

2

Physiology of the Cardiac Conduction System

Peter S. Fischbach

The diagnosis and management of cardiac arrhythmias has progressed rapidly as a science. Advances in the ability to diagnose and either suppress or eliminate arrhythmic substrates has taken an exponential trajectory. Whether utilizing three-dimensional electroanatomic mapping systems for examining complex arrhythmias in patients with palliated congenital heart disease or genetic analysis in a search for evidence of heritable arrhythmia syndromes, technological advances have improved our ability to observe, diagnosis, and manage rhythm disturbances in patients from fetal life through adulthood. To fully harness the possibilities offered by these new technologies, a detailed understanding of cardiac anatomy and cellular electrophysiology is imperative.

The orderly spread of electrical activity through the myocardium is a well-choreographed process involving the coordinated actions of multiple intracellular and membrane proteins. Abnormalities in the physical structure of the heart or the function of these cellular proteins may serve as the substrate for arrhythmias. Cardiac myocytes like other excitable cells maintain an electrical gradient across the cell membrane. Various

proteins including ion channels, ion pumps, and ion exchangers span the membrane contributing to the voltage difference between the inside and outside of the cell. Because these integral membrane proteins, along with membrane receptors and regulatory proteins, form the basis of the electrophysiologic properties of the heart, a knowledge of their structure and function is necessary to understand fully cardiac arrhythmias, as well as for the appropriate selection of antiarrhythmic pharmacological agents.

RESTING MEMBRANE POTENTIAL

At rest, cardiac myocytes maintain a voltage gradient across the sarcolemmal membrane with the inside being negatively charged relative to the outside of the cell. The sarcolemmal membrane is a lipid bilayer that prevents the free exchange of intracellular contents with the extracellular space. The transmembrane potential is generated by an unequal distribution of charged ions between the intracellular and extracellular compartments. The maintenance of the resting

membrane potential is an active, energy dependent process relying in part on ion channels, ion pumps, and ion exchangers, as well as by large intracellular non-mobile anionic proteins. The ions are not free to move across the membrane and can only do so through the selective ion channels or via the pumps and exchangers. The net result is a resting membrane potential generally ranging from -80 to -90 mV. The most important membrane proteins for establishing the resting membrane potential are the Na^+/K^+ -ATPase (ion exchanger) and the inwardly rectifying potassium channel (I_K). The Na^+/K^+ -ATPase is an electrogenic pump that exchanges three sodium ions from the inside of the cell for two potassium ions in the extracellular space, resulting in a net outward flow of positive charge.

The unequal distribution of charged ions across the sarcolemmal membrane leads to both an electrical and a chemical force causing the ions to move into or out of the cell. If the membrane is permeable to only a single ion at a time, then for each ion, there is a membrane potential, the "equilibrium potential," at which there is no net driving force acting on the ion. The equilibrium potential may be calculated if the ionic concentrations on both sides of the membrane are known using the Nernst equation:

$$E_x = RT/F \ln[X]_o/[X]_i.$$

In this equation, R = the gas constant, T = absolute temperature, F = the Faraday constant and X is the ion in question. As an example, the usual intracellular and extracellular concentration of potassium is 4.0 mM and 140 mM, respectively. Substituting these values into the Nernst equation gives the following values:

$$E_k = -61 \ln[4]/[140] = -94.$$

At rest, the sarcolemmal membrane is nearly impermeable to sodium and calcium ions while the conductance (conductance = $1/\text{resistance}$) for potassium ions is high. It is not surprising therefore that the resting

membrane potential of most cardiac myocytes approaches the equilibrium potential for potassium. The sarcolemmal membrane, however, is a dynamic structure with changing permeability to various ions with a resultant change in the membrane potential. If the cellular membrane were permeable only to potassium then the Nernst equation would suffice to describe the membrane potential for all circumstances. As the membrane becomes permeable to various ions at different moments in time during the action potential, the Nernst equation is insufficient to fully describe the changes in the alteration of the membrane potential. The membrane potential at any given moment may be calculated if the corresponding instantaneous intra- and extracellular concentrations of the ions and the permeability of the respective ion channels are known. The Goldman-Hodgkin-Katz equation describes the membrane potential for any given set of concentrations and permeability's (P). The equation is:

$$V_m = -RT/F \ln \{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_i\} / \{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_o\}.$$

The Goldman-Hodgkin-Katz equation more closely approximates the cellular potential than the Nernst equation because it accounts for the permeability of the membrane for all active ions. This equation can also be used to computer model single cells and cellular syncytia.

ION CHANNELS

The lipid bilayer that makes up the sarcolemmal membrane has a high resistance to the flow of electrical charge and therefore requires specialized channels to allow the selective movement of ions into and out of the cell. Ion channels are macromolecular proteins that span the sarcolemmal membrane and provide a low resistance pathway for ions to enter or

exit the cell. The ion channels are selective for specific ions and upon opening provide a low resistance pathway that allows ions to pass down their electrochemical gradient. The ion channels have three general properties: (1) a central water filled pore through which the ions pass; (2) a selectivity filter; and (3) a gating mechanism to open and close the channel. The channels may be classified not only by their selectivity for specific ions, but also by the stimulus that causes the channel to open. Channels may open in response to changes in the transmembrane potential (voltage gated) in response to activation with various ligands, in response to mechanical forces (stretch activated), and in response to changes in the metabolic state of the cell (ATP gated potassium channels).

Sodium Channels

The sodium current is the principal current responsible for cellular depolarization in atrial, ventricular, and Purkinje fibers. The

rapid flow of ions through the sodium channel permits rapid depolarization of the sarcolemmal membrane and rapid conduction of the electrical signal. Sodium channels are closed at normal hyperpolarized resting membrane potentials. When stimulated by membrane depolarization, they open allowing the rapid influx of sodium ions, which changes the membrane potential from -90 mV towards the equilibrium potential for sodium ($+40$ mV). The channel inactivates rapidly over a few milliseconds in a time dependent fashion. That is, even in the face of a sustained depolarized membrane potential, the channel will close after a short time.

