads and cause contraction to proceed. Although this is a hypothetical mechanism, it does emphasize that the normal relation between the troponin-tropomyosin complex and actin is altered by calcium ions, producing a new condition that leads to contraction.

Interaction Between the "Activated" Actin Filament and the Myosin Cross-Bridges—The "Walk-Along" Theory of Contraction. As soon as the actin filament becomes activated by the calcium ions, the heads of the cross-bridges from the myosin filaments become attracted to the active sites of the actin filament, and this, in some way, causes contraction to occur. Although the precise manner by which this interaction between the cross-bridges and the actin causes contraction is still partly theoretical, one hypothesis for which considerable evidence exists is the "walk-along" theory (or *"ratchet" theory*) of contraction.

Figure 6-8 demonstrates this postulated walk-along mechanism for contraction. The figure shows the heads of two cross-bridges attaching to and disengaging from active sites of an actin filament. It is postulated that when a head attaches to an active site, this attachment simultaneously causes profound changes in the intramolecular forces between the head and arm of its cross-bridge. The new alignment of forces causes the head to tilt toward the arm and to drag the actin filament along with it. This tilt of the head is called the *power stroke.* Then, immediately after tilting, the head automatically breaks away from the active site. Next, the head returns to its extended direction. In this position, it combines with a new active site farther down along the actin filament; then the head tilts again to cause a new power stroke, and the actin filament moves another step. Thus, the heads of the cross-bridges bend back and forth and step by step walk along the actin filament, pulling the ends of two successive actin filaments toward the center of the myosin filament.

Each one of the cross-bridges is believed to operate independently of all others, each attaching and pulling in a continuous repeated cycle. Therefore, the greater the number of cross-bridges in contact with the actin filament at any given time, the greater the force of contraction.

ATP as the Source of Energy for Contraction—Chemical Events in the Motion of the Myosin Heads. When a muscle contracts, work is performed and energy is required. Large amounts of ATP are cleaved to form ADP during the contraction process; the greater the amount of work performed by the muscle, the greater the amount of ATP that is cleaved, which is called the *Fenn effect.* The following sequence of events is believed to be the means by which this occurs:

1. Before contraction begins, the heads of the cross-bridges bind with ATP. The ATPase activity of the myosin head immediately cleaves the ATP but leaves the cleavage products, ADP plus phosphate ion, bound to the head. In this state, the conformation of the head is such that it extends perpendicularly toward the actin filament but is not yet attached to the actin.
2. When the troponin-tropomyosin complex binds with calcium ions, active sites on the actin filament are uncovered and the myosin heads then bind with these, as shown in Figure 6-8.
3. The bond between the head of the cross-bridge and the active site of the actin filament causes a conformational change in the head, prompting the head to tilt toward the arm of the cross-bridge. This provides the *power stroke* for pulling the actin filament. The energy that activates the power stroke is the energy already stored, like a "cocked" spring, by the conformational change that occurred in the head when the ATP molecule was cleaved earlier.
4. Once the head of the cross-bridge tilts, this allows release of the ADP and phosphate ion that were previously attached to the head. At the site of release of the ADP, a new molecule of ATP binds. This binding of new ATP causes detachment of the head from the actin.
5. After the head has detached from the actin, the new molecule of ATP is cleaved to begin the next cycle, leading to a new power stroke. That is, the energy again "cocks" the head back to its perpendicular condition, ready to begin the new power stroke cycle.
6. When the cocked head (with its stored energy derived from the cleaved ATP) binds with a new active site on the actin filament, it becomes uncocked and once again provides a new power stroke.

Thus, the process proceeds again and again until the actin filaments pull the Z membrane up against the ends of the myosin filaments or until the load on the muscle becomes too great for further pulling to occur.

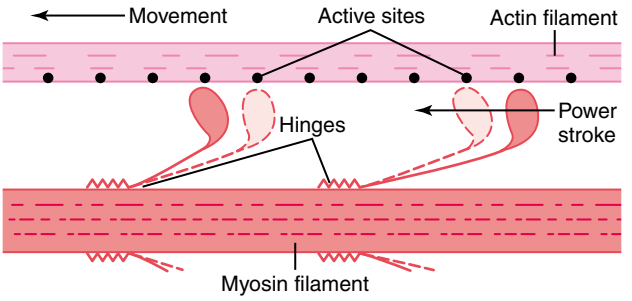


Figure 6-8 "Walk-along" mechanism for contraction of the muscle.

The Amount of Actin and Myosin Filament Overlap Determines Tension Developed by the Contracting Muscle

Figure 6-9 shows the effect of sarcomere length and amount of myosin-actin filament overlap on the active tension developed by a contracting muscle fiber. To the right, shown in black, are different degrees of overlap of the myosin and actin filaments at different sarcomere lengths. At point D on the diagram, the actin filament has pulled all the way out to the end of the myosin filament, with no actin-myosin overlap. At this point, the tension developed by the activated muscle is zero. Then, as the sarcomere shortens and the actin filament begins to overlap the myosin filament, the tension increases progressively until the sarcomere length decreases to about 2.2 micrometers. At this point, the actin filament has already overlapped all the cross-bridges of the myosin filament but has not yet reached the center of the myosin filament. With further shortening, the sarcomere maintains full tension until point B is reached, at a sarcomere length of about 2 micrometers. At this point, the ends of the two actin filaments begin to overlap each other in addition to overlapping the myosin filaments. As the sarcomere length falls from 2 micrometers down to about 1.65 micrometers, at point A, the strength of contraction decreases rapidly. At this point, the two Z discs of the sarcomere abut the ends of the myosin filaments. Then, as contraction proceeds to still shorter sarcomere lengths, the ends of the myosin filaments are crumpled and, as shown in the figure, the strength of contraction approaches zero, but the sarcomere has now contracted to its shortest length.

Effect of Muscle Length on Force of Contraction in the Whole Intact Muscle. The top curve of Figure 6-10 is similar to that in Figure 6-9, but the curve in Figure 6-10 depicts tension of the intact, whole muscle rather than of a single muscle fiber. The whole muscle has a large amount of connective tissue in it; also, the sarcomeres in different parts of the muscle do not always contract the same amount. Therefore, the curve has somewhat different dimensions from those shown for the individual muscle fiber, but it exhibits the same general form for the slope *in the normal range of contraction,* as noted in Figure 6-10.

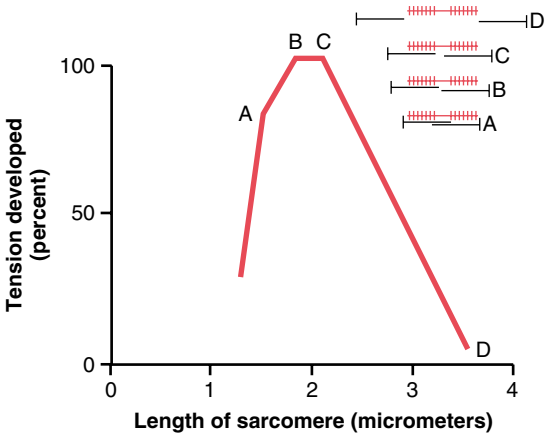


Figure 6-9 Length-tension diagram for a single fully contracted sarcomere, showing maximum strength of contraction when the sarcomere is 2.0 to 2.2 micrometers in length. At the upper right are the relative positions of the actin and myosin filaments at different sarcomere lengths from *point A* to *point D.* (Modified from Gordon AM, Huxley AF, Julian FJ: The length-tension diagram of single vertebrate striated muscle fibers. J Physiol 171:28P, 1964.)

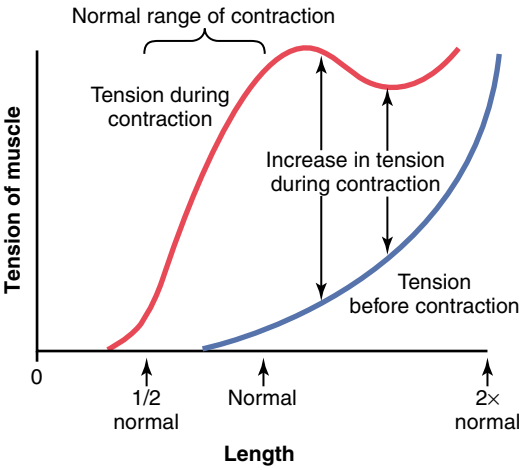


Figure 6-10 Relation of muscle length to tension in the muscle both before and during muscle contraction.

Note in Figure 6-10 that when the muscle is at its normal *resting* length, which is at a sarcomere length of about 2 micrometers, it contracts upon activation with the approximate maximum force of contraction. However, the *increase* in tension that occurs during contraction, called *active tension,* decreases as the muscle is stretched beyond its normal length—that is, to a sarcomere length greater than about 2.2 micrometers. This is demonstrated by the decreased length of the arrow in the figure at greater than normal muscle length.

Relation of Velocity of Contraction to Load

A skeletal muscle contracts rapidly when it contracts against no load—to a state of full contraction in about 0.1 second for the average muscle. When loads are applied, the velocity of contraction becomes progressively less as the load increases, as shown in Figure 6-11. That is, when the

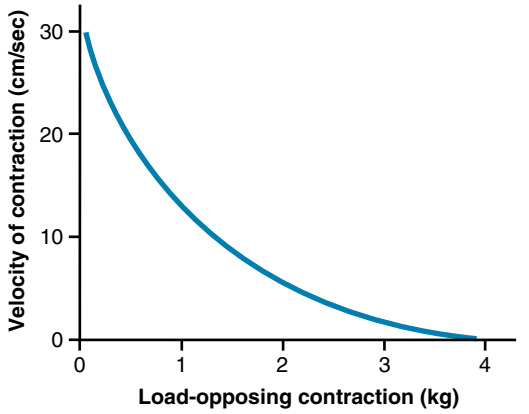


Figure 6-11 Relation of load to velocity of contraction in a skeletal muscle with a cross section of 1 square centimeter and a length of 8 centimeters.

load has been increased to equal the maximum force that the muscle can exert, the velocity of contraction becomes zero and no contraction results, despite activation of the muscle fiber.

This decreasing velocity of contraction with load is caused by the fact that a load on a contracting muscle is a reverse force that opposes the contractile force caused by muscle contraction. Therefore, the net force that is available to cause velocity of shortening is correspondingly reduced.

Energetics of Muscle Contraction

Work Output During Muscle Contraction

When a muscle contracts against a load, it performs *work.* This means that *energy* is transferred from the muscle to the external load to lift an object to a greater height or to overcome resistance to movement.

In mathematical terms, work is defined by the following equation:

$$W = L \times D$$

in which W is the work output, L is the load, and D is the distance of movement against the load. The energy required to perform the work is derived from the chemical reactions in the muscle cells during contraction, as described in the following sections.

Sources of Energy for Muscle Contraction

We have already seen that muscle contraction depends on energy supplied by ATP. Most of this energy is required to actuate the walk-along mechanism by which the cross-bridges pull the actin filaments, but small amounts are required for (1) pumping calcium ions from the sarcoplasm into the sarcoplasmic reticulum after the contraction is over and (2) pumping sodium and potassium ions through the muscle fiber membrane to maintain appropriate ionic environment for propagation of muscle fiber action potentials.

The concentration of ATP in the muscle fiber, about 4 millimolar, is sufficient to maintain full contraction for only 1 to 2 seconds at most. The ATP is split to form ADP, which transfers energy from the ATP molecule to the contracting machinery of the muscle fiber. Then, as described in Chapter 2, the ADP is rephosphorylated to form new ATP within another fraction of a second, which allows the muscle to continue its contraction. There are several sources of the energy for this rephosphorylation.

The first source of energy that is used to reconstitute the ATP is the substance *phosphocreatine,* which carries a high-energy phosphate bond similar to the bonds of ATP. The high-energy phosphate bond of phosphocreatine has a slightly higher amount of free energy than that of each ATP bond, as is discussed more fully in Chapters 67 and 72. Therefore, phosphocreatine is instantly cleaved, and its released energy causes bonding of a new phosphate ion to ADP to reconstitute the ATP. However, the total amount of phosphocreatine in the muscle fiber is also very little—only about five times as great as the ATP. Therefore, the combined energy of both the stored ATP and the phosphocreatine in the muscle is capable of causing maximal muscle contraction for only 5 to 8 seconds.

The second important source of energy, which is used to reconstitute both ATP and phosphocreatine, is "glycolysis" of *glycogen* previously stored in the muscle cells. Rapid enzymatic breakdown of the glycogen to pyruvic acid and lactic acid liberates energy that is used to convert ADP to ATP; the ATP can then be used directly to energize additional muscle contraction and also to re-form the stores of phosphocreatine.

The importance of this glycolysis mechanism is twofold. First, the glycolytic reactions can occur even in the absence of oxygen, so muscle contraction can be sustained for many seconds and sometimes up to more than a minute, even when oxygen delivery from the blood is not available. Second, the rate of formation of ATP by the glycolytic process is about 2.5 times as rapid as ATP formation in response to cellular foodstuffs reacting with oxygen. However, so many end products of glycolysis accumulate in the muscle cells that glycolysis also loses its capability to sustain maximum muscle contraction after about 1 minute.

The third and final source of energy is *oxidative metabolism.* This means combining oxygen with the end products of glycolysis and with various other cellular foodstuffs to liberate ATP. More than 95 percent of all energy used by the muscles for sustained, long-term contraction is derived from this source. The foodstuffs that are consumed are carbohydrates, fats, and protein. For extremely long-term maximal muscle activity—over a period of many hours—by far the greatest proportion of energy comes from fats, but for periods of 2 to 4 hours, as much as one half of the energy can come from stored carbohydrates.

The detailed mechanisms of these energetic processes are discussed in Chapters 67 through 72. In addition, the importance of the different mechanisms of energy release during performance of different sports is discussed in Chapter 84 on sports physiology.

Efficiency of Muscle Contraction. The efficiency of an engine or a motor is calculated as the percentage of energy input that is converted into work instead of heat. The percentage of the input energy to muscle (the chemical energy in nutrients) that can be converted into work, even under the best conditions, is less than 25 percent, with the remainder becoming heat. The reason for this low efficiency is that about one half of the energy in foodstuffs is lost during the formation of ATP, and even then, only 40 to 45 percent of the energy in the ATP itself can later be converted into work.

Maximum efficiency can be realized only when the muscle contracts at a moderate velocity. If the muscle contracts slowly or without any movement, small amounts of *maintenance heat* are released during contraction, even though little or no work is performed, thereby decreasing the con-

version efficiency to as little as zero. Conversely, if contraction is too rapid, large proportions of the energy are used to overcome viscous friction within the muscle itself, and this, too, reduces the efficiency of contraction. Ordinarily, maximum efficiency is developed when the velocity of contraction is about 30 percent of maximum.

Characteristics of Whole Muscle Contraction

Many features of muscle contraction can be demonstrated by eliciting single *muscle twitches.* This can be accomplished by instantaneous electrical excitation of the nerve to a muscle or by passing a short electrical stimulus through the muscle itself, giving rise to a single, sudden contraction lasting for a fraction of a second.

Isometric Versus Isotonic Contraction. Muscle contraction is said to be *isometric* when the muscle does not shorten during contraction and *isotonic* when it does shorten but the tension on the muscle remains constant throughout the contraction. Systems for recording the two types of muscle contraction are shown in Figure 6-12.

In the isometric system, the muscle contracts against a force transducer without decreasing the muscle length, as shown on the right in Figure 6-12. In the isotonic system, the muscle shortens against a fixed load; this is illustrated on the left in the figure, showing a muscle lifting a pan of weights. The characteristics of isotonic contraction depend on the load against which the muscle contracts, as well as the inertia of the load. However, the isometric system records strictly changes in force of muscle contraction itself. Therefore, the isometric system is most often used when comparing the functional characteristics of different muscle types.

Characteristics of Isometric Twitches Recorded from Different Muscles. The human body has many sizes of skeletal muscles—from the small stapedius muscle in the middle ear, measuring only a few millimeters long and a millimeter or so in diameter, up to the large quadriceps muscle, a half million times as large as the stapedius. Further, the fibers may be as small as 10 micrometers in diameter or as large as 80 micrometers. Finally, the energetics of muscle contraction vary considerably from one muscle to another. Therefore, it is no wonder that the mechanical characteristics of muscle contraction differ among muscles.

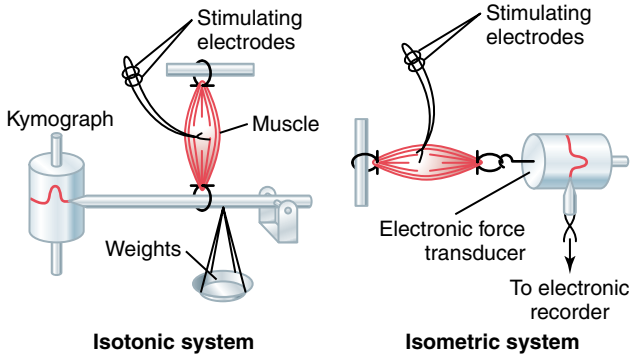


Figure 6-12 Isotonic and isometric systems for recording muscle contractions.

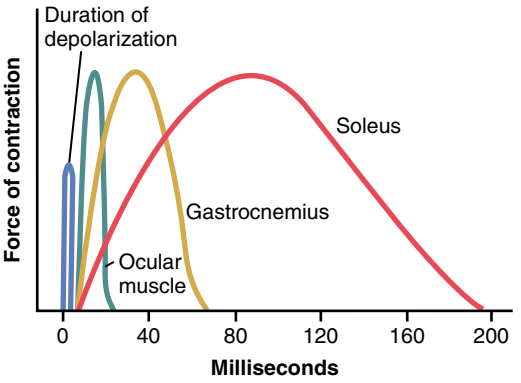


Figure 6-13 Duration of isometric contractions for different types of mammalian skeletal muscles, showing a latent period between the action potential (depolarization) and muscle contraction.

Figure 6-13 shows records of isometric contractions of three types of skeletal muscle: an ocular muscle, which has a duration of *isometric* contraction of less than 1/50 second; the gastrocnemius muscle, which has a duration of contraction of about 1/15 second; and the soleus muscle, which has a duration of contraction of about 1/5 second. It is interesting that these durations of contraction are adapted to the functions of the respective muscles. Ocular movements must be extremely rapid to maintain fixation of the eyes on specific objects to provide accuracy of vision. The gastrocnemius muscle must contract moderately rapidly to provide sufficient velocity of limb movement for running and jumping, and the soleus muscle is concerned principally with slow contraction for continual, long-term support of the body against gravity.

Fast Versus Slow Muscle Fibers. As we discuss more fully in Chapter 84 on sports physiology, every muscle of the body is composed of a mixture of so-called *fast* and *slow* muscle fibers, with still other fibers gradated between these two extremes. Muscles that react rapidly, including anterior tibialis, are composed mainly of "fast" fibers with only small numbers of the slow variety. Conversely, muscles such as soleus that respond slowly but with prolonged contraction are composed mainly of "slow" fibers. The differences between these two types of fibers are as follows.

