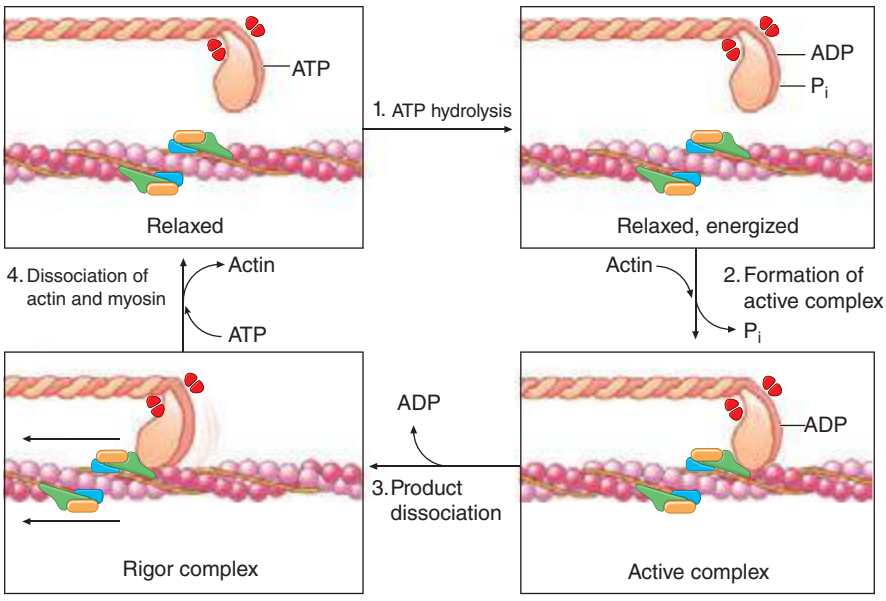

FIGURE 265e-5 Four steps in cardiac muscle contraction and relaxation. In relaxed muscle (***upper left***), ATP bound to the myosin cross-bridge dissociates the thick and thin filaments. ***Step 1:*** Hydrolysis of myosin-bound ATP by the ATPase site on the myosin head transfers the chemical energy of the nucleotide to the activated cross-bridge (***upper right***). When cytosolic Ca^{2+} concentration is low, as in relaxed muscle, the reaction cannot proceed because tropomyosin and the troponin complex on the thin filament do not allow the active sites on actin to interact with the cross-bridges. Therefore, even though the cross-bridges are energized, they cannot interact with actin. ***Step 2:*** When Ca^{2+} binding to troponin C has exposed active sites on the thin filament, actin interacts with the myosin cross-bridges to form an active complex (***lower right***) in which the energy derived from ATP is retained in the actin-bound cross-bridge, whose orientation has not yet shifted. ***Step 3:*** The muscle contracts when ADP dissociates from the cross-bridge. This step leads to the formation of the low-energy rigor complex (***lower left***) in which the chemical energy derived from ATP hydrolysis has been expended to perform mechanical work (the "rowing" motion of the cross-bridge). ***Step 4:*** The muscle returns to its resting state, and the cycle ends when a new molecule of ATP binds to the rigor complex and dissociates the cross-bridge from the thin filament. This cycle continues until calcium is dissociated from troponin C in the thin filament, which causes the contractile proteins to return to the resting state with the cross-bridge in the energized state. ADP, adenosine diphosphate; ATP, adenosine triphosphate; ATPase, adenosine triphosphatase. *(From AM Katz: Heart failure: Cardiac function and dysfunction, in Atlas of Heart Diseases, 3rd ed, WS Colucci [ed]. Philadelphia, Current Medicine, 2002. Reprinted with permission.)*

Dystrophin is a long cytoskeletal protein that has an amino-terminal actin-binding domain and a carboxy-terminal domain that binds to the dystroglycan complex at adherens junctions on the cell membrane, thus tethering the sarcomere to the cell membrane at regions tightly coupled to adjacent contracting myocytes. Mutations in components of the dystrophin complex lead to muscular dystrophy and associated cardiomyopathy.