The sodium channels are proteins composed of a large pore forming an alpha subunit and two smaller regulatory beta subunits. The alpha subunit consists of four homologous domains, each of which consists of six transmembrane segments (S1–S6, Figure 1), a motif that is consistent across the voltage-gated ion channels. The transmembrane segments are hydrophobic and have an alpha-helical

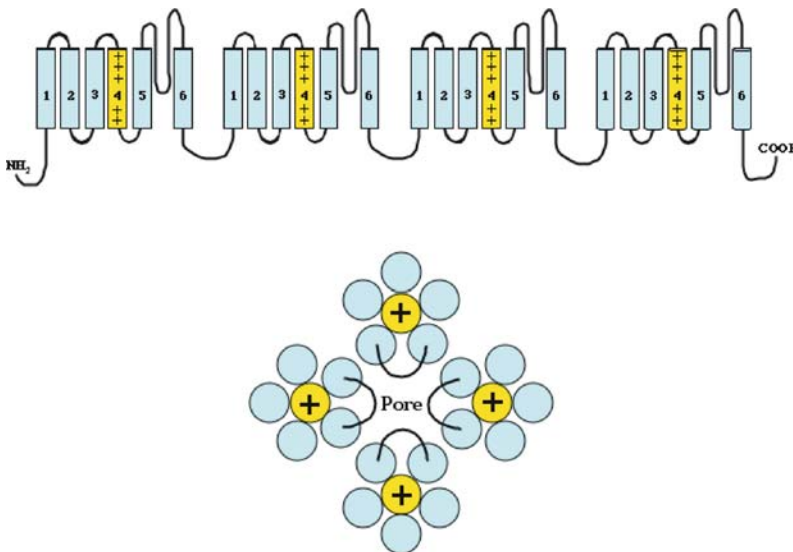


FIGURE 1. Top: Drawing of a voltage-gated sodium channel. The channel is composed of four domains, each of which has six membrane spanning hydrophobic helical segments. The fourth transmembrane segment is highly charged and acts as the voltage sensor for the channel. The linker segment between the 5th and 6th transmembrane segment in each domain bends back into the channel pore and is important in channel selectivity and gating. Bottom: This idealized drawing viewed from the extracellular surface demonstrates how the four domains organize to form a single pore with the S5–S6 linker segment of each domain contributing to the pore. (Downloaded from the internet).

conformation. The fourth transmembrane segment (S4) in each domain is highly charged with arginine and lysine residues located at every third position. The S4 segment acts as the voltage sensor for the channel with membrane depolarization causing an outward movement of all of the S4 domains leading to an opening of the transmembrane pore. The channel pore is formed by the S5 and S6 segments of each of the four domains in addition to the extracellular linker between S5 and S6. The transmembrane segments are linked by short loops, which alternate between intra- and extracellular. The extracellular linker loop between S5 and S6 is particularly long and curves back into the lipid bilayer to line the pore through which the ions pass. The four extracellular S5–S6 linker loops contribute to the selectivity of the channel.

The function of the beta subunit continues to be investigated. Much of the early work on beta subunits was in neuronal cells and recently attention has turned to cardiac cells. The beta subunits, in addition to modulating channel gating properties, are cell adhesion molecules that interact with the extracellular matrix serving an anchoring function. The beta subunits also regulate the level of channel expression in the plasma membrane.

The sodium channel opens rapidly in response to a depolarization in the membrane potential above a threshold value, reaching its maximal conductance within half a millisecond. After opening, the sodium current then rapidly dissipates, falling to almost zero within a few milliseconds. The inactivation of the sodium channel is the result of two separate processes, which may be differentiated based on their time constants. An initial rapid inactivation has a fast recovery constant and is, in part, caused by a conformational change in the intracellular linker between S3 and S4 that acts like a ball valve swinging into and occluding the pore-forming region. Rapid inactivation may occur without the channel opening, a process known as “closed state inactivation.” A slower, more stable inactivated state also exists and may last from hundreds

of milliseconds to several seconds. The mechanism(s) underlying slow inactivation are not well understood but likely results from the linker sequences between S5 and S6 in each domain bending back into the pore of the channel and occluding it.

The *SCN5A* gene located on chromosome 3 encodes the cardiac sodium channel. The cardiac sodium channel may be differentiated from the neuronal and skeletal muscle channel by its insensitivity to tetrodotoxin, which is isolated from puffer fish. Several diseases in humans resulting from sodium channel gene defects have been identified (Chapter 18).

Potassium Channels

Potassium channels are more numerous and diverse than any other type of ion channel in the heart (Figure 2). Over 200 genes have been identified that code for potassium channels. The channels may be categorized by their molecular structure, time, and voltage dependant properties, as well as their pharmacological sensitivities. Potassium channels are major components in the establishment of the resting membrane potential, automaticity, and the plateau phase of the action potential, as well as repolarization (phase 3, Figure 5). Within the heart a tremendous amount of heterogeneity exists in the density and expression of the potassium channels. The varied expression level of potassium channels contributes to the variability of the action potential morphology in different regions of the heart including transmural differences within the ventricular myocardium (Figure 3). In addition to the natural variability in the expression of potassium channels, many disease processes such as congestive heart failure and persistent tachyarrhythmias alter the density of these channels, as well as their functional properties, thereby leading to disruption of the normal electrical stability of the heart. This alteration in the density and function of these channels has been termed “electrical remodeling.”