Slow Fibers (Type 1, Red Muscle). (1) Smaller fibers. (2) Also innervated by smaller nerve fibers. (3) More extensive blood vessel system and capillaries to supply extra amounts of oxygen. (4) Greatly increased numbers of mitochondria, also to support high levels of oxidative metabolism. (5) Fibers contain large amounts of myoglobin, an iron-containing protein similar to hemoglobin in red blood cells. Myoglobin combines with oxygen and stores it until needed; this also greatly speeds oxygen transport to the mitochondria. The myoglobin gives the slow muscle a reddish appearance and the name *red muscle.*

Fast Fibers (Type II, White Muscle). (1) Large fibers for great strength of contraction. (2) Extensive sarcoplasmic reticulum for rapid release of calcium ions to initiate contraction. (3) Large amounts of glycolytic enzymes for rapid release of energy by the glycolytic process. (4) Less extensive blood supply because oxidative metabolism is of secondary importance. (5) Fewer mitochondria, also because oxidative metabolism is secondary. A deficit of red myoglobin in fast muscle gives it the name *white muscle.*

Mechanics of Skeletal Muscle Contraction

Motor Unit—All the Muscle Fibers Innervated by a Single Nerve Fiber. Each motoneuron that leaves the spinal cord innervates multiple muscle fibers, the number depending on the type of muscle. All the muscle fibers innervated by a single nerve fiber are called a *motor unit.* In general, small muscles that react rapidly and whose control must be exact have more nerve fibers for fewer muscle fibers (for instance, as few as two or three muscle fibers per motor unit in some of the laryngeal muscles). Conversely, large muscles that do not require fine control, such as the soleus muscle, may have several hundred muscle fibers in a motor unit. An average figure for all the muscles of the body is questionable, but a good guess would be about 80 to 100 muscle fibers to a motor unit.

The muscle fibers in each motor unit are not all bunched together in the muscle but overlap other motor units in microbundles of 3 to 15 fibers. This interdigitation allows the separate motor units to contract in support of one another rather than entirely as individual segments.

Muscle Contractions of Different Force—Force Summation. *Summation* means the adding together of individual twitch contractions to increase the intensity of overall muscle contraction. Summation occurs in two ways: (1) by increasing the number of motor units contracting simultaneously, which is called *multiple fiber summation,* and (2) by increasing the frequency of contraction, which is called *frequency summation* and can lead to *tetanization.*

Multiple Fiber Summation. When the central nervous system sends a weak signal to contract a muscle, the smaller motor units of the muscle may be stimulated in preference to the larger motor units. Then, as the strength of the signal increases, larger and larger motor units begin to be excited as well, with the largest motor units often having as much as 50 times the contractile force of the smallest units. This is called the *size principle.* It is important because it allows the gradations of muscle force during weak contraction to occur in small steps, whereas the steps become progressively greater when large amounts of force are required. The cause of this size principle is that the smaller motor units are driven by small motor nerve fibers, and the small motoneurons in the spinal cord are more excitable than the larger ones, so naturally they are excited first.

Another important feature of multiple fiber summation is that the different motor units are driven asynchronously by the spinal cord, so contraction alternates among motor units one after the other, thus providing smooth contraction even at low frequencies of nerve signals.

Frequency Summation and Tetanization. Figure 6-14 shows the principles of frequency summation and tetanization. To the left are displayed individual twitch contractions occurring one after another at low frequency of stimulation. Then, as the frequency increases, there comes a point where each new contraction occurs before the preceding one is over. As a result, the second contraction is added partially to the first, so the total strength of contraction rises progressively with increasing frequency. When the frequency reaches a critical level, the successive contractions eventually become so rapid that they fuse together and the whole muscle contraction appears to be completely smooth and continuous, as shown in the figure. This is called *tetanization.* At a slightly higher frequency, the strength of contraction reaches its maximum, so any additional increase in frequency beyond that point has no further effect in increasing contractile force. This occurs because enough calcium ions are maintained in the muscle sarcoplasm, even between action potentials, so that full contractile state is sustained without allowing any relaxation between the action potentials.

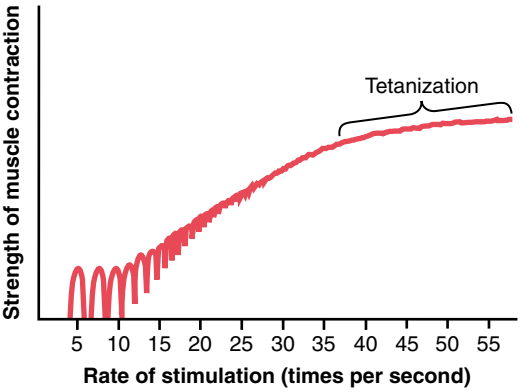


Figure 6-14 Frequency summation and tetanization.

Maximum Strength of Contraction. The maximum strength of tetanic contraction of a muscle operating at a normal muscle length averages between 3 and 4 kilograms per square centimeter of muscle, or 50 pounds per square inch. Because a quadriceps muscle can have up to 16 square inches of muscle belly, as much as 800 pounds of tension may be applied to the patellar tendon. Thus, one can readily understand how it is possible for muscles to pull their tendons out of their insertions in bone.

Changes in Muscle Strength at the Onset of Contraction—The Staircase Effect (Treppe). When a muscle begins to contract after a long period of rest, its initial strength of contraction may be as little as one-half its strength 10 to 50 muscle twitches later. That is, the strength of contraction increases to a plateau, a phenomenon called the *staircase effect,* or *treppe.*

Although all the possible causes of the staircase effect are not known, it is believed to be caused primarily by increasing calcium ions in the cytosol because of the release of more and more ions from the sarcoplasmic reticulum with each successive muscle action potential and failure of the sarcoplasm to recapture the ions immediately.

Skeletal Muscle Tone. Even when muscles are at rest, a certain amount of tautness usually remains. This is called *muscle tone.* Because normal skeletal muscle fibers do not contract without an action potential to stimulate the fibers, skeletal muscle tone results entirely from a low rate of nerve impulses coming from the spinal cord. These, in turn, are controlled partly by signals transmitted from the brain to the appropriate spinal cord anterior motoneurons and partly by signals that originate in *muscle spindles* located in the muscle itself. Both of these are discussed in relation to muscle spindle and spinal cord function in Chapter 54.

Muscle Fatigue. Prolonged and strong contraction of a muscle leads to the well-known state of muscle fatigue. Studies in athletes have shown that muscle fatigue increases in almost direct proportion to the rate of depletion of muscle glycogen. Therefore, fatigue results mainly from inability of the contractile and metabolic processes of the muscle fibers to continue supplying the same work output. However, experiments have also shown that transmission of the nerve signal

through the neuromuscular junction, which is discussed in Chapter 7, can diminish at least a small amount after intense prolonged muscle activity, thus further diminishing muscle contraction. Interruption of blood flow through a contracting muscle leads to almost complete muscle fatigue within 1 or 2 minutes because of the loss of nutrient supply, especially loss of oxygen.

Lever Systems of the Body. Muscles operate by applying tension to their points of insertion into bones, and the bones in turn form various types of lever systems. Figure 6-15 shows the lever system activated by the biceps muscle to lift the forearm. If we assume that a large biceps muscle has a cross-sectional area of 6 square inches, the maximum force of contraction would be about 300 pounds. When the forearm is at right angles with the upper arm, the tendon attachment of the biceps is about 2 inches anterior to the fulcrum at the elbow and the total length of the forearm lever is about 14 inches. Therefore, the amount of lifting power of the biceps at the hand would be only one seventh of the 300 pounds of muscle force, or about 43 pounds. When the arm is fully extended, the attachment of the biceps is much less than 2 inches anterior to the fulcrum and the force with which the hand can be brought forward is also much less than 43 pounds.

In short, an analysis of the lever systems of the body depends on knowledge of (1) the point of muscle insertion, (2) its distance from the fulcrum of the lever, (3) the length of the lever arm, and (4) the position of the lever. Many types of movement are required in the body, some of which need great strength and others of which need large distances of movement. For this reason, there are many different types of muscle; some are long and contract a long distance, and some are short but have large cross-sectional areas and can provide extreme strength of contraction over short distances. The study of different types of muscles, lever systems, and their movements is called *kinesiology* and is an important scientific component of human physioanatomy.

"Positioning" of a Body Part by Contraction of Agonist and Antagonist Muscles on Opposite Sides of a Joint—"Coactivation" of Antagonist Muscles. Virtually all body movements are caused by simultaneous contraction of agonist and antagonist muscles on opposite sides of joints. This is called coactivation of the agonist and antagonist muscles, and it is controlled by the motor control centers of the brain and spinal cord.

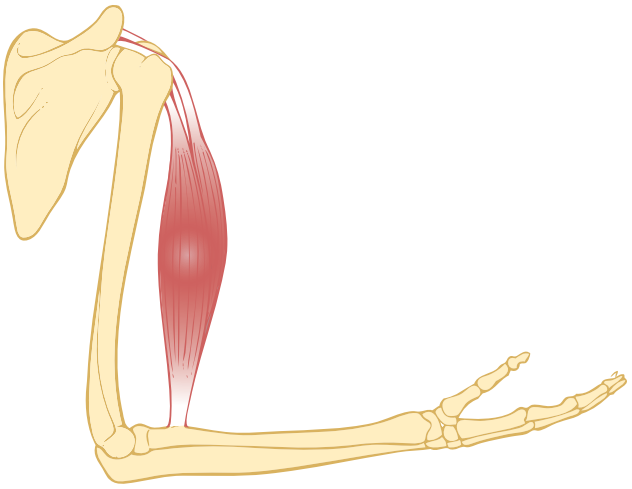


Figure 6-15 Lever system activated by the biceps muscle.

The position of each separate part of the body, such as an arm or a leg, is determined by the relative degrees of contraction of the agonist and antagonist sets of muscles. For instance, let us assume that an arm or a leg is to be placed in a midrange position. To achieve this, agonist and antagonist muscles are excited about equally. Remember that an elongated muscle contracts with more force than a shortened muscle, which was demonstrated in Figure 6-10, showing maximum strength of contraction at full functional muscle length and almost no strength of contraction at half-normal length. Therefore, the elongated muscle on one side of a joint can contract with far greater force than the shorter muscle on the opposite side. As an arm or leg moves toward its midposition, the strength of the longer muscle decreases, whereas the strength of the shorter muscle increases until the two strengths equal each other. At this point, movement of the arm or leg stops. Thus, by varying the ratios of the degree of activation of the agonist and antagonist muscles, the nervous system directs the positioning of the arm or leg.

We learn in Chapter 54 that the motor nervous system has additional important mechanisms to compensate for different muscle loads when directing this positioning process.

Remodeling of Muscle to Match Function

All the muscles of the body are continually being remodeled to match the functions that are required of them. Their diameters are altered, their lengths are altered, their strengths are altered, their vascular supplies are altered, and even the types of muscle fibers are altered at least slightly. This remodeling process is often quite rapid, within a few weeks. Indeed, experiments in animals have shown that muscle contractile proteins in some smaller, more active muscles can be replaced in as little as 2 weeks.

Muscle Hypertrophy and Muscle Atrophy. When the total mass of a muscle increases, this is called *muscle hypertrophy.* When it decreases, the process is called *muscle atrophy.*

Virtually all muscle hypertrophy results from an increase in the number of actin and myosin filaments in each muscle fiber, causing enlargement of the individual muscle fibers; this is called simply *fiber hypertrophy.* Hypertrophy occurs to a much greater extent when the muscle is loaded during the contractile process. Only a few strong contractions each day are required to cause significant hypertrophy within 6 to 10 weeks.

The manner in which forceful contraction leads to hypertrophy is not known. It is known, however, that the rate of synthesis of muscle contractile proteins is far greater when hypertrophy is developing, leading also to progressively greater numbers of both actin and myosin filaments in the myofibrils, often increasing as much as 50 percent. In turn, some of the myofibrils themselves have been observed to split within hypertrophying muscle to form new myofibrils, but how important this is in usual muscle hypertrophy is still unknown.

Along with the increasing size of myofibrils, the enzyme systems that provide energy also increase. This is especially true of the enzymes for glycolysis, allowing rapid supply of energy during short-term forceful muscle contraction.

When a muscle remains unused for many weeks, the rate of degradation of the contractile proteins is more rapid than the rate of replacement. Therefore, muscle atrophy occurs. The pathway that appears to account for much of the protein degradation in a muscle undergoing atrophy is the *ATP-dependent ubiquitin-proteasome pathway*. Proteasomes are large protein complexes that degrade damaged or unneeded proteins by *proteolysis,* a chemical reaction that breaks peptide bonds. Ubiquitin is a regulatory protein that basically labels which cells will be targeted for proteasomal degradation.

Adjustment of Muscle Length. Another type of hypertrophy occurs when muscles are stretched to greater than normal length. This causes new sarcomeres to be added at the ends of the muscle fibers, where they attach to the tendons. In fact, new sarcomeres can be added as rapidly as several per minute in newly developing muscle, illustrating the rapidity of this type of hypertrophy.

Conversely, when a muscle continually remains shortened to less than its normal length, sarcomeres at the ends of the muscle fibers can actually disappear. It is by these processes that muscles are continually remodeled to have the appropriate length for proper muscle contraction.

Hyperplasia of Muscle Fibers. Under rare conditions of extreme muscle force generation, the actual number of muscle fibers has been observed to increase (but only by a few percentage points), in addition to the fiber hypertrophy process. This increase in fiber number is called *fiber hyperplasia.* When it does occur, the mechanism is linear splitting of previously enlarged fibers.

Effects of Muscle Denervation. When a muscle loses its nerve supply, it no longer receives the contractile signals that are required to maintain normal muscle size. Therefore, atrophy begins almost immediately. After about 2 months, degenerative changes also begin to appear in the muscle fibers themselves. If the nerve supply to the muscle grows back rapidly, full return of function can occur in as little as 3 months, but from that time onward, the capability of functional return becomes less and less, with no further return of function after 1 to 2 years.

In the final stage of denervation atrophy, most of the muscle fibers are destroyed and replaced by fibrous and fatty tissue. The fibers that do remain are composed of a long cell membrane with a lineup of muscle cell nuclei but with few or no contractile properties and little or no capability of regenerating myofibrils if a nerve does regrow.

The fibrous tissue that replaces the muscle fibers during denervation atrophy also has a tendency to continue shortening for many months, which is called *contracture.* Therefore, one of the most important problems in the practice of physical therapy is to keep atrophying muscles from developing debilitating and disfiguring contractures. This is achieved by daily stretching of the muscles or use of appliances that keep the muscles stretched during the atrophying process.

Recovery of Muscle Contraction in Poliomyelitis: Development of Macromotor Units. When some but not all nerve fibers to a muscle are destroyed, as commonly occurs in poliomyelitis, the remaining nerve fibers branch off to form new axons that then innervate many of the paralyzed muscle fibers. This causes large motor units called *macromotor units,* which can contain as many as five times the normal number of muscle fibers for each motoneuron coming from the spinal cord. This decreases the fineness of control one has over the muscles but does allow the muscles to regain varying degrees of strength.

Rigor Mortis

Several hours after death, all the muscles of the body go into a state of *contracture* called "rigor mortis"; that is, the muscles contract and become rigid, even without action potentials. This rigidity results from loss of all the ATP, which is required to cause separation of the cross-bridges from the actin filaments during the relaxation process. The muscles remain in rigor until the muscle proteins deteriorate about 15 to 25 hours later, which presumably results from autolysis caused by enzymes released from lysosomes. All these events occur more rapidly at higher temperatures.

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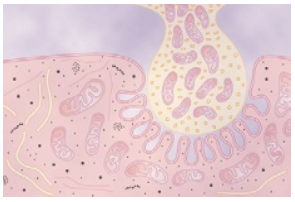
CHAPTER 7

Excitation of Skeletal Muscle: Neuromuscular Transmission and Excitation-Contraction Coupling



Transmission of Impulses from Nerve Endings to Skeletal Muscle Fibers: The Neuromuscular Junction

The skeletal muscle fibers are innervated by large, myelinated nerve fibers that originate from large motoneurons in the anterior horns of the spinal cord. As pointed out in Chapter 6, each nerve fiber, after entering the muscle belly, normally branches and stimulates from three to several hundred skeletal muscle fibers. Each nerve ending makes a junction, called the *neuromuscular junction,* with the muscle fiber near its midpoint. The action potential initiated in the muscle fiber by the nerve signal travels in both directions toward the muscle fiber ends. With the exception of about 2 percent of the muscle fibers, there is only one such junction per muscle fiber.

Physiologic Anatomy of the Neuromuscular Junction—The Motor End Plate. Figure 7-1*A* and *B* shows the neuromuscular junction from a large, myelinated nerve fiber to a skeletal muscle fiber. The nerve fiber forms a complex of *branching nerve terminals* that invaginate into the surface of the muscle fiber but lie outside the muscle fiber plasma membrane. The entire structure is called the *motor end plate.* It is covered by one or more Schwann cells that insulate it from the surrounding fluids.

Figure 7-1*C* shows an electron micrographic sketch of the junction between a single axon terminal and the muscle fiber membrane. The invaginated membrane is called the *synaptic gutter* or *synaptic trough,* and the space between the terminal and the fiber membrane is called the *synaptic space* or *synaptic cleft.* This space is 20 to 30 nanometers wide. At the bottom of the gutter are numerous smaller *folds* of the muscle membrane called *subneural clefts,* which greatly increase the surface area at which the synaptic transmitter can act.

In the axon terminal are many mitochondria that supply adenosine triphosphate (ATP), the energy source that is used for synthesis of an excitatory transmitter, *acetylcholine.* The acetylcholine in turn excites the muscle fiber membrane. Acetylcholine is synthesized in the cytoplasm of the terminal, but it is absorbed rapidly into many small *synaptic vesicles,* about 300,000 of which are normally in the terminals of a single end plate. In the synaptic space are large quantities of the enzyme *acetylcholinesterase,* which destroys acetylcholine a few milliseconds after it has been released from the synaptic vesicles.

Secretion of Acetylcholine by the Nerve Terminals

When a nerve impulse reaches the neuromuscular junction, about 125 vesicles of acetylcholine are released from the terminals into the synaptic space. Some of the details of this mechanism can be seen in Figure 7-2, which shows an expanded view of a synaptic space with the neural membrane above and the muscle membrane and its subneural clefts below.

On the inside surface of the neural membrane are linear *dense bars,* shown in cross section in Figure 7-2. To each side of each dense bar are protein particles that penetrate the neural membrane; these are *voltage-gated calcium channels.* When an action potential spreads over the terminal, these channels open and allow calcium ions to diffuse from the synaptic space to the interior of the nerve terminal. The calcium ions, in turn, are believed to exert an attractive influence on the acetylcholine vesicles, drawing them to the neural membrane adjacent to the dense bars. The vesicles then fuse with the neural membrane and empty their acetylcholine into the synaptic space by the process of *exocytosis.*

Although some of the aforementioned details are speculative, it is known that the effective stimulus for causing acetylcholine release from the vesicles is entry of calcium ions and that acetylcholine from the vesicles is then emptied through the neural membrane adjacent to the dense bars.

Effect of Acetylcholine on the Postsynaptic Muscle Fiber Membrane to Open Ion Channels. Figure 7-2 also shows many small *acetylcholine receptors* in the muscle fiber membrane; these are *acetylcholine-gated ion channels,* and they are located almost entirely near the mouths of the subneural clefts lying immediately below the dense bar areas, where the acetylcholine is emptied into the synaptic space.