During activation of the cardiac myocyte, Ca^{2+} becomes attached to one of three components of the heterotrimer troponin C, which results in a conformational change in the regulatory protein tropomyosin; the latter, in turn, exposes the actin cross-bridge interaction sites (Fig. 265e-5). Repetitive interaction between myosin heads and actin filaments is termed *cross-bridge cycling*, which results in sliding of the actin along the myosin filaments, ultimately causing muscle shortening and/or the development of tension. The splitting of ATP then dissociates the myosin cross-bridge from actin. In the presence of ATP (Fig. 265e-5), linkages between actin and myosin filaments are made and broken cyclically as long as sufficient Ca^{2+} is present; these linkages cease when $[Ca^{2+}]$ falls below a critical level, and the troponin-tropomyosin complex once more prevents interactions between the myosin cross-bridges and actin filaments (Fig. 265e-6).

Intracytoplasmic Ca^{2+} is a principal determinant of the inotropic state of the heart. Most agents that stimulate myocardial contractility (positive inotropic stimuli), including the digitalis glycosides and β-adrenergic agonists, increase the $[Ca^{2+}]$ in the vicinity of the myofilaments, which in turn triggers cross-bridge cycling. Increased impulse traffic in the cardiac adrenergic nerves stimulates myocardial contractility as a consequence of the release of norepinephrine from cardiac adrenergic nerve endings. Norepinephrine activates myocardial β receptors and, through the G_s-stimulated guanine nucleotide-binding protein, activates the enzyme adenylyl cyclase, which leads to the formation of the intracellular second messenger cyclic AMP from ATP (Fig. 265e-6). Cyclic AMP in turn activates protein kinase A (PKA), which phosphorylates the Ca^{2+} channel in the myocardial sarcolemma, thereby enhancing the influx of Ca^{2+} into the myocyte. Other functions of PKA are discussed below.

The *sarcoplasmic reticulum* (SR) (Fig. 265e-7), a complex network of anastomosing intracellular channels, invests the myofibrils. Its longitudinally disposed tubules closely invest the surfaces of individual sarcomeres but have no direct continuity with the outside of the cell. However, closely related to the SR, both structurally and functionally, are the transverse tubules, or T system, formed by tubelike invaginations of the sarcolemma that extend into the myocardial fiber along the Z lines, i.e., the ends of the sarcomeres.

CARDIAC ACTIVATION

In the inactive state, the cardiac cell is electrically polarized; i.e., the interior has a negative charge relative to the outside of the cell, with a transmembrane potential of –80 to –100 mV (Chap. 273e). The sarcolemma, which in the resting state is largely impermeable to Na^+, has a Na^+- and K^+-stimulating pump energized by ATP that extrudes Na^+ from the cell; this pump plays a critical role in establishing the resting potential. Thus, intracellular $[K^+]$ is relatively high and $[Na^+]$ is far lower; conversely, extracellular $[Na^+]$ is high and $[K^+]$ is low. At the same time, in the resting state, extracellular $[Ca^{2+}]$ greatly exceeds free intracellular $[Ca^{2+}]$.

The action potential has four phases (see Fig. 273e-1*B*). During the plateau of the action potential (phase 2), there is a slow inward current through L-type Ca^{2+} channels in the sarcolemma (Fig. 265e-7). The depolarizing current not only extends across the surface of the cell but penetrates deeply into the cell by way of the ramifying T tubular system. The absolute quantity of Ca^{2+} that crosses the sarcolemma and the T system is relatively small and by itself appears to be insufficient to bring about full activation of the contractile apparatus. However, this Ca^{2+} current triggers the release of much larger quantities of Ca^{2+} from the SR, a process termed *Ca^{2+}-induced Ca^{2+} release*. The latter is a major determinant of intracytoplasmic $[Ca^{2+}]$ and therefore of myocardial contractility.

Ca^{2+} is released from the SR through a Ca^{2+} release channel, a cardiac isoform of the ryanodine receptor (RyR2), which controls intracytoplasmic $[Ca^{2+}]$ and, as in vascular smooth-muscle cells, leads to the local changes in intracellular $[Ca^{2+}]$ called calcium sparks. A number of regulatory proteins, including *calstabin 2*, inhibit RyR2 and thereby the release of Ca^{2+} from the SR. PKA dissociates calstabin from the RyR2, enhancing Ca^{2+} release and thereby myocardial contractility. Excessive plasma catecholamine levels and cardiac sympathetic neuronal release of norepinephrine cause hyperphosphorylation of PKA, leading to calstabin 2–depleted RyR2. The latter depletes SR Ca^{2+} stores and thereby impairs cardiac contraction, leading to heart failure, and also triggers ventricular arrhythmias.