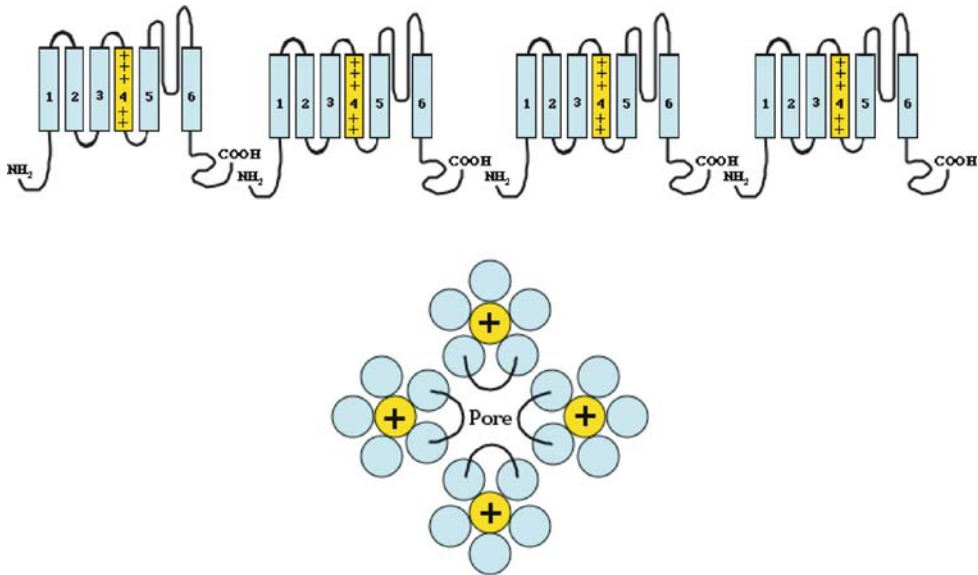


FIGURE 2. Similar to the voltage-gated sodium channels, the voltage-gated potassium channels are composed of four domains (α -subunits) composed of six membrane spanning segments. Unlike the sodium channels, the potassium channel domains are separate subunits that co-assemble to form a functional channel (compared with the sodium channel, which is a single large α -subunit composed of four domains). The voltage-gated potassium channels structurally are very similar to the sodium channels. The four α -subunits assemble to form a single pore with the S5–S6 linker from all α -subunits contributing to the pore. Similar to the voltage-gated sodium channel, the S4 subunit is also highly charged and serves as the voltage sensor leading to channel opening and closing. (Downloaded from the internet).

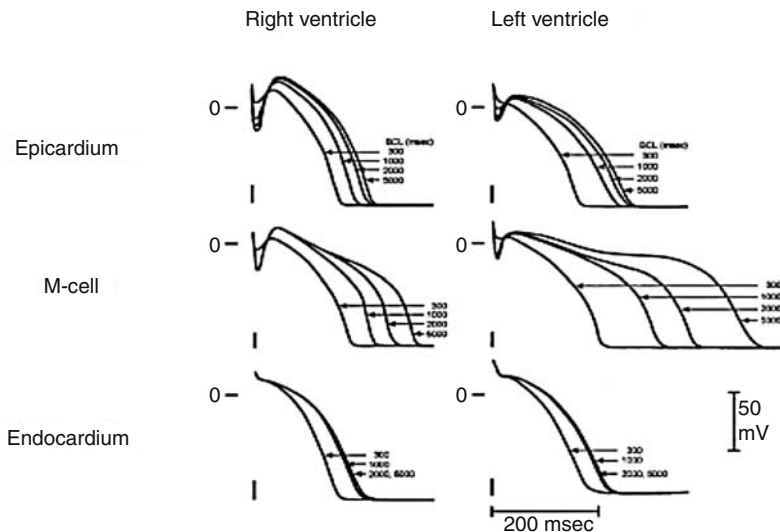


FIGURE 3. Action potential heterogeneity: The action potentials in this figure were recorded from strips of ventricular myocardium isolated from canine right and left ventricle. The difference in the morphology of the action potentials across the ventricular wall is obvious with a longer action potential found in the M-cells, which are located in the mid-myocardium. Additionally, the spike and dome configuration of the action potential generated by the activity of the transient outward current is prominent in the epicardial cells and nearly absent in the endocardium. Differences between the action potential morphology are also evident between the right and left ventricles. Finally, the action potentials were recorded at various paced cycle lengths. The rate adaptation of the cells from the different regions of the ventricle is strikingly different. (Reproduced from Antzelevitch C, Fish J. *Basic Res Cardiol* 2001;96(6):517–527, Springer Science + Business Media, Inc.)

*Voltage-Gated Potassium Channel:
 I_{to} and I_K*

Voltage-gated potassium channels are structurally very similar to the voltage-gated sodium channels. One major difference is that instead of the channels being composed of a single large α -subunit containing four domains, they are heteromultimeric complexes consisting of four α -subunits that form the channel pore and covalently attached regulatory β -subunits. The α -subunits are the equivalents of the separate domains of the sodium channel and are composed of six membrane spanning segments. The voltage sensor is contained in the S4 transmembrane segments that possess the same highly charged construct as in the sodium channel with alternating arginine and lysine in every third position. The mechanism supporting channel activation has not been as clearly delineated in potassium channels as in sodium channels. Identical to the sodium channel, the fifth and sixth transmembrane segments and the extracellular linker loop between S5 and S6 form the pore. While multiple sub-families of potassium channel α -subunits exist, only closely related sub-families of α -subunits are capable of co-assembling to form functioning channels.

I_{to} . The transient outward current is responsible for the early repolarization of the myocytes, creating the “spike and dome” configuration of the action potential noted in epicardial ventricular myocytes (Figure 5). The current may be divided into two components: a Ca independent and 4-aminopyridine sensitive current that is carried by K, and a Ca dependent and 4-aminopyridine insensitive current carried by the Cl ion. There is further evidence to suggest that the portion of I_{to} carried by potassium may be further subdivided into a fast and slow component. The level of expression of I_{to} is highly variable, with greater density in the atrium than the ventricles, greater density in the right ventricle than the left ventricle, and greater den-

sity in the epicardium than in the endocardium (Figure 3).