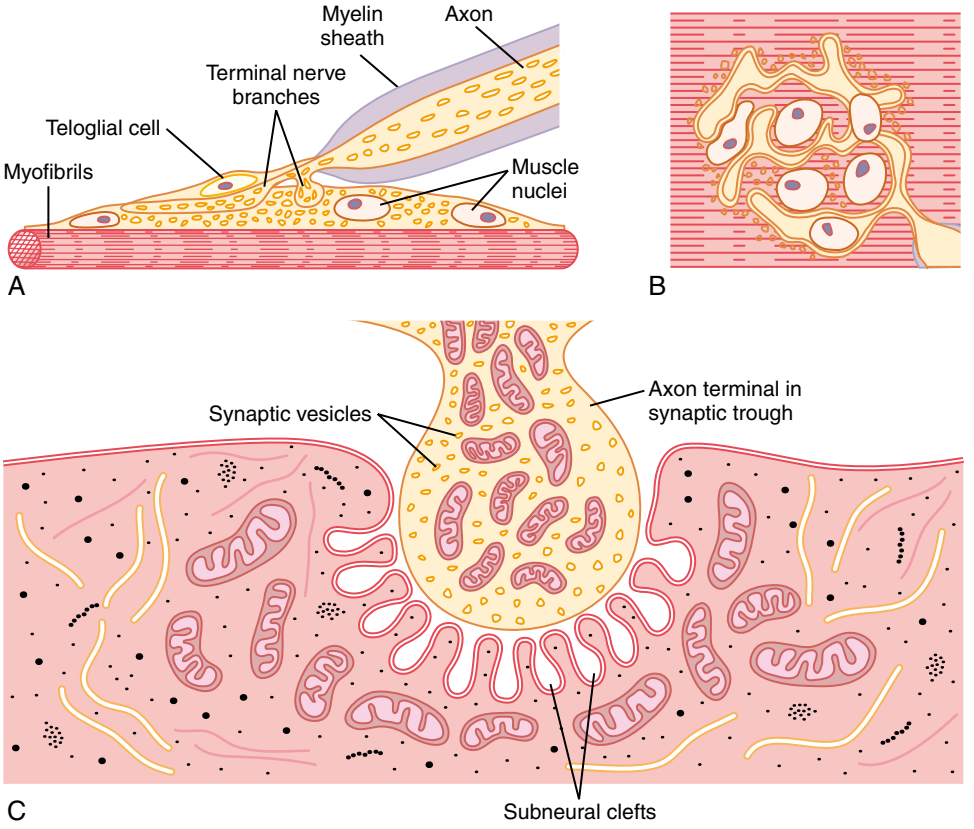


Figure 7-1 Different views of the motor end plate. *A,* Longitudinal section through the end plate. *B,* Surface view of the end plate. *C,* Electron micrographic appearance of the contact point between a single axon terminal and the muscle fiber membrane. (Redrawn from Fawcett DW, as modified from Couteaux R, in Bloom W, Fawcett DW: A Textbook of Histology. Philadelphia: WB Saunders, 1986.)

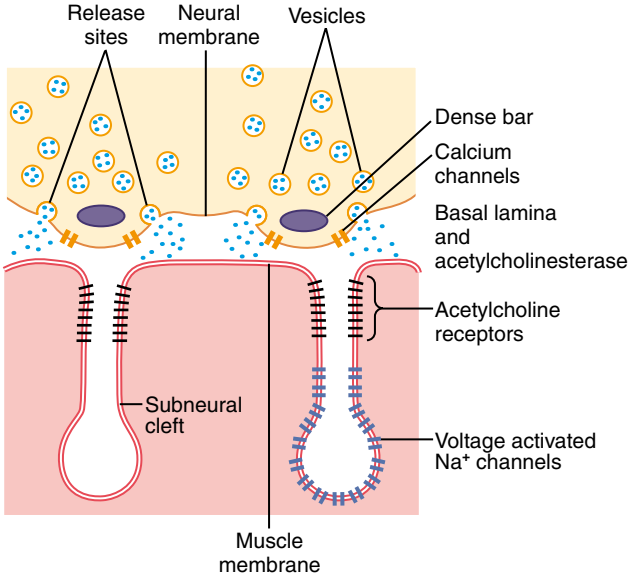


Figure 7-2 Release of acetylcholine from synaptic vesicles at the neural membrane of the neuromuscular junction. Note the proximity of the release sites in the neural membrane to the acetylcholine receptors in the muscle membrane, at the mouths of the subneural clefts.

Each receptor is a protein complex that has a total molecular weight of 275,000. The complex is composed of five subunit proteins, two *alpha* proteins and one each of *beta, delta,* and *gamma* proteins. These protein molecules penetrate all the way through the membrane, lying side by side in a circle to form a tubular channel, illustrated in Figure 7-3. The channel remains constricted, as shown in section A of the figure, until two acetylcholine molecules attach respectively to the two *alpha* subunit proteins. This causes a conformational change that opens the channel, as shown in section B of the figure.

The acetylcholine-gated channel has a diameter of about 0.65 nanometer, which is large enough to allow the important positive ions—sodium (Na^+), potassium (K^+), and calcium (Ca^{++})—to move easily through the opening. Conversely, negative ions, such as chloride ions, do not pass through because of strong negative charges in the mouth of the channel that repel these negative ions.

In practice, far more sodium ions flow through the acetylcholine-gated channels than any other ions, for two reasons. First, there are only two positive ions in large concentration: sodium ions in the extracellular fluid and potassium ions in the intracellular fluid. Second, the negative potential on the inside of the muscle membrane, −80 to −90 millivolts, pulls the positively charged sodium ions to the inside of the fiber, while simultaneously preventing efflux of the positively charged potassium ions when they attempt to pass outward.

As shown in Figure 7-3*B*, the principal effect of opening the acetylcholine-gated channels is to allow large numbers of sodium ions to pour to the inside of the fiber, carrying with them large numbers of positive charges. This creates a local positive potential change inside the muscle fiber membrane, called the *end plate potential.* In turn, this end plate potential initiates an action potential that spreads along the muscle membrane and thus causes muscle contraction.

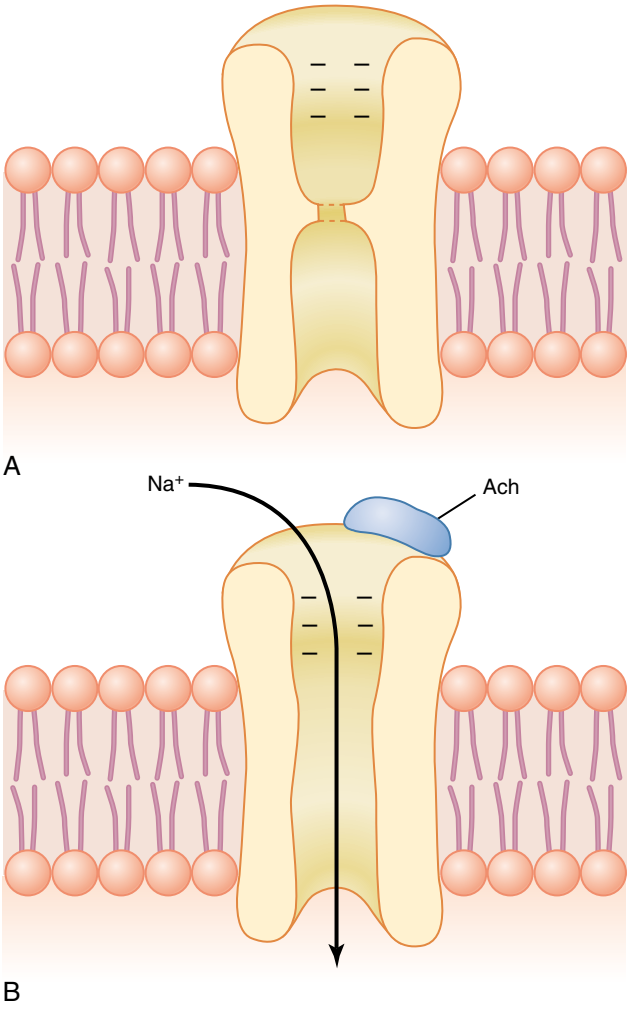


Figure 7-3 Acetylcholine-gated channel. *A,* Closed state. *B,* After acetylcholine (Ach) has become attached and a conformational change has opened the channel, allowing sodium ions to enter the muscle fiber and excite contraction. Note the negative charges at the channel mouth that prevent passage of negative ions such as chloride ions.

Destruction of the Released Acetylcholine by Acetylcholinesterase. The acetylcholine, once released into the synaptic space, continues to activate the acetylcholine receptors as long as the acetylcholine persists in the space. However, it is removed rapidly by two means: (1) Most of the acetylcholine is destroyed by the enzyme *acetylcholinesterase,* which is attached mainly to the spongy layer of fine connective tissue that fills the synaptic space between the presynaptic nerve terminal and the postsynaptic muscle membrane. (2) A small amount of acetylcholine diffuses out of the synaptic space and is then no longer available to act on the muscle fiber membrane.

The short time that the acetylcholine remains in the synaptic space—a few milliseconds at most—normally is sufficient to excite the muscle fiber. Then the rapid removal of the acetylcholine prevents continued muscle re-excitation after the muscle fiber has recovered from its initial action potential.

End Plate Potential and Excitation of the Skeletal Muscle Fiber. The sudden insurgence of sodium ions into the muscle fiber when the acetylcholine-gated channels open causes the electrical potential inside the fiber at the *local area of the end plate* to increase in the positive direction as much as 50 to 75 millivolts, creating a *local potential* called the *end plate potential.* Recall from Chapter 5 that a sudden increase in nerve membrane potential of more than 20 to 30 millivolts is normally sufficient to initiate more and more sodium channel opening, thus initiating an action potential at the muscle fiber membrane.

Figure 7-4 shows the principle of an end plate potential initiating the action potential. This figure shows three separate end plate potentials. End plate potentials A and C are too weak to elicit an action potential, but they do produce weak local end plate voltage changes, as recorded in the figure. By contrast, end plate potential B is much stronger and causes enough sodium channels to open so that the self-regenerative effect of more and more sodium ions flowing to the interior of the fiber initiates an action potential. The weakness of the end plate potential at point A was caused by poisoning of the muscle fiber with *curare,* a drug that blocks the gating action of acetylcholine on the acetylcholine channels by competing for the acetylcholine receptor sites. The weakness of the end plate potential at point C resulted from the effect of *botulinum toxin,* a bacterial poison that decreases the quantity of acetylcholine release by the nerve terminals.

Safety Factor for Transmission at the Neuromuscular Junction; Fatigue of the Junction. Ordinarily, each impulse that arrives at the neuromuscular junction causes about three times as much end plate potential as that required to stimulate the muscle fiber. Therefore, the normal neuromuscular junction is said to have a high *safety factor.* However, stimulation of the nerve fiber at rates greater than 100 times per second for several minutes often diminishes the number of acetylcholine vesicles so much that impulses fail to pass into the muscle

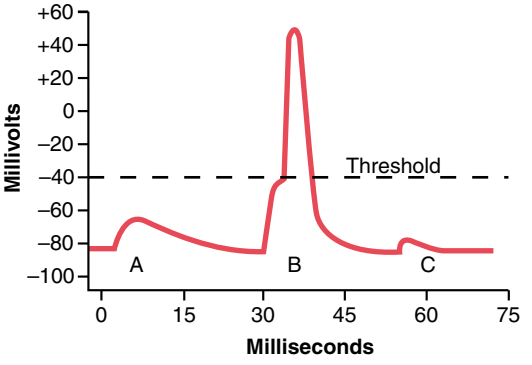


Figure 7-4 End plate potentials (in millivolts). *A,* Weakened end plate potential recorded in a curarized muscle, too weak to elicit an action potential. *B,* Normal end plate potential eliciting a muscle action potential. *C,* Weakened end plate potential caused by botulinum toxin that decreases end plate release of acetylcholine, again too weak to elicit a muscle action potential.

fiber. This is called *fatigue* of the neuromuscular junction, and it is the same effect that causes fatigue of synapses in the central nervous system when the synapses are overexcited. Under normal functioning conditions, measurable fatigue of the neuromuscular junction occurs rarely, and even then only at the most exhausting levels of muscle activity.

Molecular Biology of Acetylcholine Formation and Release

Because the neuromuscular junction is large enough to be studied easily, it is one of the few synapses of the nervous system for which most of the details of chemical transmission have been worked out. The formation and release of acetylcholine at this junction occur in the following stages:

1. Small vesicles, about 40 nanometers in size, are formed by the Golgi apparatus in the cell body of the motoneuron in the spinal cord. These vesicles are then transported by axoplasm that "streams" through the core of the axon from the central cell body in the spinal cord all the way to the neuromuscular junction at the tips of the peripheral nerve fibers. About 300,000 of these small vesicles collect in the nerve terminals of a single skeletal muscle end plate.
2. Acetylcholine is synthesized in the cytosol of the nerve fiber terminal but is immediately transported through the membranes of the vesicles to their interior, where it is stored in highly concentrated form, about 10,000 molecules of acetylcholine in each vesicle.
3. When an action potential arrives at the nerve terminal, it opens many calcium channels in the membrane of the nerve terminal because this terminal has an abundance of voltage-gated calcium channels. As a result, the calcium ion concentration inside the terminal membrane increases about 100-fold, which in turn increases the rate of fusion of the acetylcholine vesicles with the terminal membrane about 10,000-fold. This fusion makes many of the vesicles rupture, allowing *exocytosis* of acetylcholine into the synaptic space. About 125 vesicles usually rupture with each action potential. Then, after a few milliseconds, the acetylcholine is split by acetylcholinesterase into acetate ion and choline and the choline is reabsorbed actively into the neural terminal to be reused to form new acetylcholine. This sequence of events occurs within a period of 5 to 10 milliseconds.
4. The number of vesicles available in the nerve ending is sufficient to allow transmission of only a few thousand nerve-to-muscle impulses. Therefore, for continued function of the neuromuscular junction, new vesicles need to be re-formed rapidly. Within a few seconds after each action potential is over, "coated pits" appear in the terminal nerve membrane, caused by contractile proteins in the nerve ending, especially the protein *clathrin,* which is attached to the membrane in the areas of the original vesicles. Within about 20 seconds, the proteins contract and cause the pits to break away to the interior of the membrane, thus forming new vesicles. Within another few seconds, acetylcholine is transported to the interior of these vesicles, and they are then ready for a new cycle of acetylcholine release.

Drugs That Enhance or Block Transmission at the Neuromuscular Junction

Drugs That Stimulate the Muscle Fiber by Acetylcholine-Like Action. Many compounds, including *methacholine, carbachol,* and *nicotine,* have the same effect on the muscle fiber as does acetylcholine. The difference between these drugs and acetylcholine is that the drugs are not destroyed by cholinesterase or are destroyed so slowly that their action often persists for many minutes to several hours. The drugs work by causing localized areas of depolarization of the muscle fiber membrane at the motor end plate where the acetylcholine receptors are located. Then, every time the muscle fiber recovers from a previous contraction, these depolarized areas, by virtue of leaking ions, initiate a new action potential, thereby causing a state of muscle spasm.

Drugs That Stimulate the Neuromuscular Junction by Inactivating Acetylcholinesterase. Three particularly well-known drugs, *neostigmine, physostigmine,* and *diisopropyl fluorophosphate,* inactivate the acetylcholinesterase in the synapses so that it no longer hydrolyzes acetylcholine. Therefore, with each successive nerve impulse, additional acetylcholine accumulates and stimulates the muscle fiber repetitively. This causes *muscle spasm* when even a few nerve impulses reach the muscle. Unfortunately, it can also cause death due to laryngeal spasm, which smothers the person.

Neostigmine and physostigmine combine with acetylcholinesterase to inactivate the acetylcholinesterase for up to several hours, after which these drugs are displaced from the acetylcholinesterase so that the esterase once again becomes active. Conversely, diisopropyl fluorophosphate, which is a powerful "nerve" gas poison, inactivates acetylcholinesterase for weeks, which makes this a particularly lethal poison.

Drugs That Block Transmission at the Neuromuscular Junction. A group of drugs known as *curariform drugs* can prevent passage of impulses from the nerve ending into the muscle. For instance, D-tubocurarine blocks the action of acetylcholine on the muscle fiber acetylcholine receptors, thus preventing sufficient increase in permeability of the muscle membrane channels to initiate an action potential.

Myasthenia Gravis Causes Muscle Paralysis

Myasthenia gravis, which occurs in about 1 in every 20,000 persons, causes muscle paralysis because of inability of the neuromuscular junctions to transmit enough signals from the nerve fibers to the muscle fibers. Pathologically, antibodies that attack the acetylcholine receptors have been demonstrated in the blood of most patients with myasthenia gravis. Therefore, it is believed that myasthenia gravis is an autoimmune disease in which the patients have developed antibodies that block or destroy their own acetylcholine receptors at the postsynaptic neuromuscular junction.

Regardless of the cause, the end plate potentials that occur in the muscle fibers are mostly too weak to initiate opening of the voltage-gated sodium channels so that muscle fiber depolarization does not occur. If the disease is intense enough, the patient dies of paralysis—in particular, paralysis of the respiratory muscles. The disease can usually be

ameliorated for several hours by administering *neostigmine* or some other anticholinesterase drug, which allows larger than normal amounts of acetylcholine to accumulate in the synaptic space. Within minutes, some of these paralyzed people can begin to function almost normally, until a new dose of neostigmine is required a few hours later.

Muscle Action Potential

Almost everything discussed in Chapter 5 regarding initiation and conduction of action potentials in nerve fibers applies equally to skeletal muscle fibers, except for quantitative differences. Some of the quantitative aspects of muscle potentials are the following:

1. Resting membrane potential: about −80 to −90 millivolts in skeletal fibers—the same as in large myelinated nerve fibers.
2. Duration of action potential: 1 to 5 milliseconds in skeletal muscle—about five times as long as in large myelinated nerves.
3. Velocity of conduction: 3 to 5 m/sec—about 1/13 the velocity of conduction in the large myelinated nerve fibers that excite skeletal muscle.

Spread of the Action Potential to the Interior of the Muscle Fiber by Way of "Transverse Tubules"

The skeletal muscle fiber is so large that action potentials spreading along its surface membrane cause almost no current flow deep within the fiber. Yet to cause maximum muscle contraction, current must penetrate deeply into the muscle fiber to the vicinity of the separate myofibrils. This is achieved by transmission of action potentials along *transverse tubules* (T tubules) that penetrate all the way through the muscle fiber from one side of the fiber to the other, as illustrated in Figure 7-5. The T tubule action potentials cause release of calcium ions inside the muscle fiber in the immediate vicinity of the myofibrils, and these calcium ions then cause contraction. This overall process is called *excitation-contraction* coupling.

