The Action Potential

Cardiac function depends on the appropriate timing of contraction in various regions, as well as appropriate heart rate. The initiating event in cardiac excitation–contraction coupling is the action potential (AP). The AP is the membrane potential waveform that is determined by a complex interplay of many ion transporters and the calcium transient itself. The AP is also responsible for the propagation of excitation information from cell to cell through gap junctions, and allows the heart to function as an electrical and mechanical syncytium. The normal cardiac impulse originates in a group of cardiac pacemaker cells located in the sinoatrial (SA) node and propagates through the atria to reach the atrioventricular node. From the atrioventricular node, electrical activity passes rapidly through the cable-like His-Purkinje system to reach the ventricles, triggering myocyte excitation–contraction coupling and cardiac pumping. The cells in the SA node have normally the fastest intrinsic pacemaker activity. The SA node consists of cells with very few contractile elements and a relatively simple action potential. As the pacemaker cells controlling the rate and the rhythm of the beating heart, SA cells have ever changing membrane potentials. In contrast, ventricular cells are packed with contractile elements and have more complex, triggered action potentials.

The SA node is paced by the i_f current ("funny" Na currents; hyperpolarization activated) and by decreasing opposition to depolarization by the inward rectifier, i_k, current. i_f is a nonselective inward current allowing sodium, potassium, and some calcium ions to enter the cell between –35 and –100 mV of membrane potential. This inward current drives the membrane potential (Em) toward E_f (–20 mV). i_f is opposed by the outward, inwardly rectifying K^+ current, i_{k1}, resulting in a slow but carefully timed pacemaker depolarization to –40 mV. At –40 mV, Ca^{2+} channels begin to open, more rapidly depolarizing the membrane. The slow upstroke of the action potential in nodal cells results from a relative lack of Na^+ channels and dependence of repolarization on the fewer, slower inward Ca^{2+} channels. The first Ca^{2+} channel to be activated is the transient (T type) Ca^{2+} current, i_{CaT}. This current drives Em toward E_{Ca} and in the process triggers the activation of the L-type voltage-activated Ca^{2+} current (i_{CaL}) at –30 mV. Almost at the same time these inward currents are activated, competing outwardly conducting delayed rectifying K^+ currents (i_k) are triggered at Em depolarized to –40 mV. The result is again a tug of war between the inward conductance's (i_{CaT}, i_{CaL}, and $i_{Na/Ca}$; collectively the forces of depolarization) and the outward hyperpolarizing K^+ currents, i_k. The balance is reached at a peak depolarization of +10 mV before the outward K^+ current, i_k, slowly overcomes the inward currents, is joined by i_{k1}, and repolarizes the cell back toward E_k. A schematic presentation of individual ionic currents responsible for depolarization of a pacemaker cell in the SA node is presented in figure 11.1. In the resting heart, a high level of parasympathetic tone slows spontaneous depolarization of the SA node. Blocking of both parasympathetic and sympathetic activity increases the heart rate to about 100 beats