I_K (*Delayed Rectifier*). The delayed rectifier current is the ionic current primarily responsible for repolarization (phase 3) of the myocytes. It opens slowly relative to the sodium channel in response to membrane depolarization near the plateau potential of the myocytes (+10 to +20 mV). Following the initial description of the delayed rectifier current, two distinct components of the current were identified: a rapidly activating and a slowly activating portion. Recently a third component has been isolated. The different subsets may be differentiated based on their activation/inactivation kinetics, pharmacological sensitivity, and conductance. The rapidly activating component (I_{Kr}) has a large single channel conductance, demonstrates marked inward rectification, activates rapidly, and is selectively blocked by several pharmacological agents including sotalol and dofetilide. Non-cardiovascular drugs associated with heart rate corrected QT interval prolongation almost exclusively interact with I_{Kr} to produce their action potential prolonging effects. I_{Kr} is the product of the *KCNH2* (*HERG*) gene located on chromosome 7 and abnormalities of this channel result in LQTS type 2 (Chapter 20). The slowly activating portion of the current (I_{Ks}) has a smaller single channel conductance and is selectively inhibited by chromanol 293b. I_{Ks} inactivates more slowly than I_{Kr} and becomes the dominant repolarizing current at more rapid heart rates. I_{Ks} is the product of the *KCNQ1* (*KvLQT1*) gene on chromosome 11 and abnormalities of this channel result in LQTS type 1 (Chapter 20). The third subset of delayed rectifier current (I_{Kur} , the ultra-rapid delayed rectifier) has very rapid activation kinetics and slow inactivation kinetics with a single channel conductance that is close to that of I_{Kr} . I_{Kur} is significantly more sensitive to the potassium channel blockers 4-aminopyridine and TEA than either I_{Kr} or I_{Ks} and the channel may be selectively inhibited by the experimental

compound S9947. I_{Kur} is the product of the *KCNA5* gene on chromosome 12.

The expression of the subtypes of the delayed rectifier channel is heterogeneous. The expression of all three subtypes is greater in the atrium than in the ventricle, in part explaining the shorter action potential in atrial compared to ventricular myocytes. I_{Kur} is exclusively expressed in the atrium and has not been isolated from ventricular tissue. Within the ventricle, I_{Ks} density is low in the mid-myocardium, the so-called M-cells, compared with cells in the epi- and endocardium. The transmural difference in the distribution of potassium channels across the ventricular wall accounts for the longer duration of the action potential in Purkinje fibers as compared to the action potential in the epicardium and underlies to the configuration of the T-wave in the surface electrocardiogram.

Inwardly Rectifying Currents: I_{K-Ach} , I_{K-ATP} , and I_{K1}

The inwardly rectifying channels are structurally distinct from the voltage-gated channels. As opposed to the four membrane spanning subunits in voltage-gated channels, the inwardly rectifying channels have two membrane spanning subunits (M1 and M2). The association of four subunits forms a pore. The ATP-gated channel (I_{K-ATP}) is more complex with the four pore forming subunits co-assembling with four sulfonylurea receptors to form a functional channel. Inward rectification occurs via gating of the channels by magnesium and polyamines (spermine, spermidine, etc.) that block the inner opening of the pore.

I_{K1} . I_{K1} is the dominant resting conductance in the heart, setting the resting membrane potential in atrial, ventricular, and Purkinje cells. The heterogeneous density of channel distribution is greater in the ventricles relative to the atrium, but relatively sparse in nodal cells. I_{K1} has been demonstrated to inactivate at sustained depolarized potentials,

such as during the plateau phase of the action potential.

I_{K-Ach} . Acetylcholine, which is released from the cardiac parasympathetic nerves, acts on type 2 muscarinic receptors to open the channels via a G-protein dependent mechanism. The channels are localized primarily in nodal cells and atrial myocytes. The presence of I_{K-Ach} channels in the ventricle has been identified, although interestingly, the sensitivity to ACh is less than in the nodal cells and atrial myocytes. Activation of the channels causes hyperpolarization of nodal cells and a slowing of the rate of spontaneous depolarization and shortening of the action potential in atrial and ventricular myocytes.

I_{K-ATP} . I_{K-ATP} is tonically inhibited by physiological concentrations of intracellular ATP. During periods of metabolic stress, when the ATP level decreases and the ATP/ADP ratio is altered, the inhibition on the channel is lost and the channel opens, providing a large conductance repolarizing current (outward movement of K^+). Two molecularly distinct populations of I_{K-ATP} have been described in the heart: one existing in the sarcolemmal membrane and the other in the inner mitochondrial membrane. I_{K-ATP} , and in particular the mitochondrial channel, has been demonstrated to be important in ischemic preconditioning.

Calcium Channels

Calcium channels, like the voltage-gated potassium channels and the voltage-gated sodium channels, share the same basic structural motif. The channels are composed of a single large pore forming α -subunit, with two regulatory subunits (β , $\alpha_2\delta$). The α -subunit is similar in structure to that of the sodium channel, consisting of a single large protein with four domains composed of six membrane-spanning segments. The voltage sensor is also localized on S4 and the pore is composed of S5, S6, and the S5–S6 linker of

each of the four domains. However, the pore-forming loop between S5 and S6 is significantly different between calcium and sodium channels. The calcium channel has several calcium-binding sites on the pore-forming loop and the presence of calcium at these sites blocks sodium from entering the channel pore. When these sites are devoid of calcium, the channel passes sodium ions freely.

There are two main types of sarcolemmal calcium channels, which are differentiated by their conductance, activation/inactivation, and pharmacological sensitivities. The L-type calcium channel ($I_{Ca,L}$ —long acting) compared with the T-type channel ($I_{Ca,T}$ —transient channel) activates at more positive membrane potentials, inactivates more slowly, has a larger single channel conductance, and is sensitive to dihydropyridines. $I_{Ca,L}$ is expressed abundantly in all myocytes while the expression of $I_{Ca,T}$ is more heterogeneous, being most prominent in nodal cells. The $I_{Ca,L}$ serves to bring calcium into working myocytes throughout the plateau phase of the action potential and leading to calcium-dependent calcium release from the sarcoplasmic reticulum. $I_{Ca,T}$ is more important for depolarization in nodal cells.