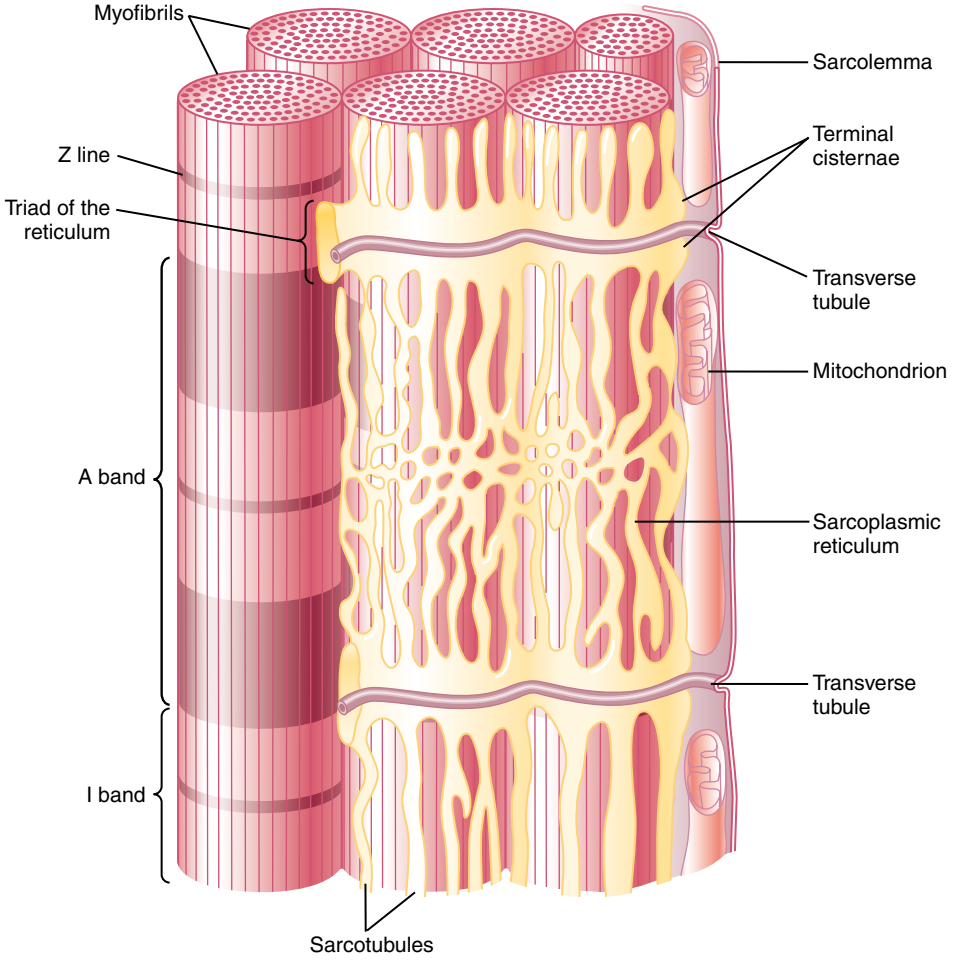


Figure 7-5 Transverse (T) tubule–sarcoplasmic reticulum system. Note that the T tubules communicate with the outside of the cell membrane, and deep in the muscle fiber, each T tubule lies adjacent to the ends of longitudinal sarcoplasmic reticulum tubules that surround all sides of the actual myofibrils that contract. This illustration was drawn from frog muscle, which has one T tubule per sarcomere, located at the Z line. A similar arrangement is found in mammalian heart muscle, but mammalian skeletal muscle has two T tubules per sarcomere, located at the A-I band junctions.

Excitation-Contraction Coupling

Transverse Tubule–Sarcoplasmic Reticulum System

Figure 7-5 shows myofibrils surrounded by the T tubule–sarcoplasmic reticulum system. The T tubules are small and run transverse to the myofibrils. They begin at the cell membrane and penetrate all the way from one side of the muscle fiber to the opposite side. Not shown in the figure is the fact that these tubules branch among themselves and form entire *planes* of T tubules interlacing among all the separate myofibrils. Also, *where the T tubules originate from the cell membrane, they are open to the exterior of the muscle fiber.* Therefore, they communicate with the extracellular fluid surrounding the muscle fiber and they themselves contain extracellular fluid in their lumens. In other words, the T tubules are actually internal extensions of the cell membrane. Therefore, when an action potential spreads over a muscle fiber membrane, a potential change also spreads along the T tubules to the deep interior of the muscle fiber. The electrical currents surrounding these T tubules then elicit the muscle contraction.

Figure 7-5 also shows a *sarcoplasmic reticulum,* in yellow. This is composed of two major parts: (1) large chambers called *terminal cisternae* that abut the T tubules and (2) long longitudinal tubules that surround all surfaces of the actual contracting myofibrils.

Release of Calcium Ions by the Sarcoplasmic Reticulum

One of the special features of the sarcoplasmic reticulum is that within its vesicular tubules is an excess of calcium ions in high concentration, and many of these ions are released from each vesicle when an action potential occurs in the adjacent T tubule.

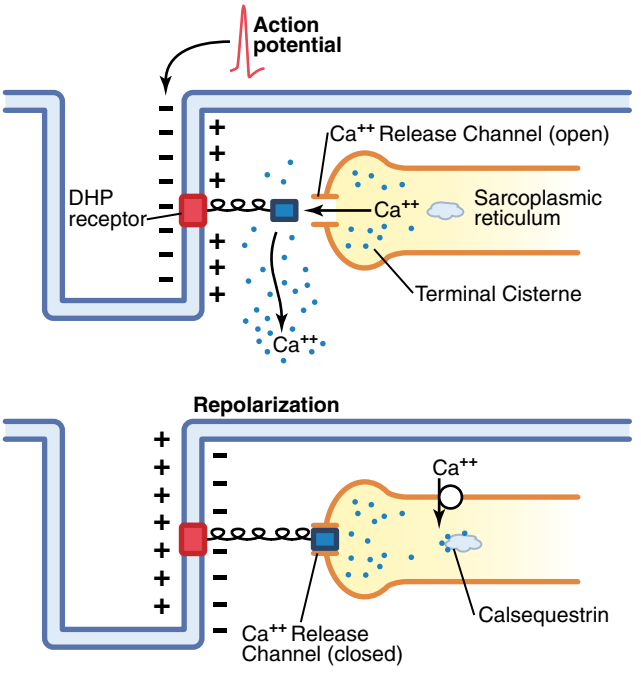
Figure 7-6 Excitation-contraction coupling in skeletal muscle. The *top panel* shows an action potential in the T tubule that causes a conformational change in the voltage-sensing dihydropyridine (DHP) receptors, opening the Ca^{++} release channels in the terminal cisternae of the sarcoplasmic reticulum and permitting Ca^{++} to rapidly diffuse into the sarcoplasm and initiate muscle contraction. During repolarization (*bottom panel*) the conformational change in the DHP receptor closes the Ca^{++} release channels and Ca^{++} is transported from the sarcoplasm into the sarcoplasmic reticulum by an ATP-dependent calcium pump.

Figures 7-6 and 7-7 show that the action potential of the T tubule causes current flow into the sarcoplasmic reticular cisternae where they abut the T tubule. As the action potential reaches the T tubule, the voltage change is sensed by *dihydropyridine receptors* that are linked to *calcium release channels,* also called *ryanodine receptor channels,* in the adjacent sarcoplasmic reticular cisternae (see Figure 7-6). Activation of dihydropyridine receptors triggers the opening of the calcium release channels in the cisternae, as well as in their attached longitudinal tubules. These channels remain open for a few milliseconds, releasing calcium ions into the sarcoplasm surrounding the myofibrils and causing contraction, as discussed in Chapter 6.

Calcium Pump for Removing Calcium Ions from the Myofibrillar Fluid After Contraction Occurs. Once the calcium ions have been released from the sarcoplasmic tubules and have diffused among the myofibrils, muscle contraction continues as long as the calcium ions remain in high concentration. However, a continually active calcium pump located in the walls of the sarcoplasmic reticulum pumps calcium ions away from the myofibrils back into the sarcoplasmic tubules (see Figure 7-6). This pump can concentrate the calcium ions about 10,000-fold inside the tubules. In addition, inside the reticulum is a protein called *calsequestrin* that can bind up to 40 times more calcium.

Excitatory "Pulse" of Calcium Ions. The normal resting state concentration ($<10^{-7}$ molar) of calcium ions in the cytosol that bathes the myofibrils is too little to elicit contraction. Therefore, the troponin-tropomyosin complex keeps the actin filaments inhibited and maintains a relaxed state of the muscle.

Conversely, full excitation of the T tubule and sarcoplasmic reticulum system causes enough release of calcium ions to increase the concentration in the



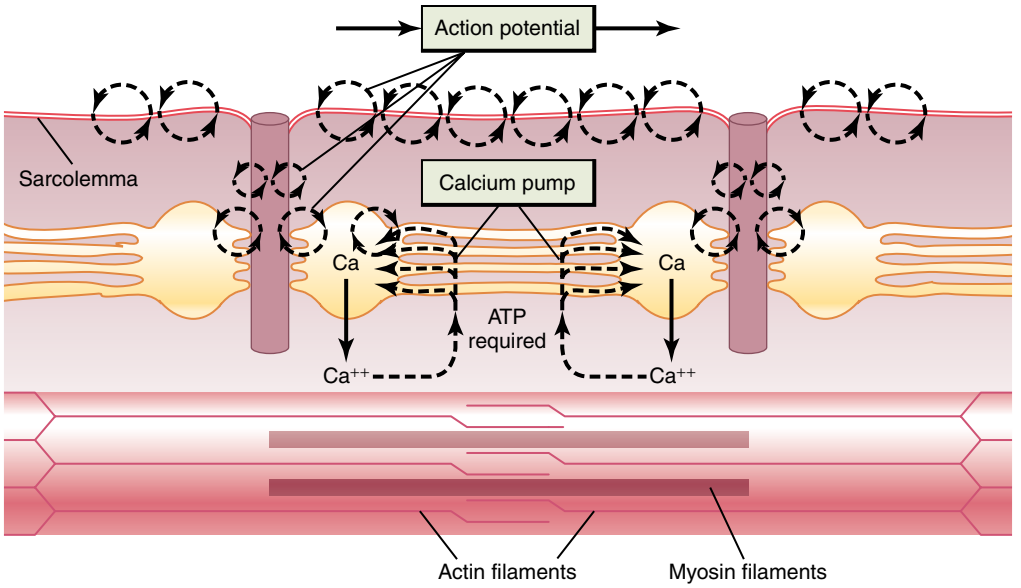


Figure 7-7 Excitation-contraction coupling in the muscle, showing (1) an action potential that causes release of calcium ions from the sarcoplasmic reticulum and then (2) re-uptake of the calcium ions by a calcium pump.

myofibrillar fluid to as high as 2×10^{-4} molar concentration, a 500-fold increase, which is about 10 times the level required to cause maximum muscle contraction. Immediately thereafter, the calcium pump depletes the calcium ions again. The total duration of this calcium "pulse" in the usual *skeletal muscle* fiber lasts about 1/20 of a second, although it may last several times as long in some fibers and several times less in others. (In heart muscle, the calcium pulse lasts about one third of a second because of the long duration of the cardiac action potential.)

During this calcium pulse, muscle contraction occurs. If the contraction is to continue without interruption for long intervals, a series of calcium pulses must be initiated by a continuous series of repetitive action potentials, as discussed in Chapter 6.

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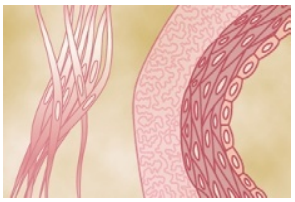
Excitation and Contraction of Smooth Muscle



Contraction of Smooth Muscle

In Chapters 6 and 7, the discussion was concerned with skeletal muscle. We now turn to smooth muscle, which is composed of far smaller fibers—usually 1 to 5 micrometers in diameter and only 20 to 500 micrometers in length. In contrast, skeletal muscle fibers are as much as 30 times greater in diameter and hundreds of times as long. Many of the same principles of contraction apply to smooth muscle as to skeletal muscle. Most important, essentially the same attractive forces between myosin and actin filaments cause contraction in smooth muscle as in skeletal muscle, but the internal physical arrangement of smooth muscle fibers is different.

Types of Smooth Muscle

The smooth muscle of each organ is distinctive from that of most other organs in several ways: (1) physical dimensions, (2) organization into bundles or sheets, (3) response to different types of stimuli, (4) characteristics of innervation, and (5) function. Yet for the sake of simplicity, smooth muscle can generally be divided into two major types, which are shown in Figure 8-1: *multi-unit smooth muscle* and *unitary* (or *single-unit*) *smooth muscle.*

Multi-Unit Smooth Muscle. This type of smooth muscle is composed of discrete, separate smooth muscle fibers. Each fiber operates independently of the others and often is innervated by a single nerve ending, as occurs for skeletal muscle fibers. Further, the outer surfaces of these fibers, like those of skeletal muscle fibers, are covered by a thin layer of basement membrane–like substance, a mixture of fine collagen and glycoprotein that helps insulate the separate fibers from one another.

The most important characteristic of multi-unit smooth muscle fibers is that each fiber can contract independently of the others, and their control is exerted mainly by nerve signals. In contrast, a major share of control of unitary smooth muscle is exerted by non-nervous stimuli. Some examples of multi-unit smooth muscle are the ciliary muscle of the eye, the iris muscle of the eye, and the pilo-erector muscles that cause erection of the hairs when stimulated by the sympathetic nervous system.

Unitary Smooth Muscle. This type is also called *syncytial smooth muscle* or *visceral smooth muscle.* The term "unitary" is confusing because it does not mean single muscle fibers. Instead, it means a mass of hundreds to thousands of smooth muscle fibers that contract together as a single unit. The fibers usually are arranged in sheets or bundles, and their cell membranes are adherent to one another at multiple points so that force generated in one muscle fiber can be transmitted to the next. In addition, the cell membranes are joined by many *gap junctions* through which ions can flow freely from one muscle cell to the next so that action potentials or simple ion flow without action potentials can travel from one fiber to the next and cause the muscle fibers to contract together. This type of smooth muscle is also known as *syncytial smooth muscle* because of its syncytial interconnections among fibers. It is also called *visceral smooth muscle* because it is found in the walls of most viscera of the body, including the gastrointestinal tract, bile ducts, ureters, uterus, and many blood vessels.

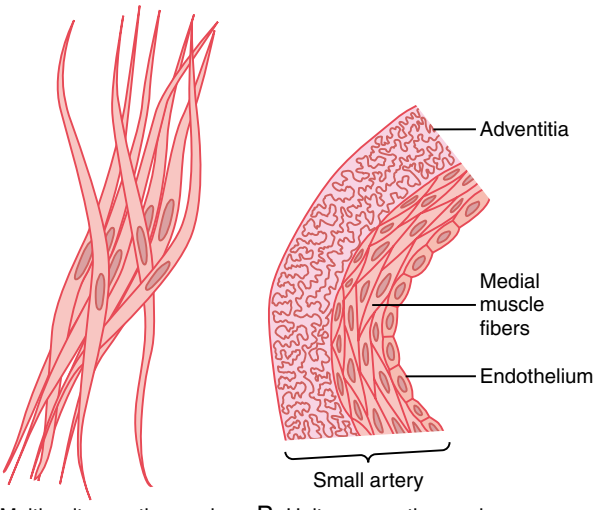


Figure 8-1 Multi-unit (*A*) and unitary (*B*) smooth muscle.

Contractile Mechanism in Smooth Muscle

Chemical Basis for Smooth Muscle Contraction

Smooth muscle contains both *actin* and *myosin filaments*, having chemical characteristics similar to those of the actin and myosin filaments in skeletal muscle. It does not contain the normal troponin complex that is required in the control of skeletal muscle contraction, so the mechanism for control of contraction is different. This is discussed in detail later in this chapter.

Chemical studies have shown that actin and myosin filaments derived from smooth muscle interact with each other in much the same way that they do in skeletal muscle. Further, the contractile process is activated by calcium ions, and adenosine triphosphate (ATP) is degraded to adenosine diphosphate (ADP) to provide the energy for contraction.

There are, however, major differences between the physical organization of smooth muscle and that of skeletal muscle, as well as differences in excitation-contraction coupling, control of the contractile process by calcium ions, duration of contraction, and amount of energy required for contraction.

Physical Basis for Smooth Muscle Contraction

Smooth muscle does not have the same striated arrangement of actin and myosin filaments as is found in skeletal muscle. Instead, electron micrographic techniques suggest the physical organization exhibited in Figure 8-2. This figure shows large numbers of actin filaments attached to so-called *dense bodies.* Some of these bodies are attached to the cell membrane. Others are dispersed inside the cell. Some of the membrane-dense bodies of adjacent cells are bonded together by intercellular protein bridges. It is mainly through these bonds that the force of contraction is transmitted from one cell to the next.

Interspersed among the actin filaments in the muscle fiber are myosin filaments. These have a diameter more than twice that of the actin filaments. In electron micrographs, one usually finds 5 to 10 times as many actin filaments as myosin filaments.

To the right in Figure 8-2 is a postulated structure of an individual contractile unit within a smooth muscle cell, showing large numbers of actin filaments radiating from two dense bodies; the ends of these filaments overlap a myosin filament located midway between the dense bodies. This contractile unit is similar to the contractile unit of skeletal muscle, but without the regularity of the skeletal muscle structure; in fact, the dense bodies of smooth muscle serve the same role as the Z discs in skeletal muscle.

There is another difference: Most of the myosin filaments have what are called "sidepolar" cross-bridges arranged so that the bridges on one side hinge in one direction and those on the other side hinge in the opposite direction. This allows the myosin to pull an actin filament in one direction on one side while simultaneously pulling another actin filament in the opposite direction on the other side. The value of this organization is that it allows smooth muscle cells to contract as much as 80 percent of their length instead of being limited to less than 30 percent, as occurs in skeletal muscle.

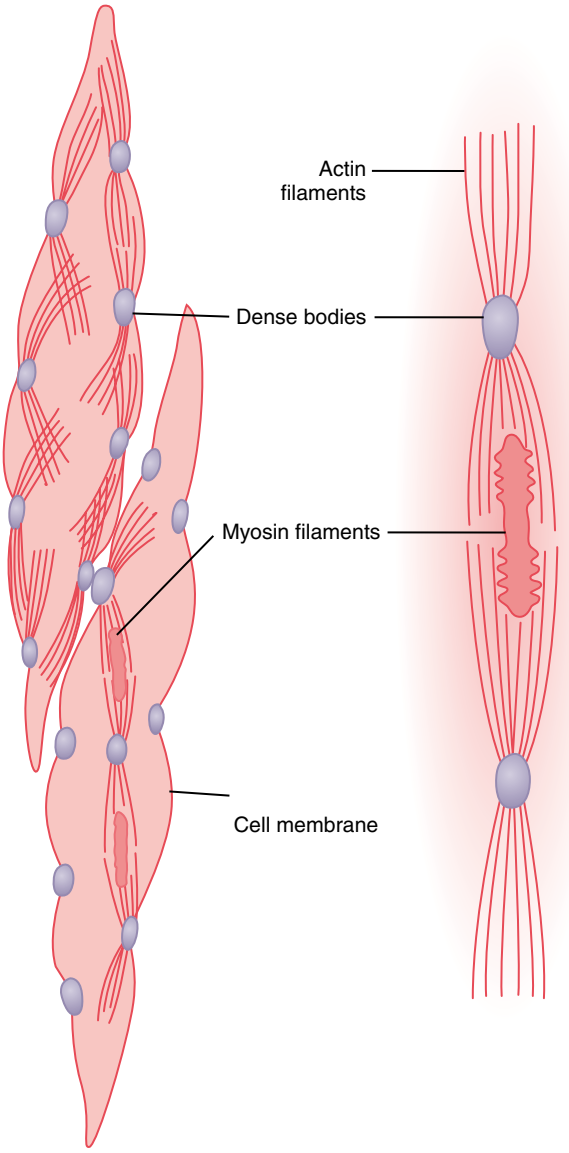


Figure 8-2 Physical structure of smooth muscle. The upper left-hand fiber shows actin filaments radiating from dense bodies. The lower left-hand fiber and the right-hand diagram demonstrate the relation of myosin filaments to actin filaments.