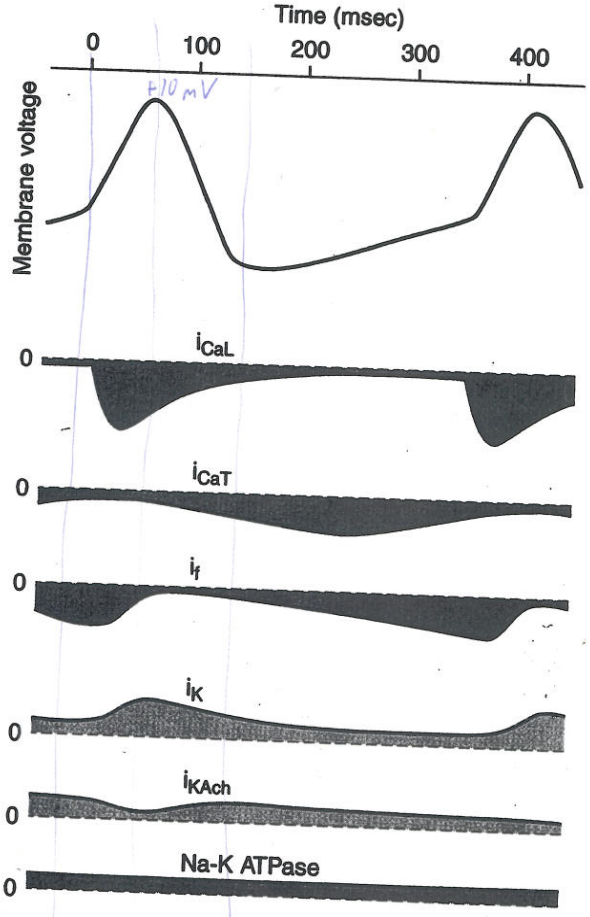

Figure 11.1 Individual ionic currents responsible for depolarization of a pacemaker cell in the SA node. Upper tracing: voltage changes. Diastolic depolarization is caused by declines in three inward currents shown as solid lines (i_{CaL}, i_{CaT}, i_f) and increases in two outward currents shown as dotted lines (i_k and $i_{K.Ach}$). A background outward current generated by the Na-K ATPase (dashed line) also participates in pacemaker activity. For description and definition of the individual ionic currents, see text.

Adapted from A.M. Katz, 2001, *Physiology of the heart* (3rd ed.). (Philadelphia, PA: Lippincott, Williams, and Wilkins).

per minute, which represents the intrinsic or true resting heart rate. Sympathetic activity increases substantially during acute endurance exercise; during strenuous activity in this situation, the heart rate increases up to the individual's maximum, which ranges from about 150 to 230 beats per minute in healthy humans. A signature of the endurance-trained state is resting and submaximal bradycardia. This is due to increased parasympathetic and reduced sympathetic activity. The effects of vagal and sympathetic stimulation on the SA node are largely mediated through G-protein-coupled receptors ($G\alpha_i$ and $G\alpha_s$) (Yatani et al. 1990). The ability of sympathetic stimulation to increase heart rate occurs when $G\alpha_s$ acts directly on the i_f channels. $G\alpha_s$ also stimulates adenylyl cyclase, which activates protein kinase A to phosphorylate calcium channels.

Parasympathetic slowing of heart rate is mediated by $G\alpha_i$, which directly activates the inward rectifier current $i_{K,ACh}$ (inward-rectifying acetylcholine-activated potassium channels) and inhibits cAMP production; both responses hyperpolarize the cells of the SA node (Katz 2001).

In the atrioventricular (AV) node, the AP resembles that in the SA node. In atrial and ventricular muscle cells, the resting membrane potential is about –80 mV and the AP has a very fast upstroke attributable to a Na^+ current, reaching a peak at +30 to 50 mV. Repolarization is much faster in atria than in ventricular myocytes and Purkinje fibers. Thus in ventricular cells there is a more prominent plateau. Moreover, the ventricular AP duration is shortest in epicardial cells, longer in endocardial cells, and longest in midmyocardial cells, partly due to differences in ion channel expression. The long AP duration in ventricular myocytes serves two functions. First, it prevents electrical re-excitation by keeping the membrane depolarized and thus Na^+ and Ca^{2+} channels inactivated. Second, it allows contraction to relax before the next beat, since the AP duration is almost as long as the calcium transient and contraction (Bers 2002). This also prevents tetanization of cardiac muscle. Figure 11.2 summarizes the key features of 10 principal currents involved in the generation of the ventricular myocardial action potential. The action potential is initiated by a rapid depolarization: The fast upstroke in ventricular cells is accomplished by Na^+ channels (i_{Na}). Once the threshold potential is reached, Na^+ channels are activated, resulting in an enormous but brief (<2 msec) inward Na^+ current driving the cell toward E_{Na}. The fast Na^+ channels open as a function of time and voltage, and inactivation causes the current to shut down almost as quickly as it turns on. The threshold-dependent activation of i_{Na} quickly depolarizes the membrane to the levels of activation of both inward Ca^{2+} currents and outward