Chloride Channels

Far less is known about the structure and function of cardiac channels that carry anions. There are at least three distinct chloride channels in the heart. The first is the cardiac isoform of the cystic fibrosis transmembrane conductance regulator (CFTR), which is regulated by cAMP and protein kinase A. The second is a calcium-activated current that participates in early repolarization ($I_{to,2}$), and the third is a swelling activated channel. To date, no role for abnormal function of chloride channels has been found for arrhythmia formation, and the channels are not targeted by any of the currently available antiarrhythmic drugs. However, chloride channels do appear to play an important role in maintaining the normal action potential. While chloride con-

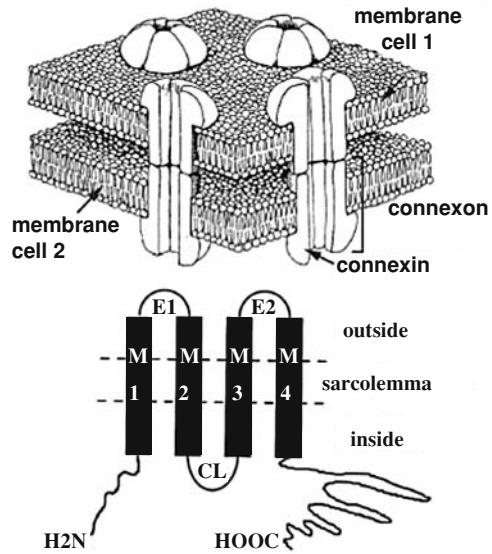


FIGURE 4. Schematic representation of part of a gap junction. The individual gap junction channels consist of two connexons that are non-covalently attached. Each connexon is composed of six connexins. The individual connexins has four membrane spanning regions (M1–M4), two extracellular loops (E1 and E2), and one cytoplasmic loop (CL). (Reproduced with permission from van der Velden et al. *Cardiovasc Res* 2002;54: 270–279, The European Society of Cardiology.)

ductance does not play a role in establishing the resting membrane potential, experiments in which the extracellular chloride was replaced with an impermeant anion resulted in markedly prolonged action potentials.

Gap Junctions

Gap junctions are tightly packed protein channels that provide a low resistance connection between adjacent cells, allowing the intercellular passage of ions and small molecules (Figure 4). These channels allow the rapid spread of the electrical signal from cell to cell. The gap junctions are produced by the non-covalent interaction of two hemi-channels (connexins) that are embedded in the plasma membranes of adjacent cells. The connexon is formed by the association of six connexin subunits, each of which have four transmembrane spanning domains and two extracellular

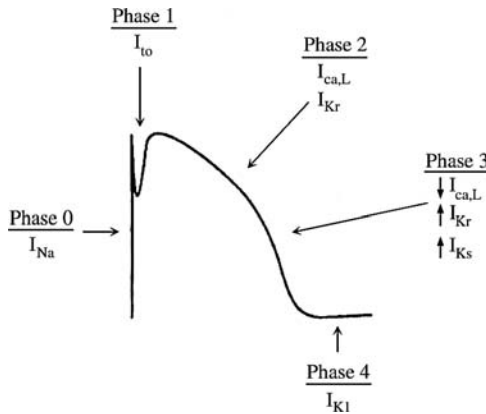


FIGURE 5. Shown is a typical action potential recorded from an epicardial ventricular myocyte. Phase 0 is the rapid depolarization of the membrane driven by opening of the voltage-gated sodium channel. Phase 1 is rapid initial repolarization resulting from closing of the sodium channel and opening of the transient outward current carried primarily by potassium. Phase 2, the plateau phase of the action potential, is notable for a balanced flow of inward (calcium) and outward (potassium) currents resulting in no significant change in the membrane potential. Phase 3 of the action potential, rapid repolarization, results from time dependent inactivation of the calcium channel in leaving the outward potassium current relatively unopposed. Phase 4 of the action potential is the resting membrane potential for myocytes without automaticity, and is principally defined by outward potassium current flow through I_{K1} .

loops. There are greater than 12 types of connexins expressed in myocardium. The trans-membrane domains and extracellular loops in all of the connexins are highly preserved while the intracellular loop between the second and third domain and the carboxy-terminus are highly variable. The differences in the intracellular portions of the connexins account for the difference in molecular weight and physiological properties such as the junction conductance, pH dependence, voltage dependence, and selectivity.

THE ACTION POTENTIAL

Myocytes may be broadly divided into two distinct cell types; fast response cells (atrial, ventricular, and Purkinje cells) and

slow response cells [sinoatrial (SA) and atrioventricular (AV) nodal cells]. The action potentials of fast response cells are notable for having a rapid upstroke (large V_{max}) generated by the large conductance voltage-gated sodium channel and hyperpolarized resting membrane potentials. The action potentials of slow response cells do not have a fixed resting membrane potential and have a slower upstroke driven by activation of L-type calcium channels. The rate at which the membrane is depolarized (V_{max}) determines how rapidly the electrical signal is conducted through tissue.

The action potential is divided into five phases, which may be delineated by the dominant membrane conductance. The action potential of fast response and slow response cells differ and will be addressed separately below:

Rapid Response Cells

Phase 0. This phase includes the rapid depolarization of the membrane. At rest, the membrane of a fast response cell is permeable almost exclusively to potassium. This drives the resting membrane potential towards the equilibrium potential of potassium (-94 mV). If the membrane potential is depolarized beyond a set threshold value, the voltage-gated sodium channels open and the membrane's dominant conductance changes to sodium. The membrane potential therefore moves towards the equilibrium potential of sodium ($\sim +40$ mV). The stimulus that generates the action potential elicits an all or nothing response. If the stimulus is sub threshold, the membrane is transiently depolarized and then quickly returns to the resting potential. If the stimulus is of sufficient intensity to raise the membrane potential above the threshold level, a maximal response is elicited and an action potential is generated. If the threshold potential is reached, phase 0 of the action potential is not altered by the intensity of the stimulus (i.e., a stimulus of greater intensity does not result in an increase in V_{max}). The number of available sodium channels is

dependent on the resting membrane potential of the cell and determines the $V_{\max}$. If the resting membrane potential is depolarized relative to the normal value, fewer sodium channels are available to be recruited to participate in the action potential due to a greater number of sodium channels in inactivated states and the $V_{\max}$ is lower. Clinically this may occur during myocardial ischemia or other instances of stress. Phase 0 is also delayed during the use of sodium channel blocking antiarrhythmic drugs producing a decrease in $V_{\max}$.