Comparison of Smooth Muscle Contraction and Skeletal Muscle Contraction

Although most skeletal muscles contract and relax rapidly, most smooth muscle contraction is prolonged tonic contraction, sometimes lasting hours or even days. Therefore, it is to be expected that both the physical and the chemical characteristics of smooth muscle versus skeletal muscle contraction would differ. Following are some of the differences.

Slow Cycling of the Myosin Cross-Bridges. The rapidity of cycling of the myosin cross-bridges in smooth muscle—that is, their attachment to actin, then release from the actin, and reattachment for the next cycle—is much slower

than in skeletal muscle; in fact, the frequency is as little as 1/10 to 1/300 that in skeletal muscle. Yet the *fraction of time* that the cross-bridges remain attached to the actin filaments, which is a major factor that determines the force of contraction, is believed to be greatly increased in smooth muscle. A possible reason for the slow cycling is that the cross-bridge heads have far less ATPase activity than in skeletal muscle, so degradation of the ATP that energizes the movements of the cross-bridge heads is greatly reduced, with corresponding slowing of the rate of cycling.

Low Energy Requirement to Sustain Smooth Muscle Contraction. Only 1/10 to 1/300 as much energy is required to sustain the same tension of contraction in smooth muscle as in skeletal muscle. This, too, is believed to result from the slow attachment and detachment cycling of the cross-bridges and because only one molecule of ATP is required for each cycle, regardless of its duration.

This sparsity of energy utilization by smooth muscle is exceedingly important to the overall energy economy of the body because organs such as the intestines, urinary bladder, gallbladder, and other viscera often maintain tonic muscle contraction almost indefinitely.

Slowness of Onset of Contraction and Relaxation of the Total Smooth Muscle Tissue. A typical smooth muscle tissue begins to contract 50 to 100 milliseconds after it is excited, reaches full contraction about 0.5 second later, and then declines in contractile force in another 1 to 2 seconds, giving a total contraction time of 1 to 3 seconds. This is about 30 times as long as a single contraction of an average skeletal muscle fiber. But because there are so many types of smooth muscle, contraction of some types can be as short as 0.2 second or as long as 30 seconds.

The slow onset of contraction of smooth muscle, as well as its prolonged contraction, is caused by the slowness of attachment and detachment of the cross-bridges with the actin filaments. In addition, the initiation of contraction in response to calcium ions is much slower than in skeletal muscle, as discussed later.

Maximum Force of Contraction Is Often Greater in Smooth Muscle Than in Skeletal Muscle. Despite the relatively few myosin filaments in smooth muscle, and despite the slow cycling time of the cross-bridges, the maximum force of contraction of smooth muscle is often greater than that of skeletal muscle—as great as 4 to 6 kg/cm^2 cross-sectional area for smooth muscle, in comparison with 3 to 4 kilograms for skeletal muscle. This great force of smooth muscle contraction results from the prolonged period of attachment of the myosin cross-bridges to the actin filaments.

"Latch" Mechanism Facilitates Prolonged Holding of Contractions of Smooth Muscle. Once smooth muscle has developed full contraction, the amount of continuing excitation can usually be reduced to far less than the initial level yet the muscle maintains its full force of contraction. Further, the energy consumed to maintain contraction is often minuscule, sometimes as little as 1/300 the energy required for comparable sustained skeletal muscle contraction. This is called the "latch" mechanism.

The importance of the latch mechanism is that it can maintain prolonged tonic contraction in smooth muscle for hours with little use of energy. Little continued excitatory signal is required from nerve fibers or hormonal sources.

Stress-Relaxation of Smooth Muscle. Another important characteristic of smooth muscle, especially the visceral unitary type of smooth muscle of many hollow organs, is its ability to return to nearly its original *force* of contraction seconds or minutes after it has been elongated or shortened. For example, a sudden increase in fluid volume in the urinary bladder, thus stretching the smooth muscle in the bladder wall, causes an immediate large increase in pressure in the bladder. However, during the next 15 seconds to a minute or so, despite continued stretch of the bladder wall, the pressure returns almost exactly back to the original level. Then, when the volume is increased by another step, the same effect occurs again.

Conversely, when the volume is suddenly decreased, the pressure falls drastically at first but then rises in another few seconds or minutes to or near to the original level. These phenomena are called *stress-relaxation* and *reverse stress-relaxation.* Their importance is that, except for short periods of time, they allow a hollow organ to maintain about the same amount of pressure inside its lumen despite long-term, large changes in volume.

Regulation of Contraction by Calcium Ions

As is true for skeletal muscle, the initiating stimulus for most smooth muscle contraction is an increase in intracellular calcium ions. This increase can be caused in different types of smooth muscle by nerve stimulation of the smooth muscle fiber, hormonal stimulation, stretch of the fiber, or even change in the chemical environment of the fiber.

Yet smooth muscle does not contain troponin, the regulatory protein that is activated by calcium ions to cause skeletal muscle contraction. Instead, smooth muscle contraction is activated by an entirely different mechanism, as follows.

Calcium Ions Combine with Calmodulin to Cause Activation of Myosin Kinase and Phosphorylation of the Myosin Head.

In place of troponin, smooth muscle cells contain a large amount of another regulatory protein called *calmodulin* (Figure 8-3). Although this protein is similar to troponin, it is different in the manner in which it initiates contraction. Calmodulin does this by activating the myosin cross-bridges. This activation and subsequent contraction occur in the following sequence:

1. The calcium ions bind with calmodulin.
2. The calmodulin-calcium complex then joins with and activates *myosin light chain kinase,* a phosphorylating enzyme.
3. One of the light chains of each myosin head, called the *regulatory chain,* becomes phosphorylated in response to this myosin kinase. When this chain is not phosphorylated, the attachment-detachment cycling of the myosin head with the actin filament does not occur.

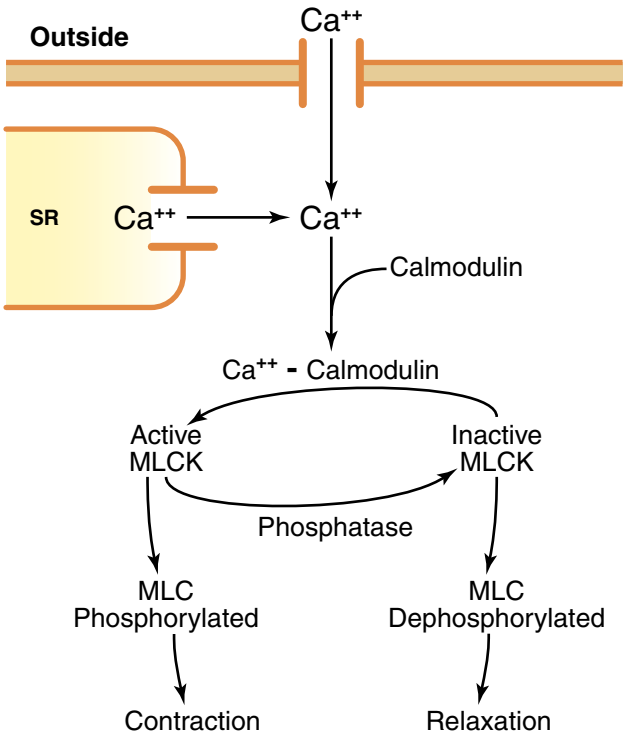


Figure 8-3 Intracellular calcium ion (Ca^{++}) concentration increases when Ca^{++} enters the cell through calcium channels in the cell membrane or the sarcoplasmic reticulum (SR). The Ca^{++} binds to calmodulin to form a Ca^{++}-calmodulin complex, which then activates myosin light chain kinase (MLCK). The MLCK phosphorylates the myosin light chain (MLC) leading to contraction of the smooth muscle. When Ca^{++} concentration decreases, due to pumping of Ca^{++} out of the cell, the process is reversed and myosin phosphatase removes the phosphate from MLC, leading to relaxation.

But when the regulatory chain is phosphorylated, the head has the capability of binding repetitively with the actin filament and proceeding through the entire cycling process of intermittent "pulls," the same as occurs for skeletal muscle, thus causing muscle contraction.

Myosin Phosphatase Is Important in Cessation of Contraction. When the calcium ion concentration falls below a critical level, the aforementioned processes automatically reverse, except for the phosphorylation of the myosin head. Reversal of this requires another enzyme, *myosin phosphatase* (see Figure 8-3), located in the cytosol of the smooth muscle cell, which splits the phosphate from the regulatory light chain. Then the cycling stops and contraction ceases. The time required for relaxation of muscle contraction, therefore, is determined to a great extent by the amount of active myosin phosphatase in the cell.

Possible Mechanism for Regulation of the Latch Phenomenon

Because of the importance of the latch phenomenon in smooth muscle, and because this phenomenon allows long-term maintenance of tone in many smooth muscle organs without much expenditure of energy, many attempts have been made to explain it. Among the many mechanisms that have been postulated, one of the simplest is the following.

When the myosin kinase and myosin phosphatase enzymes are both strongly activated, the cycling frequency of the myosin heads and the velocity of contraction are great. Then, as the activation of the enzymes decreases, the cycling frequency decreases, but at the same time, the deactivation of these enzymes allows the myosin heads to remain attached to the actin filament for a longer and longer proportion of the cycling period. Therefore, the number of heads attached to the actin filament at any given time remains large. Because the number of heads attached to the actin determines the static force of contraction, tension is maintained, or "latched"; yet little energy is used by the muscle because ATP is not degraded to ADP except on the rare occasion when a head detaches.

Nervous and Hormonal Control of Smooth Muscle Contraction

Although skeletal muscle fibers are stimulated exclusively by the nervous system, smooth muscle can be stimulated to contract by multiple types of signals: by nervous signals, by hormonal stimulation, by stretch of the muscle, and in several other ways. The principal reason for the difference is that the smooth muscle membrane contains many types of receptor proteins that can initiate the contractile process. Still other receptor proteins inhibit smooth muscle contraction, which is another difference from skeletal muscle. Therefore, in this section, we discuss nervous control of smooth muscle contraction, followed by hormonal control and other means of control.

Neuromuscular Junctions of Smooth Muscle

Physiologic Anatomy of Smooth Muscle Neuromuscular Junctions. Neuromuscular junctions of the highly structured type found on skeletal muscle fibers do not occur in smooth muscle. Instead, the *autonomic nerve fibers* that innervate smooth muscle generally branch diffusely on top of a sheet of muscle fibers, as shown in Figure 8-4. In most instances, these fibers

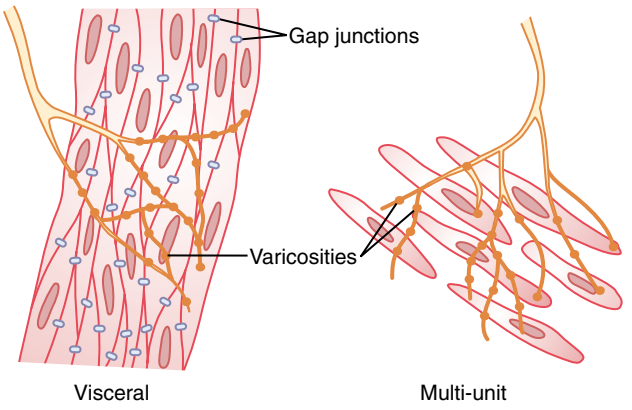


Figure 8-4 Innervation of smooth muscle.

do not make direct contact with the smooth muscle fiber cell membranes but instead form so-called *diffuse junctions* that secrete their transmitter substance into the matrix coating of the smooth muscle often a few nanometers to a few micrometers away from the muscle cells; the transmitter substance then diffuses to the cells. Furthermore, where there are many layers of muscle cells, the nerve fibers often innervate only the outer layer. Muscle excitation travels from this outer layer to the inner layers by action potential conduction in the muscle mass or by additional diffusion of the transmitter substance.

The axons that innervate smooth muscle fibers do not have typical branching end feet of the type in the motor end plate on skeletal muscle fibers. Instead, most of the fine terminal axons have multiple *varicosities* distributed along their axes. At these points the *Schwann cells* that envelop the axons are interrupted so that transmitter substance can be secreted through the walls of the varicosities. In the varicosities are vesicles similar to those in the skeletal muscle end plate that contain transmitter substance. But in contrast to the vesicles of skeletal muscle junctions, which always contain acetylcholine, the vesicles of the autonomic nerve fiber endings contain *acetylcholine* in some fibers and *norepinephrine* in others—and occasionally other substances as well.

In a few instances, particularly in the multi-unit type of smooth muscle, the varicosities are separated from the muscle cell membrane by as little as 20 to 30 nanometers—the same width as the synaptic cleft that occurs in the skeletal muscle junction. These are called *contact junctions,* and they function in much the same way as the skeletal muscle neuromuscular junction; the rapidity of contraction of these smooth muscle fibers is considerably faster than that of fibers stimulated by the diffuse junctions.

Excitatory and Inhibitory Transmitter Substances Secreted at the Smooth Muscle Neuromuscular Junction. The most important transmitter substances secreted by the autonomic nerves innervating smooth muscle are *acetylcholine* and *norepinephrine,* but they are never secreted by the same nerve fibers. Acetylcholine is an excitatory transmitter substance for smooth muscle fibers in some organs but an inhibitory transmitter for smooth muscle in other organs. When acetylcholine excites a muscle fiber, norepinephrine ordinarily inhibits it. Conversely, when acetylcholine inhibits a fiber, norepinephrine usually excites it.

But why are these responses different? The answer is that both acetylcholine and norepinephrine excite or inhibit smooth muscle by first binding with a *receptor protein* on the surface of the muscle cell membrane. Some of the receptor proteins are *excitatory receptors,* whereas others are *inhibitory receptors.* Thus, the type of receptor determines whether the smooth muscle is inhibited or excited and also determines which of the two transmitters, acetylcholine or norepinephrine, is effective in causing the excitation or inhibition. These receptors are discussed in more detail in Chapter 60 in relation to function of the autonomic nervous system.

Membrane Potentials and Action Potentials in Smooth Muscle

Membrane Potentials in Smooth Muscle. The quantitative voltage of the membrane potential of smooth muscle depends on the momentary condition of the muscle. In the normal resting state, the intracellular potential is usually about −50 to −60 millivolts, which is about 30 millivolts less negative than in skeletal muscle.

Action Potentials in Unitary Smooth Muscle. Action potentials occur in unitary smooth muscle (such as visceral muscle) in the same way that they occur in skeletal muscle. They do not normally occur in most multi-unit types of smooth muscle, as discussed in a subsequent section.

The action potentials of visceral smooth muscle occur in one of two forms: (1) spike potentials or (2) action potentials with plateaus.

Spike Potentials. Typical spike action potentials, such as those seen in skeletal muscle, occur in most types of unitary smooth muscle. The duration of this type of action potential is 10 to 50 milliseconds, as shown in Figure 8-5*A*. Such action potentials can be elicited in many ways, for example, by electrical stimulation, by the

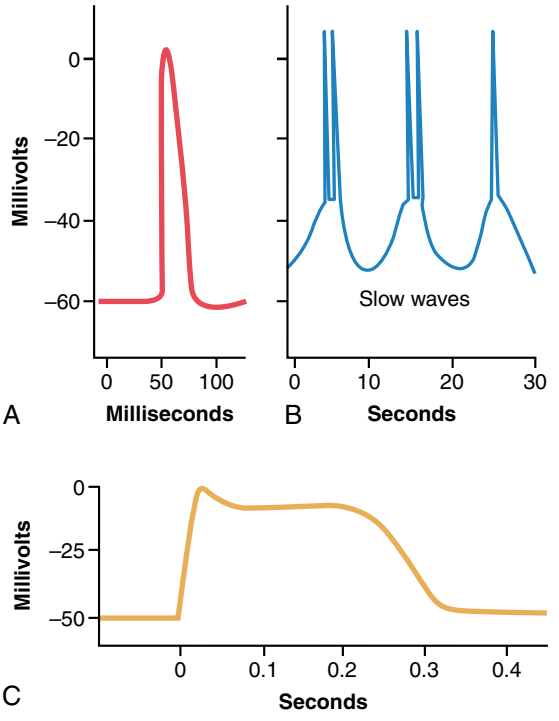


Figure 8-5 *A,* Typical smooth muscle action potential (spike potential) elicited by an external stimulus. *B,* Repetitive spike potentials, elicited by slow rhythmical electrical waves that occur spontaneously in the smooth muscle of the intestinal wall. *C,* Action potential with a plateau, recorded from a smooth muscle fiber of the uterus.

action of hormones on the smooth muscle, by the action of transmitter substances from nerve fibers, by stretch, or as a result of spontaneous generation in the muscle fiber itself, as discussed subsequently.

Action Potentials with Plateaus. Figure 8-5*C* shows a smooth muscle action potential with a plateau. The onset of this action potential is similar to that of the typical spike potential. However, instead of rapid repolarization of the muscle fiber membrane, the repolarization is delayed for several hundred to as much as 1000 milliseconds (1 second). The importance of the plateau is that it can account for the prolonged contraction that occurs in some types of smooth muscle, such as the ureter, the uterus under some conditions, and certain types of vascular smooth muscle. (Also, this is the type of action potential seen in cardiac muscle fibers that have a prolonged period of contraction, as discussed in Chapters 9 and 10.)

Calcium Channels Are Important in Generating the Smooth Muscle Action Potential. The smooth muscle cell membrane has far more voltage-gated calcium channels than does skeletal muscle but few voltage-gated sodium channels. Therefore, sodium participates little in the generation of the action potential in most smooth muscle. Instead, flow of calcium ions to the interior of the fiber is mainly responsible for the action potential. This occurs in the same self-regenerative way as occurs for the sodium channels in nerve fibers and in skeletal muscle fibers. However, the calcium channels open many times more slowly than do sodium channels, and they also remain open much longer. This accounts in large measure for the prolonged plateau action potentials of some smooth muscle fibers.

Another important feature of calcium ion entry into the cells during the action potential is that the calcium ions act directly on the smooth muscle contractile mechanism to cause contraction. Thus, the calcium performs two tasks at once.

Slow Wave Potentials in Unitary Smooth Muscle Can Lead to Spontaneous Generation of Action Potentials. Some smooth muscle is self-excitatory. That is, action potentials arise within the smooth muscle cells themselves without an extrinsic stimulus. This is often associated with a basic *slow wave rhythm* of the membrane potential. A typical slow wave in a visceral smooth muscle of the gut is shown in Figure 8-5*B.* The slow wave itself is not the action potential. That is, it is not a self-regenerative process that spreads progressively over the membranes of the muscle fibers. Instead, it is a local property of the smooth muscle fibers that make up the muscle mass.

The cause of the slow wave rhythm is unknown. One suggestion is that the slow waves are caused by waxing and waning of the pumping of positive ions (presumably sodium ions) outward through the muscle fiber membrane; that is, the membrane potential becomes more negative when sodium is pumped rapidly and less negative when the sodium pump becomes less active. Another suggestion is that the conductances of the ion channels increase and decrease rhythmically.

The importance of the slow waves is that, when they are strong enough, they can initiate action potentials. The slow waves themselves cannot cause muscle contraction. However, when the peak of the negative slow wave potential inside the cell membrane rises in the positive direction from –60 to about –35 millivolts (the approximate threshold for eliciting action potentials in most visceral smooth muscle), an action potential develops and spreads over the muscle mass and contraction occurs. Figure 8-5*B* demonstrates this effect, showing that at each peak of the slow wave, one or more action potentials occur. These repetitive sequences of action potentials elicit rhythmical contraction of the smooth muscle mass. Therefore, the slow waves are called *pacemaker waves.* In Chapter 62, we see that this type of pacemaker activity controls the rhythmical contractions of the gut.