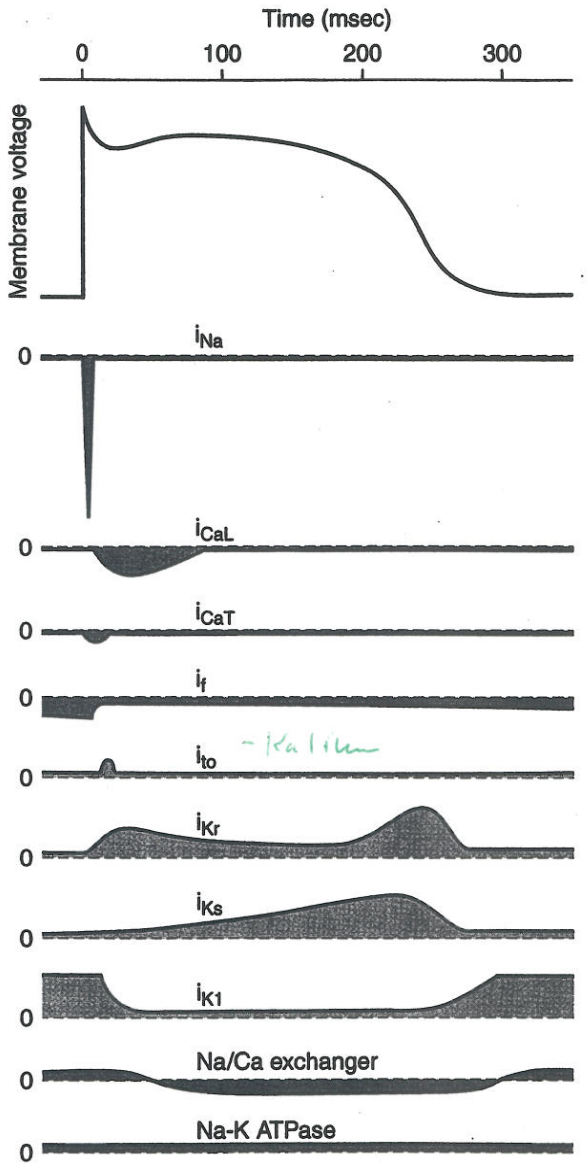

Figure 11.2 Individual ionic currents responsible for the cardiomyocyte action potential. Upper tracing: voltage changes. Lower tracings show 10 different currents: Inward currents are downward; outward currents are upward. Four depolarizing ionic currents (solid lines at the top) include i_{Na}, i_{CaL}, i_{CaT}, i_f. Four repolarization ionic currents (dotted lines in the middle) include three outward rectifiers (i_{to}, i_{Kr}, and i_{Ks}) and the inward rectifier (i_{K1}) that inactivates during the plateau. Currents generated by the Na^+-Ca^{2+} exchanger and Na^+, K-ATPase (dashed lines) are shown at the bottom. For description and definition of the individual ionic currents, see text.

Adapted from A.M. Katz, 2001, *Physiology of the heart* (3rd ed.). (Philadelphia, PA: Lippincott, Williams, and Wilkins).