Phase 1. The maximal depolarized membrane potential reaches approximately +20 mV, which is below the equilibrium potential for sodium. The failure to reach the equilibrium potential of sodium is due to the rapid time dependent inactivation of sodium channels, changing to a non-conducting conformation, as well as the opening of hyperpolarizing currents, most significantly I_{to} . The heterogeneous expression of I_{to} throughout the myocardium explains the variability in the morphology of the early portion of the action potential. Those myocytes expressing relatively more I_{to} have a profound spike and dome conformation, such as epicardial ventricular myocytes. The inactivation of I_{to} is also rapid, and so it does not contribute significantly to the plateau phase, or later repolarization of the myocyte.

Phase 2. The plateau phase of the action potential represents a balance of inward depolarizing current carried primarily by calcium with a small contribution from a background sodium window current, and outward hyperpolarizing potassium current. The calcium and potassium currents are activated by depolarization, and both are inactivated in a time-dependent fashion.

Phase 3. At the completion of phase 2, the calcium channels close leaving the effects of the potassium conductance unopposed. The membrane potential moves once again towards the equilibrium potential of potassium. The delayed rectifier potassium currents (I_{Kr}

and I_{Ks}) close during phase 3 and I_{K1} becomes the dominant conductance at the conclusion of phase 3.

Phase 4. Atrial and ventricular myocytes maintain a constant resting membrane potential awaiting the next depolarizing stimulus. The resting membrane potential is established by I_{K1} . The resting membrane potential remains slightly depolarized relative to the equilibrium potential of potassium due to an inward depolarizing leak current likely carried by sodium. During the terminal portions of phase 3 and all of phase 4, the voltage-gated sodium channels are recovering from the inactivated state into the resting state, and preparing to participate in the ensuing action potential.

Slow Response Cells

The action potential of slow response cells is morphologically distinct from fast response cells. Initial rapid depolarization (phase 0) in slow response cells is the result of current passing through voltage-gated calcium channels that activate at relatively depolarized potentials (−35 mV). The resultant $V_{\max}$ during phase 0 is considerably slower than that measured in fast response cells. Activation of phase 0 depolarization in slow response myocytes, similar to fast response myocytes, relies on the membrane potential surpassing a threshold potential with an all or none response in the depolarizing calcium current. Unlike the fast response myocytes, which require an external stimulus to raise the membrane potential past the threshold potential, the slow response myocytes generate their own depolarizing current. The slow response myocytes do not have a fixed resting membrane potential but rather hyperpolarize to a maximal diastolic potential (−50 to −65 mV for SA node cells) and then slowly depolarize towards the threshold potential of the calcium channels. Repolarization of slow response cells is the result of the time-dependent inactivation of the calcium channel in combination with the hyperpolarizing currents

carried by the delayed rectifier potassium current.

Refractory Period

Following activation, all excitable cells enter a period in which repeat activation is impossible. This is referred to as the refractory period. The refractory period is longer in myocytes than in other excitable cells such as neurons or skeletal muscle. Physiologically, the refractory period allows for relaxation of the myocardium and filling of the cardiac chambers. Due to the long refractory period in cardiac muscle, tetanic contraction is not possible as it is in skeletal muscle. The refractory period may be divided into the absolute refractory period, during which time no action potential may be generated regardless of the stimulus, and the relative refractory period, in which an action potential may be induced following a supernormal stimulus. The refractory period is the result of the slow recovery from the inactivated state of the depolarizing current (I_{Na}) combined with the slow inactivation of the repolarizing currents.

Automaticity

Automaticity is the ability of cells to spontaneously depolarize and raise the resting membrane potential past the threshold potential for triggering an action potential (phase 4 depolarization). Automaticity normally is a property of cells localized within the SA and AV nodes, as well as Purkinje fibers. Spontaneous depolarization results from a net inward current resulting from the combination of several currents. The currents involved in phase 4 spontaneous depolarization continue to be debated. They appear to include activation of several inward cation channels including the pacemaker current (I_f), which is activated by hyperpolarization and closes shortly after the activation potential for the inward calcium channel is passed, I_{Ca-T} , I_{Ca-L} (mostly at the end of phase 4 depolarization as the activation potential is -40 mV for this current) and I_b , an inward time independent background

current carried by sodium. The decay of the inward hyperpolarizing I_K also contributes to the net depolarizing current. Additionally, the Na^+/K^+ and Na^+/Ca^{2+} exchangers, that are electrogenic, provide additional inward current as K^+ and Na^+ are extruded from the cell. It is important to note that I_{K1} is not expressed in nodal cells and hence the hyperpolarizing effects do not influence phase 4 depolarization. The mechanism of phase 4 depolarization in Purkinje cells appears to be somewhat different compared to nodal cells, with I_f playing a far more prominent role. The maximal diastolic potential is approximately -85 mV in Purkinje cells rather than -60 mV in nodal cells, so the contribution of calcium current is thought to be less.

There is a hierarchical pattern to the rate of spontaneous depolarization, with the most rapid depolarization occurring in the SA node followed by the AV node with the Purkinje fibers being the slowest. The rate of automatic discharge is under tight autonomic control. Vagal input into the heart via release of acetylcholine activates the muscarinic receptor-gated potassium channel (I_{K-Ach}), which leads to hyperpolarization of the nodal cells. The hyperpolarization of the nodal cells creates a greater difference between the maximal diastolic potential and the threshold potential that is unchanged by the vagal stimulation. If the slope of diastolic depolarization remains unchanged, the time it takes to reach the threshold potential will increase and the rate of depolarization will decrease. Vagal stimulation, however, also inhibits I_f and I_{Ca-L} leading to a decrease in the slope of phase 4 depolarization, and further slowing the rate of spontaneous depolarization. Sympathetic stimulation conversely, via cAMP-dependent pathways, enhances I_f and I_{Ca-L} increasing the slope of phase 4 depolarization and increasing the rate of spontaneous depolarization.