Excitation of Visceral Smooth Muscle by Muscle Stretch. When visceral (unitary) smooth muscle is stretched sufficiently, spontaneous action potentials are usually generated. They result from a combination of (1) the normal slow wave potentials and (2) decrease in overall negativity of the membrane potential caused by the stretch itself. This response to stretch allows the gut wall, when excessively stretched, to contract automatically and rhythmically. For instance, when the gut is overfilled by intestinal contents, local automatic contractions often set up peristaltic waves that move the contents away from the overfilled intestine, usually in the direction of the anus.

Depolarization of Multi-Unit Smooth Muscle Without Action Potentials

The smooth muscle fibers of multi-unit smooth muscle (such as the muscle of the iris of the eye or the piloerector muscle of each hair) normally contract mainly in response to nerve stimuli. The nerve endings secrete acetylcholine in the case of some multi-unit smooth muscles and norepinephrine in the case of others. In both instances, the transmitter substances cause depolarization of the smooth muscle membrane, and this in turn elicits contraction. Action potentials usually do not develop; the reason is that the fibers are too small to generate an action potential. (When action potentials are elicited in *visceral unitary smooth muscle,* 30 to 40 smooth muscle fibers must depolarize simultaneously before a self-propagating action potential ensues.) Yet in small smooth muscle cells, even without an action potential, the local depolarization (called the *junctional potential*) caused by the nerve transmitter substance itself spreads "electrotonically" over the entire fiber and is all that is necessary to cause muscle contraction.

Effect of Local Tissue Factors and Hormones to Cause Smooth Muscle Contraction Without Action Potentials

Probably half of all smooth muscle contraction is initiated by stimulatory factors acting directly on the smooth muscle contractile machinery and without action potentials. Two types of non-nervous and nonaction potential stimulating factors often involved are (1) local tissue chemical factors and (2) various hormones.

Smooth Muscle Contraction in Response to Local Tissue Chemical Factors. In Chapter 17, we discuss control of contraction of the arterioles, meta-arterioles, and precapillary sphincters. The smallest of these vessels have little or no nervous supply. Yet the smooth muscle is highly contractile, responding rapidly to changes in local chemical conditions in the surrounding interstitial fluid.

In the normal resting state, many of these small blood vessels remain contracted. But when extra blood flow to the tissue is necessary, multiple factors can relax the vessel wall, thus allowing for increased flow. In this way, a powerful local feedback control system controls the blood flow to the local tissue area. Some of the specific control factors are as follows:

1. Lack of oxygen in the local tissues causes smooth muscle relaxation and, therefore, vasodilatation.
2. Excess carbon dioxide causes vasodilatation.
3. Increased hydrogen ion concentration causes vasodilatation.

Adenosine, lactic acid, increased potassium ions, diminished calcium ion concentration, and increased body temperature can all cause local vasodilatation.

Effects of Hormones on Smooth Muscle Contraction. Many circulating hormones in the blood affect smooth muscle contraction to some degree, and some have profound effects. Among the more important of these are *norepinephrine, epinephrine, acetylcholine, angiotensin, endothelin, vasopressin, oxytocin, serotonin,* and *histamine.*

A hormone causes contraction of a smooth muscle when the muscle cell membrane contains *hormone-gated excitatory receptors* for the respective hormone. Conversely, the hormone causes inhibition if the membrane contains *inhibitory receptors* for the hormone rather than excitatory receptors.

Mechanisms of Smooth Muscle Excitation or Inhibition by Hormones or Local Tissue Factors. Some hormone receptors in the smooth muscle membrane open sodium or calcium ion channels and depolarize the membrane, the same as after nerve stimulation. Sometimes action potentials result, or action potentials that are already occurring may be enhanced. In other cases, depolarization occurs without action potentials and this depolarization allows calcium ion entry into the cell, which promotes the contraction.

Inhibition, in contrast, occurs when the hormone (or other tissue factor) *closes the sodium and calcium channels* to prevent entry of these positive ions; inhibition also occurs if the normally closed *potassium channels are opened,* allowing positive potassium ions to diffuse out of the cell. Both of these actions increase the degree of negativity inside the muscle cell, a state called *hyperpolarization,* which strongly inhibits muscle contraction.

Sometimes smooth muscle contraction or inhibition is initiated by hormones without directly causing any change in the membrane potential. In these instances, the hormone may activate a membrane receptor that does not open any ion channels but instead causes an internal change in the muscle fiber, such as release of calcium ions from the intracellular sarcoplasmic reticulum; the calcium then induces contraction. To inhibit contraction, other receptor mechanisms are known to activate the enzyme *adenylate cyclase* or *guanylate cyclase* in the cell membrane; the portions of the receptors that protrude to the interior of the cells are coupled to these enzymes, causing the formation of *cyclic adenosine monophosphate* (cAMP) or *cyclic guanosine monophosphate* (cGMP), so-called *second messengers.* The cAMP or cGMP has many effects, one of which is to change the degree of phosphorylation of several enzymes that indirectly inhibit contraction. The pump that moves calcium ions from the sarcoplasm into the sarcoplasmic reticulum is activated, as well as the cell membrane pump that moves calcium ions out of the cell itself; these effects reduce the calcium ion concentration in the sarcoplasm, thereby inhibiting contraction.

Smooth muscles have considerable diversity in how they initiate contraction or relaxation in response to different hormones, neurotransmitters, and other substances. In some instances, the same substance may cause either relaxation or contraction of smooth muscles in different locations. For example, norepinephrine inhibits contraction of smooth muscle in the intestine but stimulates contraction of smooth muscle in blood vessels.

Source of Calcium Ions That Cause Contraction Through the Cell Membrane and from the Sarcoplasmic Reticulum

Although the contractile process in smooth muscle, as in skeletal muscle, is activated by calcium ions, the source of the calcium ions differs. An important difference is that the sarcoplasmic reticulum, which provides virtually all the calcium ions for skeletal muscle contraction, is only slightly developed in most smooth muscle. Instead, most of the calcium ions that cause contraction enter the muscle cell from the extracellular fluid at the time of the action potential or other stimulus. That is, the concentration of calcium ions in the extracellular fluid is greater than 10^{-3} molar, in comparison with less than 10^{-7} molar inside the smooth muscle cell; this causes rapid diffusion of the calcium ions into the cell from the extracellular fluid when the calcium channels open. The time required for this diffusion to occur averages 200 to 300 milliseconds and

is called the *latent period* before contraction begins. This latent period is about 50 times as great for smooth muscle as for skeletal muscle contraction.

Role of the Smooth Muscle Sarcoplasmic Reticulum. Figure 8-6 shows a few slightly developed sarcoplasmic tubules that lie near the cell membrane in some larger smooth muscle cells. Small invaginations of the cell membrane, called *caveolae,* abut the surfaces of these tubules. The caveolae suggest a rudimentary analog of the transverse tubule system of skeletal muscle. When an action potential is transmitted into the caveolae, this is believed to excite calcium ion release from the abutting sarcoplasmic tubules in the same way that action potentials in skeletal muscle transverse tubules cause release of calcium ions from the skeletal muscle longitudinal sarcoplasmic tubules. In general, the more extensive the sarcoplasmic reticulum in the smooth muscle fiber, the more rapidly it contracts.

Smooth Muscle Contraction Is Dependent on Extracellular Calcium Ion Concentration. Although changing the extracellular fluid calcium ion concentration from normal has little effect on the force of contraction of skeletal muscle, this is not true for most smooth muscle. When the extracellular fluid calcium ion concentration falls to about 1/3 to 1/10 normal, smooth muscle contraction usually ceases. Therefore, the force of contraction of smooth muscle is usually highly dependent on extracellular fluid calcium ion concentration.

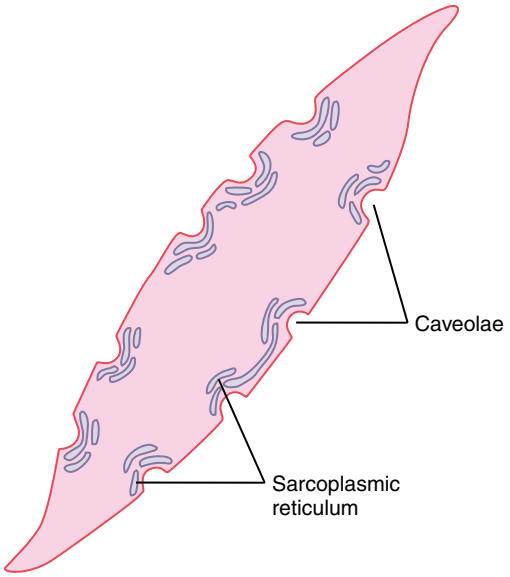


Figure 8-6 Sarcoplasmic tubules in a large smooth muscle fiber showing their relation to invaginations in the cell membrane called *caveolae*.

A Calcium Pump Is Required to Cause Smooth Muscle Relaxation. To cause relaxation of smooth muscle after it has contracted, the calcium ions must be removed from the intracellular fluids. This removal is achieved by a *calcium pump* that pumps calcium ions out of the smooth muscle fiber back into the extracellular fluid, or into a sarcoplasmic reticulum, if it is present. This pump is slow-acting in comparison with the fast-acting sarcoplasmic reticulum pump in skeletal muscle. Therefore, a single smooth muscle contraction often lasts for seconds rather than hundredths to tenths of a second, as occurs for skeletal muscle.

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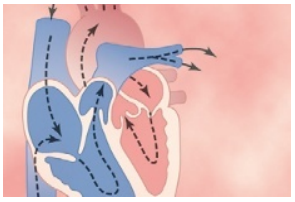
Cardiac Muscle; The Heart as a Pump and Function of the Heart Valves



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

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

Physiology of Cardiac Muscle

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

Physiologic Anatomy of Cardiac Muscle

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

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

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

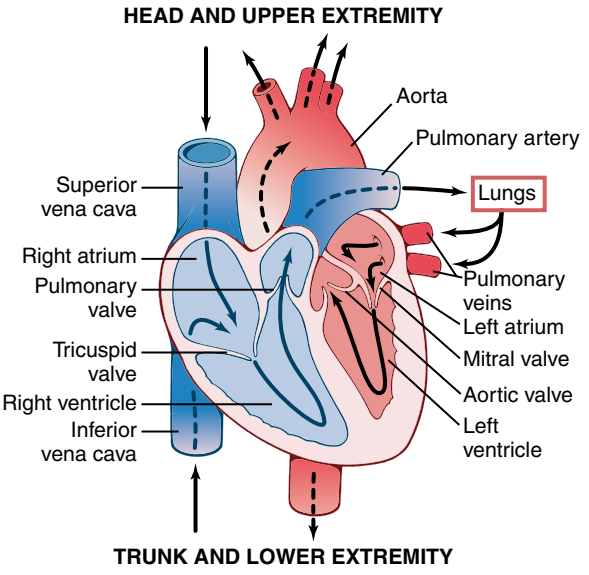


Figure 9-1 Structure of the heart, and course of blood flow through the heart chambers and heart valves.

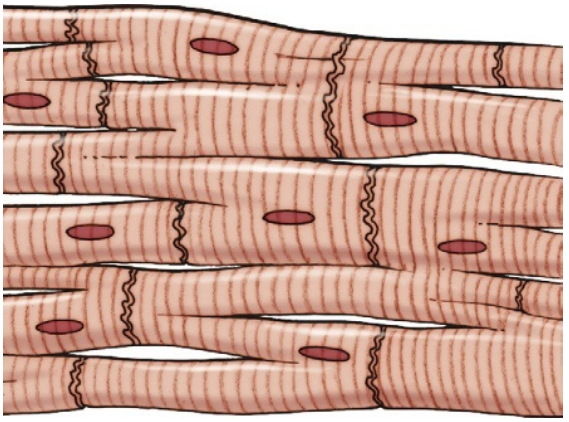


Figure 9-2 "Syncytial," interconnecting nature of cardiac muscle fibers.

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

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

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

Action Potentials in Cardiac Muscle

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

What Causes the Long Action Potential and the Plateau? At this point, we address the questions: Why is the action potential of cardiac muscle so long and why does it have a plateau, whereas that of skeletal muscle

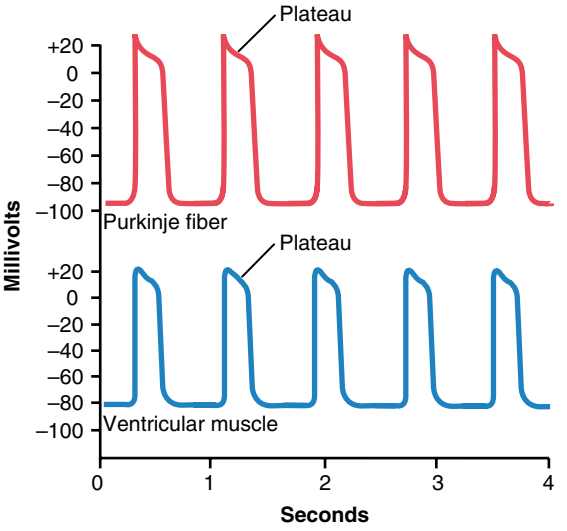


Figure 9-3 Rhythmical action potentials (in millivolts) from a Purkinje fiber and from a ventricular muscle fiber, recorded by means of microelectrodes.

does not? The basic biophysical answers to these questions were presented in Chapter 5, but they merit summarizing here as well.

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

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

The second major functional difference between cardiac muscle and skeletal muscle that helps account for both the prolonged action potential and its plateau is this: Immediately after the onset of the action potential, the permeability of the cardiac muscle membrane for potassium ions *decreases* about fivefold, an effect that does not occur

in skeletal muscle. This decreased potassium permeability may result from the excess calcium influx through the calcium channels just noted. Regardless of the cause, the decreased potassium permeability greatly decreases the outflux of positively charged potassium ions during the action potential plateau and thereby prevents early return of the action potential voltage to its resting level. When the slow calcium-sodium channels do close at the end of 0.2 to 0.3 second and the influx of calcium and sodium ions ceases, the membrane permeability for potassium ions also increases rapidly; this rapid loss of potassium from the fiber immediately returns the membrane potential to its resting level, thus ending the action potential.

Velocity of Signal Conduction in Cardiac Muscle. The velocity of conduction of the excitatory action potential signal along both *atrial and ventricular muscle fibers* is about 0.3 to 0.5 m/sec, or about ½₅₀ the velocity in very large nerve fibers and about ¹⁄₁₀ the velocity in skeletal muscle fibers. The velocity of conduction in the specialized heart conductive system—in the *Purkinje fibers*—is as great as 4 m/sec in most parts of the system, which allows reasonably rapid conduction of the excitatory signal to the different parts of the heart, as explained in Chapter 10.

Refractory Period of Cardiac Muscle. Cardiac muscle, like all excitable tissue, is refractory to restimulation during the action potential. Therefore, the refractory period of the heart is the interval of time, as shown to the left in Figure 9-4, during which a normal cardiac impulse cannot re-excite an already excited area of cardiac muscle. The normal refractory period of the ventricle is 0.25 to 0.30 second, which is about the duration of the prolonged plateau action potential. There is an additional *relative refractory period* of about 0.05 second during which the muscle is more difficult than normal to excite but nevertheless can be excited by a very strong excitatory signal, as demonstrated by the early "premature" contraction in the second example of Figure 9-4. The refractory period of atrial muscle is much shorter than that for the ventricles (about 0.15 second for the atria compared with 0.25 to 0.30 second for the ventricles).

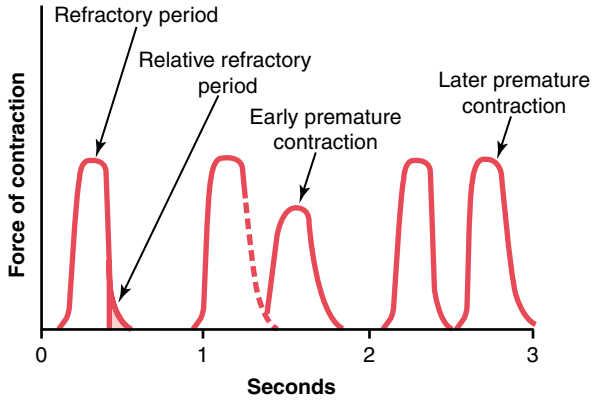


Figure 9-4 Force of ventricular heart muscle contraction, showing also duration of the refractory period and relative refractory period, plus the effect of premature contraction. Note that premature contractions do not cause wave summation, as occurs in skeletal muscle.

Excitation-Contraction Coupling—Function of Calcium Ions and the *Transverse Tubules*

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

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

Thus far, this mechanism of excitation-contraction coupling is the same as that for skeletal muscle, but there is a second effect that is quite different. In addition to the calcium ions that are released into the sarcoplasm from the cisternae of the sarcoplasmic reticulum, calcium ions also diffuse into the sarcoplasm from the T tubules themselves at the time of the action potential, which opens voltage-dependent calcium channels in the membrane of the T tubule (Figure 9-5). Calcium entering the cell then activates *calcium release channels,* also called *ryanodine receptor channels,* in the sarcoplasmic reticulum membrane, triggering the release of calcium into the sarcoplasm. Calcium ions in the sarcoplasm then interact with troponin to initiate cross-bridge formation and contraction by the same basic mechanism as described for skeletal muscle in Chapter 6.

Without the calcium from the T tubules, the strength of cardiac muscle contraction would be reduced considerably because the sarcoplasmic reticulum of cardiac muscle is less well developed than that of skeletal muscle and does not store enough calcium to provide full contraction. The T tubules of cardiac muscle, however, have a diameter 5 times as great as that of the skeletal muscle tubules, which means a volume 25 times as great. Also, inside the T tubules is a large quantity of mucopolysaccharides that are electronegatively charged and bind an abundant store of calcium ions, keeping these always available for diffusion to the interior of the cardiac muscle fiber when a T tubule action potential appears.

