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Cardiac Arrhythmias

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BASIC CELLULAR ELECTROPHYSIOLOGY

Cardiac myocytes actively maintain a negative resting membrane potential (E_m) through the differential distribution of ions between intracellular and extracellular compartments, which is an energy-dependent process that relies on ion channels, pumps, and exchangers. Transmembrane differences in voltage and ionic concentration create electrical and chemical forces that drive charged ions in and out of cells.

The resting E_m of cardiac myocytes is controlled by potassium ions (K^+). Active K^+ transport by the sodium-potassium adenosine triphosphatase pump (Na^+, K^+-ATPase) produces a transmembrane ionic gradient, with the intracellular concentration of K^+ exceeding the extracellular concentration. This favors the net efflux of K^+ from cells, yielding a resting negative charge within the cardiac myocytes. K^+ continues to flow from the intracellular to the extracellular compartment until the negative intracellular charge counterbalances the transmembrane K^+ concentration gradient at a potential called the *equilibrium potential* for K^+. This potential, at which the net K^+ current is zero, is close to the resting E_m of nonpacemaker cardiac myocytes. Pacemaker cells (i.e., sinoatrial and atrioventricular [AV] nodal cells) are characterized by a resting E_m of −50 to −60 mV. The resting E_m of atrial and ventricular myocytes is typically −80 to −90 mV.

The depolarization of a cardiac myocyte to threshold potential triggers a sequence of ionic movements resulting in a cardiac action potential (Fig. 9-1). The action potential is divided into five phases. Phase 0 is the rapid depolarization of nonpacemaker myocytes resulting from rapid sodium ion (Na^+) entry through fast Na^+ channels. These channels have three conformational states: closed (resting state), open (conducting Na^+ current), and inactivated, from which recovery is voltage dependent. Phase 1 is early, rapid, partial repolarization of the cell mediated by K^+ efflux. During phase 2, the plateau phase, there is a small net current flow, with inward calcium ion (Ca^{2+}) flow balanced by outward K^+ flow.

During phase 3, repolarization is mediated by an increase in K^+ efflux and a decline in Ca^{2+} influx. The dominant repolarizing current is I_{Kr}, the rapidly activating delayed rectifier K^+ current, a channel encoded by the *KCNE2* gene (also called *HERG*). The I_{Ks} current, or slowly activating delayed rectifier K^+ current, also contributes to repolarization. Phase 3 determines to a large degree the cellular refractory period. Importantly, I_{Kr} is inhibited by a large number of drugs that prolong the action potential duration.

Phase 4 is particularly significant in cardiac pacemaker cells because slow depolarization occurs from the resting membrane potential to the threshold potential. The resting E_m, rate of spontaneous phase 4 depolarization, and rate of phase 0 depolarization differentiate slow-response from fast-response cardiac myocytes. Slow-response cells, located in the sinoatrial node and AV node, normally display automaticity or spontaneous depolarization during phase 4. Resting E_m in slow-response cells is less negative, and Ca^{2+} current mediates phase 0 depolarization. Conduction in these pacemaker cells is slow, and recovery from

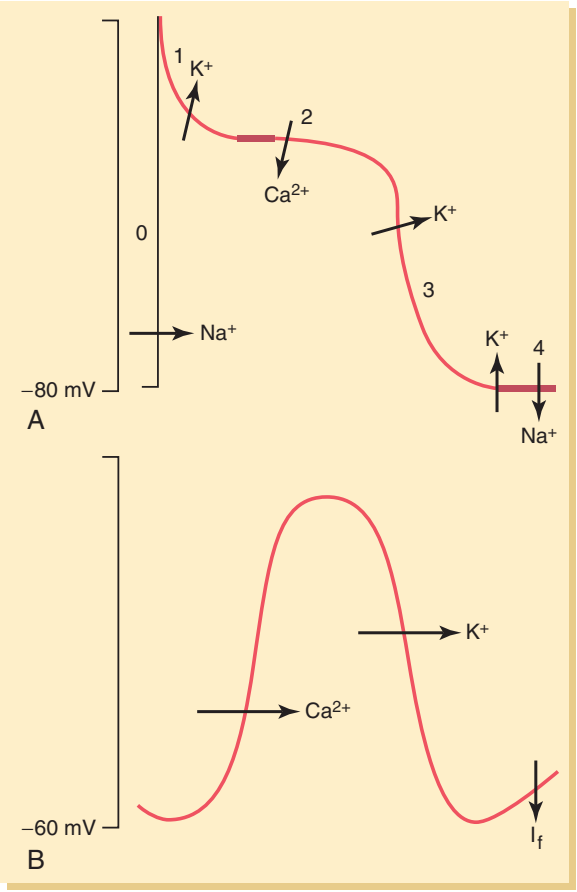

FIGURE 9-1 Electrophysiologic basis of the cardiac cellular action potential. **A,** Fast-response cells found in working myocardium and the specialized infranodal conduction system maintain a strongly negative resting membrane potential and a brisk phase 0 upstroke mediated by rapid sodium influx at the start of the action potential. **B,** In contrast, slow-response cells found in the sinus node and atrioventricular nodal tissue exhibit less-negative resting membrane potentials, slower calcium-channel–dependent action potential upstrokes, and phase 4 depolarization.