Signal Propagation

Electrical conduction through the myocardium may be considered on the level of the signal transiting along a single

myocyte, cell-to-cell conduction, and conduction through the whole organ. The electrical signal passes along a myocyte by incrementally depolarizing the membrane. At rest, an electrical gradient is maintained across the sarcolemmal membrane. When the local membrane potential is depolarized, sodium and calcium channels open, establishing a small region of positive charge on the inner surface of the membrane and leaving a small zone of negative charge extracellularly. This depolarizes the membrane in the immediately adjacent regions and leads to initiation of the depolarizing currents in the bordering regions. This forms a self-perpetuating reaction with the spread of depolarization. The more rapidly the local region of the membrane is able to change its potential, the more rapid is conduction down the length of the myocyte. Therefore, cells that depend on the rapid sodium current for the upstroke of phase 0 of the action potential conduct the signals rapidly, while cells that are dependent on the slower calcium current for phase 0 conduct signals more slowly. This concept is demonstrated by comparing the conduction velocity in the AV node (calcium dependent action potentials) with atrial and ventricular tissue (sodium channel dependent).

The myocardium is not a perfect syncytium, and conduction is discontinuous. Gap junctions that form a low resistance passageway to allow for the rapid spread of excitation from cell to cell attach the myocytes to one another. It has also been appreciated that the tissue passes electrical current more rapidly along the long axis of the myocytes than transversely. The difference that exists between the conduction velocities axially versus transversely is referred to as anisotropy. The degree of anisotropic conduction varies throughout the myocardium. In the ventricle, the ratio of conduction velocity parallel as opposed to transverse to the long axis of the cell is approximately 3:1, while along the crista terminalis in the atrium, the same ratio is 10:1.

On a macroscopic level, once the electrical signal escapes from the SA node, it rapidly

spreads throughout the atrium. A debate remains as to whether or not there exist anatomically distinct internodal tracts that connect the SA and AV nodes. Histologic studies have failed to demonstrate the presence of these tracts. The SA node is located high in the right atrium adjacent to the orifice of the superior vena cava. In this location it is susceptible to injury at the time of cannulation for cardiopulmonary bypass. Additionally, the blood supply to the SA node may be damaged during surgery that involves extensive atrial manipulation such as the Mustard operation or the hemi-Fontan procedure. The electrical signal activates the right atrium initially with conduction spread into the left atrium preferentially via Bachmann's bundle and along the coronary sinus. The atria and ventricles are electrically isolated from one another by the fibrous AV ring, with electrical continuity provided by the AV node. The compact AV node is located in the right atrium at the apex of the triangle of Koch. The AV node is composed of three regions: the atrionodal (AN), nodal (N), and nodal-His (NH). The cells in these three regions differ in the shape of their respective action potentials and their conduction velocities. The cells in the AN region have action potentials that are intermediate between atrial and SA nodal cells with a more depolarized maximal diastolic potential, slower phase 0 depolarization, and the presence of phase 4 depolarization. The N cells are similar to the SA nodal cells. The NH cells transition between the N cells and the His bundle with action potentials that reflect this transition. Conduction through the entirety of the AV node is slower than that through the atria or ventricles and is not detectable on a routine surface ECG. The AV node is richly innervated by the autonomic nervous system and receives its blood supply from the posterior descending coronary artery. Atrioventricular block may result from interruption of the blood supply, which may result from atherosclerotic disease, as well from vasospasm following the delivery of radiofrequency energy in the posteroseptal region on the tricuspid valve annulus.

After passing through the AV node, the signal passes through the His bundle and enters the Purkinje fibers that divide into the bundle branches. The Purkinje cells have large diameters and preferential end-to-end connections rather than side-to-side connections, both of which lead to accelerated conduction velocities (200 cm/sec compared with 5 cm/sec in the SA node). The right bundle branch is cord-like and passes to the apex of the right ventricle prior to ramifying into the ventricular mass initially along the moderator band. The left bundle branch is fan-like and initially activates the ventricular septum from the left ventricular side progressing towards the right. This accounts for the Q-waves inscribed in the left lateral precordial leads in D-looped hearts, and the Q-waves in the right precordium in L-looped hearts.

MECHANISM OF ARRHYTHMIA FORMATION

Arrhythmias occur when the orderly initiation and conduction of the electrical signal is altered. This may result in abnormally fast or abnormally slow heart rates. Bradycardia may result from either a failure of initiation of impulse formation such as occurs in sick sinus syndrome, or failure of the signal to be conducted (SA node exit block, AV node block). Bradycardia is not amenable to chronic pharmacological therapy and when symptomatic, requires an implantable pacemaker (Chapter 17).

Tachycardias arise from one of three general mechanisms: abnormal automaticity, triggered activity, or reentry.

Abnormal Automaticity

Abnormal automaticity implies either abnormally fast activation in cells that normally possess automatic function (enhanced automaticity), or the development of spontaneous depolarization in cells that normally do not possess automaticity. Abnormally

enhanced automaticity may result from hyperactivity of the autonomic nervous system, fever, thyrotoxicosis, or the exogenous administration of sympathomimetic agents.

Under normal physiological conditions, atrial and ventricular cells do not demonstrate phase 4 spontaneous depolarization. If the resting membrane potential is decreased (made less negative) to less than -60 mV, as may occur with ischemia, cells may develop spontaneous depolarization. Clinical examples of arrhythmias supported by abnormal automaticity include atrial ectopic tachycardia, junctional ectopic tachycardia (Chapter 10), accelerated idioventricular rhythm, and some ischemic ventricular tachycardias (Chapter 12).