The strength of contraction of cardiac muscle depends to a great extent on the concentration of calcium ions in the extracellular fluids. In fact, a heart placed in a calcium-free solution will quickly stop beating. The reason for this is that the openings of the T tubules pass directly through the cardiac muscle cell membrane into the extracellular spaces surrounding the cells, allowing the same

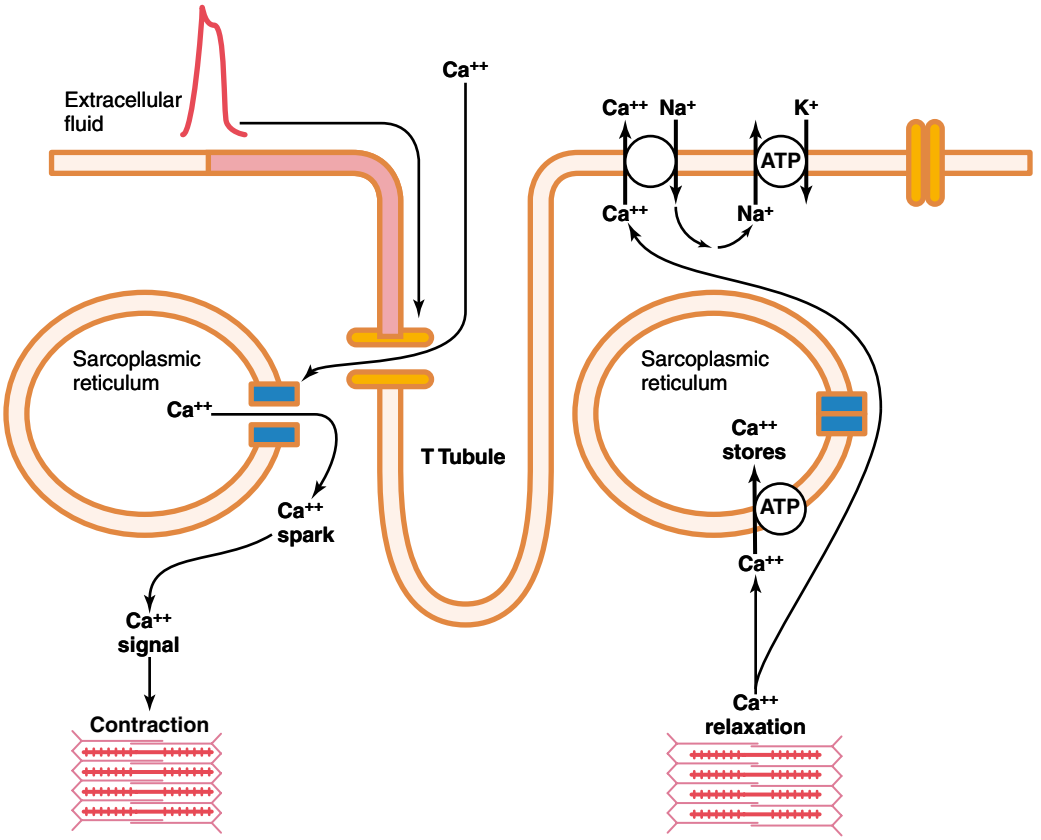


Figure 9-5 Mechanisms of excitation-contraction coupling and relaxation in cardiac muscle.

extracellular fluid that is in the cardiac muscle interstitium to percolate through the T tubules as well. Consequently, the quantity of calcium ions in the T tubule system (i.e., the availability of calcium ions to cause cardiac muscle contraction) depends to a great extent on the extracellular fluid calcium ion concentration.

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

At the end of the plateau of the cardiac action potential, the influx of calcium ions to the interior of the muscle fiber is suddenly cut off, and the calcium ions in the sarcoplasm are rapidly pumped back out of the muscle fibers into both the sarcoplasmic reticulum and the T tubule–extracellular fluid space. Transport of calcium back into the sarcoplasmic reticulum is achieved with the help of a calcium-ATPase pump (see Figure 9-5). Calcium ions are also removed from the cell by a sodium-calcium exchanger. The sodium that enters the cell during this exchange is then transported out of the cell by the sodium-potassium ATPase pump. As a result, the contraction ceases until a new action potential comes along.

Duration of Contraction. Cardiac muscle begins to contract a few milliseconds after the action potential begins and continues to contract until a few milliseconds after the action potential ends. Therefore, the duration of contraction of cardiac muscle is mainly a function of the duration of the action potential, *including the plateau*—about 0.2 second in atrial muscle and 0.3 second in ventricular muscle.

Cardiac Cycle

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

Diastole and Systole

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

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

Figure 9-6 shows the different events during the cardiac cycle for the left side of the heart. The top three curves show the pressure changes in the aorta, left ventricle, and left atrium, respectively. The fourth curve depicts the changes in left ventricular volume, the fifth the electrocardiogram, and the sixth a phonocardiogram, which is a recording of the sounds produced by the heart—mainly by the heart valves—as it pumps. It is especially important that the reader study in detail this figure and understand the causes of all the events shown.

Effect of Heart Rate on Duration of Cardiac Cycle. When heart rate increases, the duration of each cardiac cycle decreases, including the contraction and relaxation phases. The duration of the action potential and the period of contraction (systole) also decrease, but not by as great a percentage as does the relaxation phase (diastole). At a normal heart rate of 72 beats/min, systole comprises about 0.4 of the entire cardiac cycle. At three times the normal heart rate, systole is about 0.65 of the entire cardiac cycle. This means that the heart beating at a very fast rate does not remain relaxed long enough to allow complete filling of the cardiac chambers before the next contraction.

Relationship of the Electrocardiogram to the Cardiac Cycle

The electrocardiogram in Figure 9-6 shows the *P, Q, R, S,* and *T waves,* which are discussed in Chapters 11, 12, and 13. They are electrical voltages generated by the heart and recorded by the electrocardiograph from the surface of the body.

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

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

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

Function of the Atria as Primer Pumps

Blood normally flows continually from the great veins into the atria; about 80 percent of the blood flows directly through the atria into the ventricles even before the atria contract. Then, atrial contraction usually causes an additional 20 percent filling of the ventricles. Therefore, the atria simply function as primer pumps that increase the ventricular pumping effectiveness as much as 20 percent. However, the heart can continue to operate under most conditions

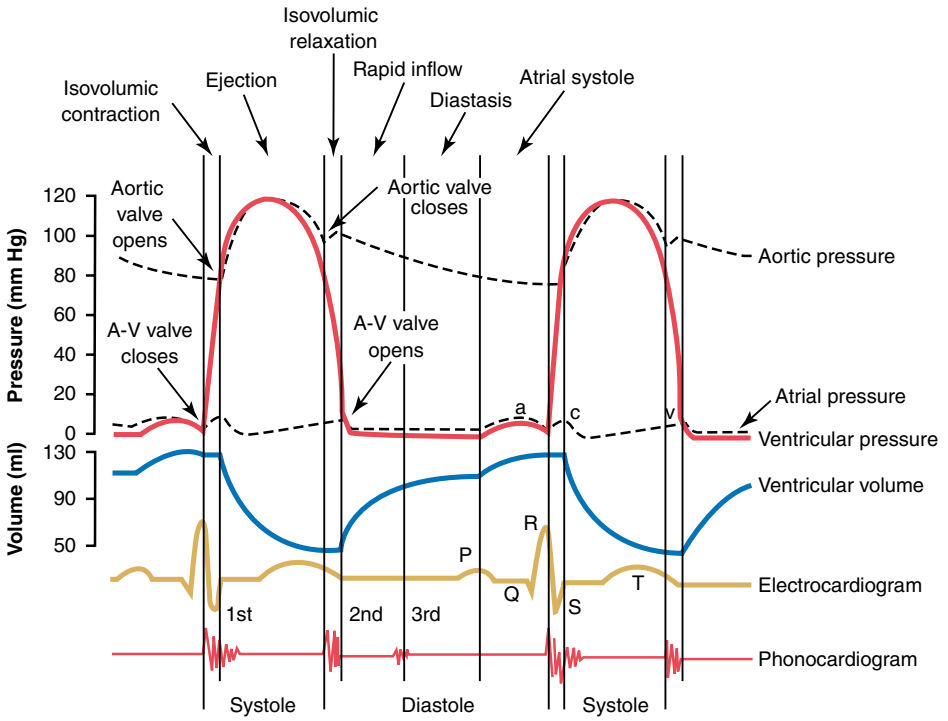


Figure 9-6 Events of the cardiac cycle for left ventricular function, showing changes in left atrial pressure, left ventricular pressure, aortic pressure, ventricular volume, the electrocardiogram, and the phonocardiogram.

even without this extra 20 percent effectiveness because it normally has the capability of pumping 300 to 400 percent more blood than is required by the resting body. Therefore, when the atria fail to function, the difference is unlikely to be noticed unless a person exercises; then acute signs of heart failure occasionally develop, especially shortness of breath.

Pressure Changes in the Atria—a, c, and v Waves. In the atrial pressure curve of Figure 9-6, three minor pressure elevations, called the *a, c,* and *v atrial pressure waves,* are noted.

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

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

The *v wave* occurs toward the end of ventricular contraction; it results from slow flow of blood into the atria from the veins while the A-V valves are closed during ventricular contraction. Then, when ventricular contraction is over, the A-V valves open, allowing this stored atrial blood to flow rapidly into the ventricles and causing the v wave to disappear.

Function of the Ventricles as Pumps

Filling of the Ventricles During Diastole. During ventricular systole, large amounts of blood accumulate in the right and left atria because of the closed A-V valves. Therefore, as soon as systole is over and the ventricular pressures fall again to their low diastolic values, the moderately increased pressures that have developed in the atria during ventricular systole immediately push the A-V valves open and allow blood to flow rapidly into the ventricles, as shown by the rise of the left *ventricular volume curve* in Figure 9-6. This is called the *period of rapid filling of the ventricles.*

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

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

Emptying of the Ventricles During Systole

Period of Isovolumic (Isometric) Contraction. Immediately after ventricular contraction begins, the ventricular pressure rises abruptly, as shown in Figure 9-6, causing the A-V valves to close. Then an additional 0.02 to 0.03 second is required for the ventricle to build up sufficient pressure to push the semilunar (aortic and pulmonary) valves open against the pressures in the aorta and pulmonary artery. Therefore, during this period, contraction is occurring in the ventricles, but there is no emptying. This is called the period of *isovolumic* or *isometric contraction,* meaning that tension is increasing in the muscle but little or no shortening of the muscle fibers is occurring.

Period of Ejection. When the left ventricular pressure rises slightly above 80 mm Hg (and the right ventricular pressure slightly above 8 mm Hg), the ventricular pressures push the semilunar valves open. Immediately, blood begins to pour out of the ventricles, with about 70 percent of the blood emptying occurring during the first third of the period of ejection and the remaining 30 percent emptying during the next two thirds. Therefore, the first third is called the *period of rapid ejection,* and the last two thirds, the *period of slow ejection.*

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

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

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

Function of the Valves

Atrioventricular Valves. The *A-V valves* (the *tricuspid* and *mitral* valves) prevent backflow of blood from the ventricles to the atria during systole, and the *semilunar valves* (the *aortic* and *pulmonary artery* valves) prevent backflow from the aorta and pulmonary arteries into the ventricles during diastole. These valves, shown in Figure 9-7 for the left ventricle, close and open *passively.* That is, they close when a backward pressure gradient pushes

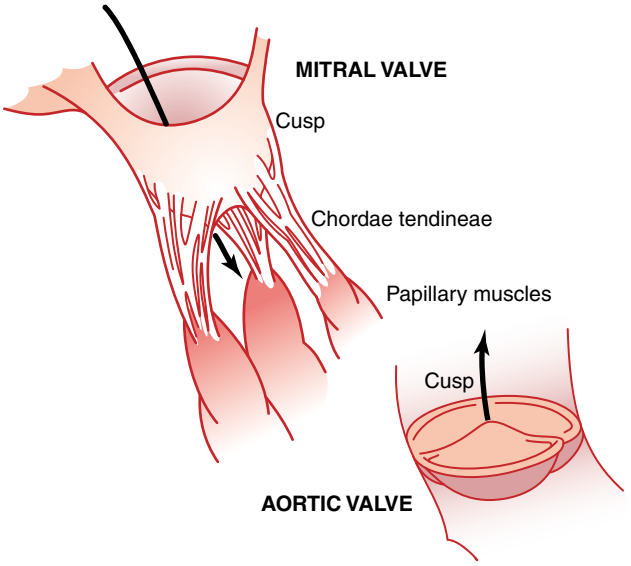


Figure 9-7 Mitral and aortic valves (the left ventricular valves).

blood backward, and they open when a forward pressure gradient forces blood in the forward direction. For anatomical reasons, the thin, filmy A-V valves require almost no backflow to cause closure, whereas the much heavier semilunar valves require rather rapid backflow for a few milliseconds.

Function of the Papillary Muscles. Figure 9-7 also shows papillary muscles that attach to the vanes of the A-V valves by the *chordae tendineae.* The papillary muscles contract when the ventricular walls contract, but contrary to what might be expected, they *do not* help the valves to close. Instead, they pull the vanes of the valves inward toward the ventricles to prevent their bulging too far backward toward the atria during ventricular contraction. If a chorda tendinea becomes ruptured or if one of the papillary muscles becomes paralyzed, the valve bulges far backward during ventricular contraction, sometimes so far that it leaks severely and results in severe or even lethal cardiac incapacity.

Aortic and Pulmonary Artery Valves. The aortic and pulmonary artery semilunar valves function quite differently from the A-V valves. First, the high pressures in the arteries at the end of systole cause the semilunar valves to snap to the closed position, in contrast to the much softer closure of the A-V valves. Second, because of smaller openings, the velocity of blood ejection through the aortic and pulmonary valves is far greater than that through the much larger A-V valves. Also, because of the rapid closure and rapid ejection, the edges of the aortic and pulmonary valves are subjected to much greater mechanical abrasion than are the A-V valves. Finally, the A-V valves are supported by the chordae tendineae, which is not true for the semilunar valves. It is obvious from the anatomy of the aortic and pulmonary valves (as shown for the aortic valve at the bottom of Figure 9-7) that they must be constructed with an especially strong yet very pliable fibrous tissue base to withstand the extra physical stresses.

Aortic Pressure Curve

When the left ventricle contracts, the ventricular pressure increases rapidly until the aortic valve opens. Then, after the valve opens, the pressure in the ventricle rises much less rapidly, as shown in Figure 9-6, because blood immediately flows out of the ventricle into the aorta and then into the systemic distribution arteries.

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

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

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

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

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

Relationship of the Heart Sounds to Heart Pumping

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

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

Work Output of the Heart

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

is equal to the stroke work output times the heart rate per minute.

Work output of the heart is in two forms. First, by far the major proportion is used to move the blood from the low-pressure veins to the high-pressure arteries. This is called *volume-pressure work* or *external work*. Second, a minor proportion of the energy is used to accelerate the blood to its velocity of ejection through the aortic and pulmonary valves. This is the *kinetic energy of blood flow* component of the work output.

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

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

Graphical Analysis of Ventricular Pumping

Figure 9-8 shows a diagram that is especially useful in explaining the pumping mechanics of the *left* ventricle. The most important components of the diagram are the two curves labeled "diastolic pressure" and "systolic pressure." These curves are volume-pressure curves.

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

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

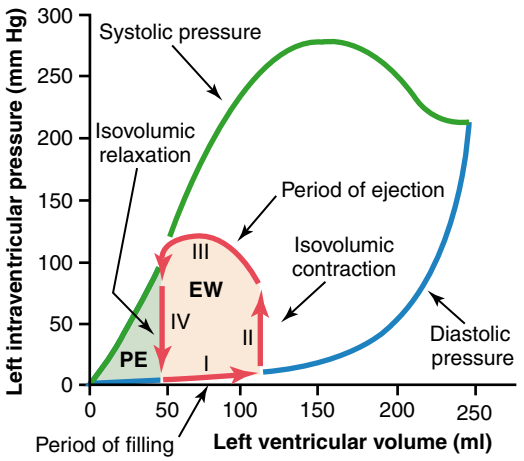


Figure 9-8 Relationship between left ventricular volume and intraventricular pressure during diastole and systole. Also shown by the heavy red lines is the "volume-pressure diagram," demonstrating changes in intraventricular volume and pressure during the normal cardiac cycle. EW, net external work.

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

During ventricular contraction, the "systolic" pressure increases even at low ventricular volumes and reaches a maximum at a ventricular volume of 150 to 170 ml. Then, as the volume increases still further, the systolic pressure actually decreases under some conditions, as demonstrated by the falling systolic pressure curve in Figure 9-8, because at these great volumes, the actin and myosin filaments of the cardiac muscle fibers are pulled apart far enough that the strength of each cardiac fiber contraction becomes less than optimal.

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

"Volume-Pressure Diagram" During the Cardiac Cycle; Cardiac Work Output. The red lines in Figure 9-8 form a loop called the *volume-pressure diagram* of the cardiac cycle for normal function of the *left* ventricle. A more detailed version of this loop is shown in Figure 9-9. It is divided into four phases.

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

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

Phase III: *Period of ejection.* During ejection, the systolic pressure rises even higher because of still more contraction of the ventricle. At the same time, the volume of the ventricle decreases because the aortic valve has now opened and blood flows out of the ventricle into the aorta. Therefore, the curve labeled "III," or "period of ejection," traces the changes in volume and systolic pressure during this period of ejection.

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

Readers well trained in the basic principles of physics will recognize that the area subtended by this functional

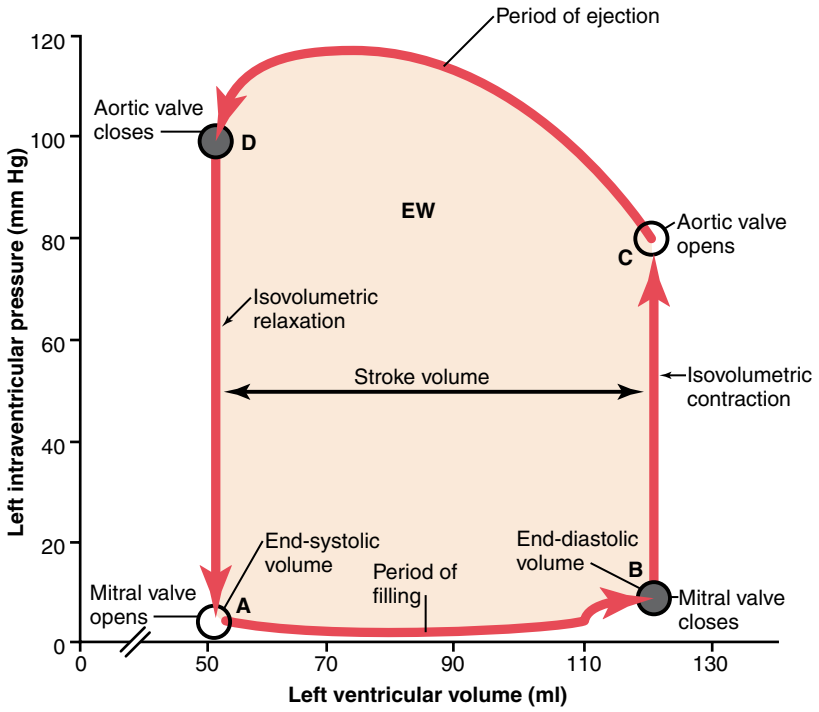


Figure 9-9 The "volume-pressure diagram" demonstrating changes in intraventricular volume and pressure during a single cardiac cycle (*red line*). The tan shaded area represents the net external work (*EW*) output by the left ventricle during the cardiac cycle.

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

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

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

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

The *afterload* of the ventricle is the pressure in the aorta leading from the ventricle. In Figure 9-8, this corresponds to the systolic pressure described by the phase III curve of the volume-pressure diagram. (Sometimes the afterload is loosely considered to be the resistance in the circulation rather than the pressure.)

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

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

Heart muscle, like skeletal muscle, uses chemical energy to provide the work of contraction. Approximately 70 to 90 percent of this energy is normally derived from oxidative metabolism of fatty acids with about 10 to 30 percent coming from other nutrients, especially lactate and glucose. Therefore, the rate of oxygen consumption by the heart is an excellent measure of the chemical energy liberated while the heart performs its work. The different chemical reactions that liberate this energy are discussed in Chapters 67 and 68.

Experimental studies have shown that oxygen consumption of the heart and the chemical energy expended during contraction are directly related to the total shaded area in Figure 9-8. This shaded portion consists of the *external work* (EW) as explained earlier and an additional portion called the *potential energy,* labeled PE. The potential energy represents additional work that could be accomplished by contraction of the ventricle if the ventricle should empty completely all the blood in its chamber with each contraction.