K^+ currents. The Ca^{2+} currents are substantially smaller than the fully activated I_{Na} but also pull the membrane potential to positive potentials. The final result is that the upstroke terminates at +47 mV before reaching E_{Na}. This is followed by the early/rapid phase of repolarization as a consequence of the rapid voltage-dependent inactivation of i_{Na}; the activation of the transient outward K^+ current (i_{to} or $i_{k.4AP}$ or i_{Kto1}); and the activation of a second type of transient outward current (i_{to2}), the Ca^{2+}-activated chloride current, $i_{Cl.Ca}$. Then a plateau phase follows, which is unique to cardiac cell electrophysiology with strikingly few channels open. The plateau phase is maintained by a fine-tuned balance between two types of inward Ca^{2+} currents and at least four types of outward K^+ currents; and the Em is driven back toward E_k. During this phase Ca^{2+} enters the cardiac myocyte via i_{CaT} and i_{CaL} to initiate contraction, with the latter dominating. Thereafter there is a phase of rapid repolarization: As the time-dependent inward currents are inactivated, the outward K^+ currents rapidly drive the membrane potential toward E_K, thus repolarizing the cell. These channels are unable to drive the cell back to E_K because they are inactivated at membrane potentials more negative than –40 mV. Delayed rectifying K^+ currents, i_K, consist of at least three distinct populations of K^+ channels: the rapid, K_r; the slow, i_{Ks}; and the ultra-rapid, i_{Kur} (the most recently described human cardiac i_K subtype). These drive the cell back to resting membrane potential and diastolic depolarization. i_{K1} does not inactivate with time and continues to repolarize the cell. During most of the repolarization phase, the heart cannot be triggered to fire another action potential because Na^+ channels are still inactivated; only hyperpolarization below –70 mV can reprime them for activation. This period of time is called the absolute refractory period. Once i_k repolarizes the cell back to –40 mV, i_{k1} begins to contribute outward currents and drive the cell toward E_k. i_{k1} conducts inward current better than outward current; hence the name inward rectifier.

Calcium Handling

In cardiac muscle, the force of contraction depends on the peak intracellular calcium concentration during systole, the sarcomere length, and the myofilaments' responsiveness to calcium. To understand the basic physiology of heart function it is important to appreciate some details concerning how calcium is moved around the various organelles of the myocyte in order to bring about excitation–contraction coupling. Failure of normal Ca^{2+} handling is a central cause of both contractile dysfunction and arrhythmias in pathophysiological conditions (Bers 2002). The brief increase in cytoplasmic calcium concentration (often called the calcium transient) allows Ca^{2+} to bind to the myofilament protein troponin C, which activates the myofilaments and transduces the chemical signal and energy (ATP) into cardiomyocyte shortening in a calcium-dependent manner.

As already described, during the action potential Ca^{2+} ions enter the cells via voltage-activated Ca^{2+} channels as an inward Ca^{2+} current (i_{Ca}^{2+}), which contributes to the action potential plateau. In addition, cardiomyocytes exhibit two types of voltage-dependent Ca^{2+} channels (L type and T type). As T-type i_{Ca}^{2+} is negligible in most ventricular myocytes, i_{Ca}^{2+} generally refers to L-type i_{Ca}^{2+} (dihydropyridine receptors). L-type Ca^{2+} channels are located primarily at sarcolemmal-SR junctions where the SR Ca^{2+} release channels (the ryanodine receptors) exist. In addition, the Na^+-Ca^{2+} exchanger contributes to calcium influx and efflux with a stoichiometry of three Na^+ ions to one Ca^{2+} ion that produce an ionic current either inward (forward mode: during high intracellular Ca^{2+} concentrations) or outward (reverse mode: during positive membrane potentials and high intracellular Na^+). The calcium entering the myocyte from the outside contributes directly only to a minor degree to myofilament activation, and its main effect is to stimulate calcium release from the intracellular pool of calcium: the SR. This is normally termed calcium-induced calcium release. Contributions from other pathways have also been proposed, such as the T-type Ca^{2+} current and one through Na^+-Ca^{2+} exchange; but both of these have been shown to be much less effective and slower than the L-type current (Bers 2002). Despite overwhelming evidence that Ca^{2+} influx is essential for cardiac excitation–contraction coupling, a few studies have suggested a voltage-dependent Ca^{2+} release that does not require Ca^{2+} influx (Ferrier & Howlett 2001). Several major concerns have strongly challenged this hypothesis, and at this point it is not convincing (Bers 2002). Inositol (1,4,5)-triphosphate ($InsP_3$) can also trigger Ca^{2+} release in cardiac myocytes, but the rate and extent of Ca^{2+} are very much lower than for calcium-induced calcium release, and action potentials are not known to stimulate $InsP_3$ production (Bers 2002).

A high load of calcium in the SR directly increases the amount of calcium available for release, but also enhances the fraction of SR Ca^{2+} that is released