Triggered Activity

Triggered activity arises from oscillations in the membrane potential, which if large enough, may reach threshold potentials and lead to additional action potentials. Triggered activity by definition is dependent on a preceding action potential or electrical stimulus to generate the oscillations in the membrane potential. An action potential generated via a triggered complex may serve as the stimulus for an ensuing action potential leading to a sustained arrhythmia. Triggered activity may result from oscillations in the membrane potential that occur either during phase 2 or 3 of the action potential (early afterdepolarization or EAD) or following full repolarization of the action potential (delayed afterdepolarization or DAD).

EADs. These oscillations occur during the plateau phase or late repolarization of the action potential. EADs may result from a decrease in outward current, an increase in inward current, or a combination of the two. During the plateau phase of the action potential, the absolute ionic flow across the membrane is small, hence a small change in either the inward or outward current may result in a large change in the membrane potential.

DADs. DADs occur after the cell has fully repolarized and returned to the resting membrane potential. The depolarization of the membrane resulting in DADs is caused by activation of the transient inward current (I_{ti}), which is a non-specific cation channel activated by intracellular calcium overload.

Reentry

Reentry is far and away the most frequent mechanism supporting arrhythmias. First described by George Mines in 1914, reentry describes the circulation of an electrical impulse around an electrical barrier leading to repetitive excitation of the heart. For reentry to occur, three conditions are required: a continuous circuit, unidirectional conduction block in part of the circuit, and conduction delay in the circuit allowing tissue previously activated to regain its excitability by the time the advancing wavefront returns. These conditions allow for a sustained circuit to be established.

Critical to the maintenance of reentrant arrhythmias are the impulse conduction velocity and the refractory period of the myocardium in the circuit. The interaction of these two properties of the myocardium determine whether the leading edge of electrical excitation will encounter myocardium capable of generating an action potential, or whether refractory tissue will block the circuit and cause the reentrant loop to extinguish. These two measurable quantities may be combined to calculate the “wavelength” of the arrhythmia.

$$\begin{aligned} \text{Conduction Velocity (m/sec)} \times \text{Refractory Period (sec)} \\ = \text{Wavelength (m)}. \end{aligned}$$

If the calculated wavelength of the arrhythmia exceeds the pathlength of the circuit, then reentry cannot occur. If the wavelength is less than the pathlength, then reentry may be sustained. This concept is the basis for the use of class III antiarrhythmic agents, which work by increasing the duration of the refractory

period of the tissue by delaying repolarization. In reentrant arrhythmias with a fixed pathlength, an excitable gap exists, which is the time interval between the return of full excitability of the tissue following depolarization and the head of the returning electrical wavefront traversing the circuit. The presence of an excitable gap allows for external stimuli to enter the reentrant circuit and either advance (speed up), delay, or terminate the tachycardia.

Many forms of tachycardia result from reentry with fixed anatomic pathways. Examples include accessory pathway mediated tachycardia (Chapter 3), AV node reentrant tachycardia (Chapter 4), atrial flutter intra-atrial reentrant tachycardia (scar mediated atrial flutter)(Chapter 8), and ischemic ventricular tachycardia. Reentry has also been demonstrated to occur in tissue in which there are no fixed physical barriers. Reentry may be supported in this case by the development of functional barriers to conduction that serve as a focal point for the circuit to rotate around. These functional centers are not fixed and continually change and move with time. This principle referred to as “leading circle reentry” is thought to underlie atrial fibrillation. These reentrant circuits do not have an excitable gap with tissue becoming activated as soon as it is no longer refractory. The cycle length in arrhythmias supported by leading circle reentry is determined by the refractory period of the tissue that determines the circuit length.

SELECTED READING

1. Hille B, *Ion Channels of Excitable Membranes*. Sunderland, MA; Sinauer, 2001.
2. Zipes DP, Jalife J, (eds). *Cardiac electrophysiology: from cell to bedside*. Philadelphia, PA; Saunders, 2000.
3. Roden DM, Balser JR, George AL, Anderson ME. Cardiac ion channels. *Annu Rev Physiol* 2002;64:431–475.
4. Schram G, Pourrier M, Melnyk P, Nattel S. Differential distribution of cardiac ion channel expression

- as a basis for regional specialization in electrical function. *Circ Res* 2002;90:939–950.
5. Members of the Sicilian Gambit. New approaches to antiarrhythmic therapy: emerging therapeutic applications of the cell biology of cardiac arrhythmias. *Eur Heart J* 2001;22:2148–2163.
 6. Singh BN, Sarma JS. Mechanisms of action of antiarrhythmic drugs relative to the origin and perpetuation of cardiac arrhythmias. *J Cardiovasc Pharm Therap* 2001;6:69–87.
 7. Barry DM, Nerbonne JM. Myocardial Potassium channels: electrophysiological and molecular diversity. *Annu Rev Physiol* 1996;58:363–394.
 8. Anderson ME, Al-Khatib SM, Roden DM, Califf RM. Duke Clinical Research Institute/American Heart Journal Expert Meeting on Repolarization Changes. *Am Heart J* 2002;144:769–781.
 9. Roden DM, George AL. Structure and function of cardiac sodium and potassium channels. *Am J Physiol* 1997;273:H511–H525.
 10. Snyders DJ. Structure and function of cardiac potassium channels. *Cardiovasc Res* 1999;42:377–390.
 11. Liu DW, Gintant GA, Antzelevitch C. Ionic bases for electrophysiological distinctions among epicardial, midmyocardial, and endocardial myocytes from the free wall of the canine left ventricle. *Circ Res* 1993;72:671–687.
 12. Allesie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The “leading circle” concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. *Circ Res* 1977;41:9–18.
 13. Antzelevitch C, Shimizu W, Yan GX, et al. The M cell: its contribution to the ECG and to normal and abnormal electrical function of the heart. *J Cardiovasc Electrophysiol* 1999;10:1124–1152.
 14. Allesie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res* 2002;54:230–246.
 15. Armondas AA, Wu R, Juang G, et al. Electrical and structural remodeling of the failing ventricle. *Pharmacol Ther* 2001;92:213–230.
 16. Antzelevitch C, Fish J. Electrical heterogeneity within the ventricular wall. *Basic Res Cardiol* 2001;96:517–527.