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

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

Regulation of Heart Pumping

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

Intrinsic Regulation of Heart Pumping—The Frank-Starling Mechanism

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

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

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

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

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

Ventricular Function Curves

One of the best ways to express the functional ability of the ventricles to pump blood is by *ventricular function curves,* as shown in Figures 9-10 and 9-11. Figure 9-10 shows a type of ventricular function curve called the *stroke work output curve.* Note that as the atrial pressure for each side of the heart increases, the stroke work output for that side increases until it reaches the limit of the ventricle's pumping ability.

Figure 9-11 shows another type of ventricular function curve called the *ventricular volume output curve.* The two curves of this figure represent function of the two ventricles of the human heart based on data extrapolated from lower animals. As the right and left atrial pressures increase, the respective ventricular volume outputs per minute also increase.

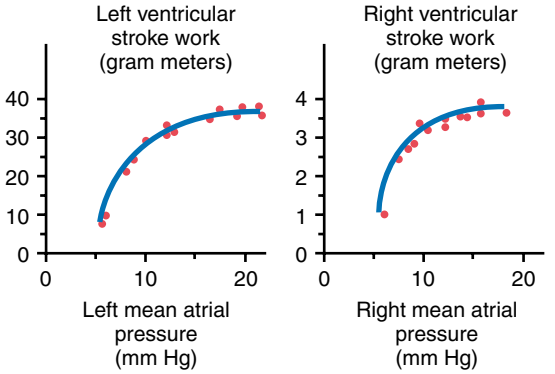


Figure 9-10 Left and right ventricular function curves recorded from dogs, depicting *ventricular stroke work output* as a function of left and right mean atrial pressures. (Curves reconstructed from data in Sarnoff SJ: Myocardial contractility as described by ventricular function curves. Physiol Rev 35:107, 1955.)

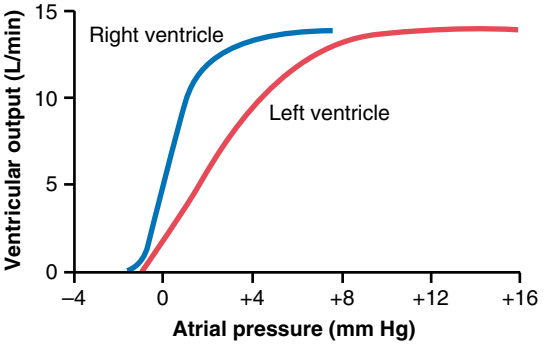


Figure 9-11 Approximate normal right and left *ventricular volume output curves* for the normal resting human heart as extrapolated from data obtained in dogs and data from human beings.

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

Control of the Heart by the Sympathetic and Parasympathetic Nerves

The pumping effectiveness of the heart also is controlled by the *sympathetic* and *parasympathetic (vagus)* nerves, which abundantly supply the heart, as shown in Figure 9-12. For given levels of atrial pressure, the amount of blood pumped each minute *(cardiac output)* often can be increased more than 100 percent by sympathetic stimulation. By contrast, the output can be decreased to as low as zero or almost zero by vagal (parasympathetic) stimulation.

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

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

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

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

Effect of Sympathetic or Parasympathetic Stimulation on the Cardiac Function Curve. Figure 9-13 shows four cardiac function curves. They are similar to the ventricular function curves of Figure 9-11. However, they represent function of the entire heart rather than of a single ventricle; they show the relation between right atrial pressure at the input of the right heart and cardiac output from the left ventricle into the aorta.

The curves of Figure 9-13 demonstrate that at any given right atrial pressure, the cardiac output increases during increased sympathetic stimulation and decreases during increased parasympathetic stimulation. These changes in output caused by autonomic nervous system stimulation result both from *changes in heart rate* and from *changes in contractile strength of the heart* because both change in response to the nerve stimulation.

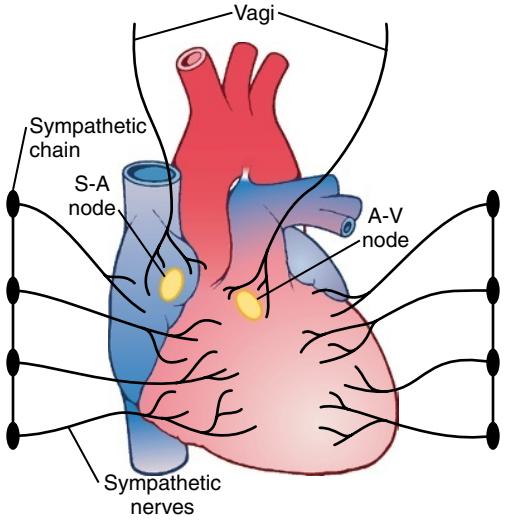


Figure 9-12 Cardiac *sympathetic* and *parasympathetic* nerves. (The vagus nerves to the heart are parasympathetic nerves.)

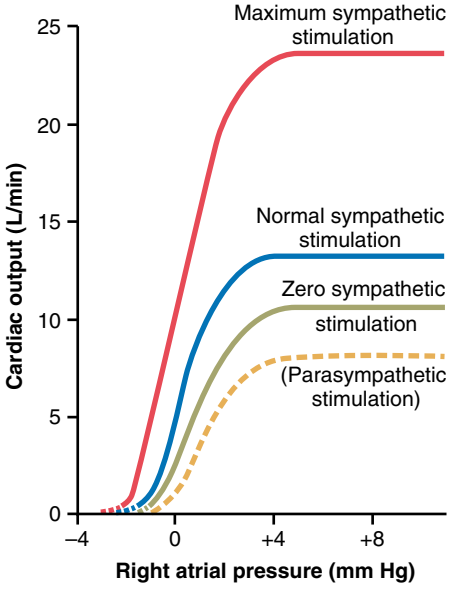


Figure 9-13 Effect on the cardiac output curve of different degrees of sympathetic or parasympathetic stimulation.

Effect of Potassium and Calcium Ions on Heart Function

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

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

These effects result partially from the fact that a high potassium concentration in the extracellular fluids decreases the resting membrane potential in the cardiac muscle fibers, as explained in Chapter 5. That is, high extracellular fluid potassium concentration partially depolarizes the cell membrane, causing the membrane potential to be less negative. As the membrane potential decreases, the intensity of the action potential also decreases, which makes contraction of the heart progressively weaker.

Effect of Calcium Ions. An excess of calcium ions causes effects almost exactly opposite to those of potassium ions, causing the heart to go toward spastic contraction. This is caused by a direct effect of calcium ions to initiate the cardiac contractile process, as explained earlier in the chapter.

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

Effect of Temperature on Heart Function

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

Contractile strength of the heart often is enhanced temporarily by a moderate increase in temperature, as occurs during body exercise, but prolonged elevation of temperature exhausts the metabolic systems of the heart and eventually causes weakness. Therefore, optimal function of the heart depends greatly on proper control of body temperature by the temperature control mechanisms explained in Chapter 73.

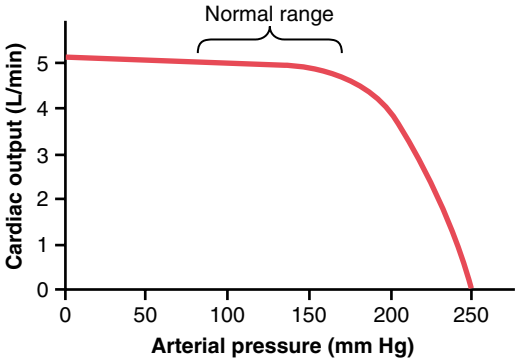


Figure 9-14 Constancy of cardiac output up to a pressure level of 160 mm Hg. Only when the arterial pressure rises above this normal limit does the increasing pressure load cause the cardiac output to fall significantly.

Increasing the Arterial Pressure Load (up to a Limit) Does Not Decrease the Cardiac Output

Note in Figure 9-14 that increasing the arterial pressure in the aorta does not decrease the cardiac output until the mean arterial pressure rises above about 160 mm Hg. In other words, during normal function of the heart at normal systolic arterial pressures (80 to 140 mm Hg), the cardiac output is determined almost entirely by the ease of blood flow through the body's tissues, which in turn controls *venous return* of blood to the heart. This is the principal subject of Chapter 20.

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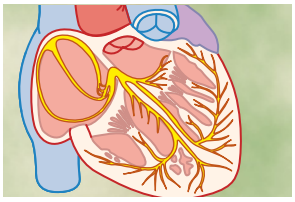
Rhythmical Excitation of the Heart



The heart is endowed with a special system for (1) generating rhythmical electrical impulses to cause rhythmical contraction of the heart muscle and (2) conducting these impulses rapidly through the heart. When this system functions normally, the atria contract about one sixth of a second ahead of ventricular contraction, which allows filling of the ventricles before they pump the blood through the lungs and peripheral circulation. Another special importance of the system is that it allows all portions of the ventricles to contract almost simultaneously, which is essential for most effective pressure generation in the ventricular chambers.

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

Specialized Excitatory and Conductive System of the Heart

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

Sinus (Sinoatrial) Node

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

Automatic Electrical Rhythmicity of the Sinus Fibers

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

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

Before attempting to explain the rhythmicity of the sinus nodal fibers, first recall from the discussions of Chapters 5 and 9 that cardiac muscle has three types of membrane ion channels that play important roles in causing the voltage changes of the action potential. They are (1) *fast sodium channels*, (2) *slow sodium-calcium channels*, and (3) *potassium channels*.

Opening of the fast sodium channels for a few 10,000ths of a second is responsible for the rapid upstroke spike of the action potential observed in ventricular muscle, because of rapid influx of positive sodium ions to the

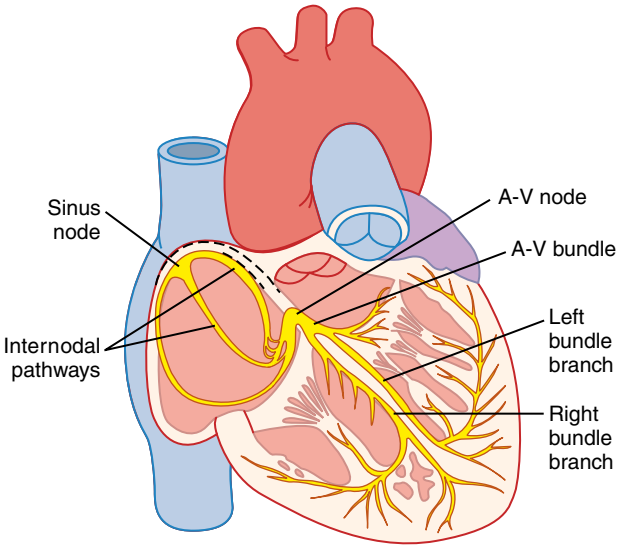


Figure 10-1 Sinus node and the Purkinje system of the heart, showing also the A-V node, atrial internodal pathways, and ventricular bundle branches.

interior of the fiber. Then the "plateau" of the ventricular action potential is caused primarily by slower opening of the slow sodium-calcium channels, which lasts for about 0.3 second. Finally, opening of potassium channels allows diffusion of large amounts of positive potassium ions in the outward direction through the fiber membrane and returns the membrane potential to its resting level.

But there is a difference in the function of these channels in the sinus nodal fiber because the "resting" potential is much less negative—only –55 millivolts in the nodal fiber instead of the –90 millivolts in the ventricular muscle fiber. At this level of –55 millivolts, the fast sodium channels mainly have already become "inactivated," which means that they have become blocked. The cause of this is that any time the membrane potential remains less negative than about –55 millivolts for more than a few milliseconds, the inactivation gates on the inside of the cell membrane that close the fast sodium channels become closed and remain so. Therefore, only the slow sodium-calcium channels can open (i.e., can become "activated")

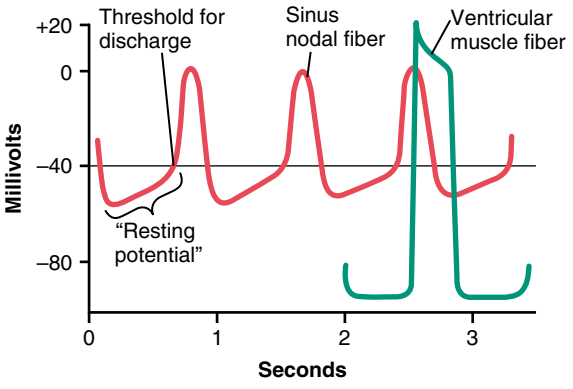


Figure 10-2 Rhythmical discharge of a sinus nodal fiber. Also, the sinus nodal action potential is compared with that of a ventricular muscle fiber.

and thereby cause the action potential. As a result, the atrial nodal action potential is slower to develop than the action potential of the ventricular muscle. Also, after the action potential does occur, return of the potential to its negative state occurs slowly as well, rather than the abrupt return that occurs for the ventricular fiber.

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

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

Why is this new state of hyperpolarization not maintained forever? The reason is that during the next few tenths of a second after the action potential is over, progressively more and more potassium channels close. The inward-leaking sodium and calcium ions once again overbalance the outward flux of potassium ions, and this causes the "resting" potential to drift upward once more, finally reaching the threshold level for discharge at a potential of about –40 millivolts. Then the entire process begins again: self-excitation to cause the action potential, recovery from the action potential, hyperpolarization after the action potential is over, drift of the "resting" potential to threshold, and finally re-excitation to elicit another cycle. This process continues indefinitely throughout a person's life.

Internodal Pathways and Transmission of the Cardiac Impulse Through the Atria

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

Atrioventricular Node and Delay of Impulse Conduction from the Atria to the Ventricles

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

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

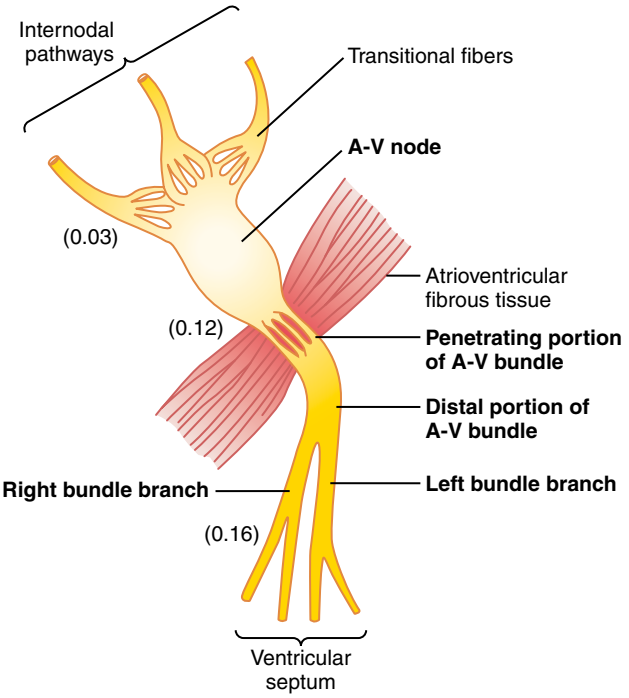


Figure 10-3 Organization of the A-V node. The numbers represent the interval of time from the origin of the impulse in the sinus node. The values have been extrapolated to human beings.

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

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

Rapid Transmission in the Ventricular Purkinje System

Special Purkinje fibers lead from the A-V node through the A-V bundle into the ventricles. Except for the initial portion of these fibers where they penetrate the A-V fibrous barrier, they have functional characteristics that are quite the opposite of those of the A-V nodal fibers. They are very large fibers, even larger than the normal ventricular muscle fibers, and they transmit action potentials at a velocity of 1.5 to 4.0 m/sec, a velocity about 6 times that in the usual ventricular muscle and 150 times that in some of the A-V nodal fibers. This allows almost instantaneous transmission of the cardiac impulse throughout the entire remainder of the ventricular muscle.

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

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

the ventricles to the atria, allowing only forward conduction from the atria to the ventricles.

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

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

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

Transmission of the Cardiac Impulse in the Ventricular Muscle

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

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

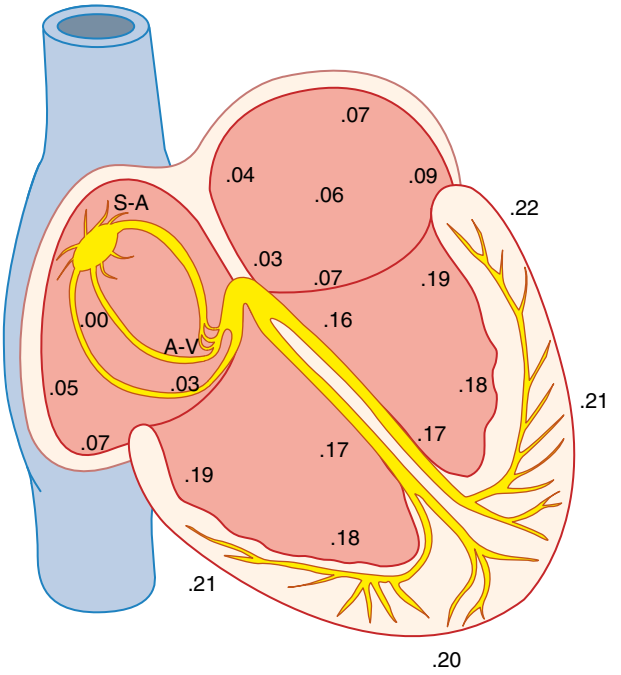


Figure 10-4 Transmission of the cardiac impulse through the heart, showing the time of appearance (in fractions of a second after initial appearance at the sinoatrial node) in different parts of the heart.

Summary of the Spread of the Cardiac Impulse Through the Heart

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

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

Control of Excitation and Conduction in the Heart

Sinus Node as the Pacemaker of the Heart

In the discussion thus far of the genesis and transmission of the cardiac impulse through the heart, we have noted that the impulse normally arises in the sinus node. In some

abnormal conditions, this is not the case. Other parts of the heart can also exhibit intrinsic rhythmical excitation in the same way that the sinus nodal fibers do; this is particularly true of the A-V nodal and Purkinje fibers.

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

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

Thus, the sinus node controls the beat of the heart because its rate of rhythmical discharge is faster than that of any other part of the heart. Therefore, the sinus node is virtually always the pacemaker of the normal heart.

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

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

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

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

Role of the Purkinje System in Causing Synchronous Contraction of the Ventricular Muscle

It is clear from our description of the Purkinje system that normally the cardiac impulse arrives at almost all portions of the ventricles within a narrow span of time, exciting the first ventricular muscle fiber only 0.03 to 0.06 second ahead of excitation of the last ventricular muscle fiber. This causes all portions of the ventricular muscle in both ventricles to begin contracting at almost the same time and then to continue contracting for about another 0.3 second.

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

Control of Heart Rhythmicity and Impulse Conduction by the Cardiac Nerves: Sympathetic and Parasympathetic Nerves

The heart is supplied with both sympathetic and parasympathetic nerves, as shown in Figure 9-10 of Chapter 9. The parasympathetic nerves (the vagi) are distributed mainly to the S-A and A-V nodes, to a lesser extent to the muscle of the two atria, and very little directly to the ventricular muscle. The sympathetic nerves, conversely, are distributed to all parts of the heart, with strong representation to the ventricular muscle, as well as to all the other areas.

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

Weak to moderate vagal stimulation slows the rate of heart pumping, often to as little as one-half normal.

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

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

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

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

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

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

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

In the A-V node and A-V bundles, increased sodium-calcium permeability makes it easier for the action potential to excite each succeeding portion of the conducting fiber bundles, thereby decreasing the conduction time from the atria to the ventricles.

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

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