Physiology of the Cardiac Conduction System

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Adam C. Kean and Peter S. Fischbach

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 as well as the native cellular heterogeneity of the heart may alter the function of these cellular proteins and thus serve as the substrate for arrhythmias. Cardiac myocytes, like other excitable cells, maintain an electrical gradient across the cell membrane (sarcolemma) via an energy-dependent process. Various proteins including ion channels, ion pumps, and ion exchangers span the sarcolemma membrane contributing to the voltage difference between the inside and outside of the cell. Because these integral membrane proteins, along with membrane receptors, regulatory proteins, and channels within the intracellular sarcoplasmic reticulum, 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 use of antiarrhythmic pharmacological agents.

A.C. Kean, M.D., M.P.H. (✉)
Section of Pediatric Cardiology, Indiana University School of Medicine, 705 Riley Hospital Drive, Riley Research Room 127, Indianapolis, IN 46202, USA
e-mail: akean@iu.edu; ackean@gmail.com

P.S. Fischbach, M.D., M.S.
Sibley Heart Center, Children's Healthcare of Atlanta, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA

Resting Membrane Potential

The sarcolemma is a lipid bilayer that prevents the free exchange of intracellular contents with the extracellular space. The unequal distribution of charged ions across the sarcolemma leads to both an electrical and a chemical force causing the ions to move into or out of the cell down their electrochemical gradient, producing the transmembrane potential. The point at which there is no net driving force acting on any single ion across the sarcolemma is the equilibrium potential for that 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 universal 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,

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respectively. Substituting these values into the Nernst equation gives the following values:

$$E_k = 61 \ln[4]/[140] = -94 \text{ mV}.$$

Ions can only move across the sarcolemma through selective ion channels, ion pumps, and ion exchangers. The sarcolemma has a dynamic permeability to various ions caused largely by opening and closing of these structures as well as their variable concentration 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 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 ion concentrations [X] and permeability's (P). For potassium [K], sodium [Na], and chloride [Cl], the equation is:

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

(The chloride ion concentration is inverted to account for its negative charge.) 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 is used to calculate ion channel permeability from single channel experiments and then apply to computer models of single cells and cellular syncytia.

The transmembrane potential for the cardiac myocyte at baseline is defined as the resting membrane potential. The sarcolemma is nearly impermeable (highly resistant) to sodium and calcium ions while the conductance (conductance = 1/resistance) for potassium ions is high. As such, the resting membrane potential of most cardiac myocytes approaches the equilibrium potential for potassium, generally ranging from –80 to –90 mV.

The maintenance of the resting membrane potential is an active, energy-dependent process. The most important membrane proteins for establishing the resting membrane potential are the Na^+/K^+-ATPase (ion exchanger) and the potassium channel responsible for the inward rectifying potassium current (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.

Ion Channels

Ion channels are macromolecular proteins that span the sarcolemma and provide a low resistance pathway for ions to enter or exit the cell. The ion channels are selective for specific 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 (messenger gated), in response to mechanical forces (stretch activated), and in response to changes in the metabolic state of the cell (ATP gated).

Sodium Channels

The sodium channels provide the pathway for the sodium current, the principal current responsible for cellular depolarization in atrial, ventricular, and Purkinje fibers. They are also present in skeletal muscle and neuronal cells which can be differentiated from cardiac sodium channels by their greater sensitivity to tetrodotoxin. The cardiac sodium channels are proteins composed of a large pore-forming α-subunit and two smaller regulatory β-subunits. The α-subunit consists of four homologous domains, each of which consists of six transmembrane segments, S1–S6 (Fig. 2.1), a motif that is consistent across the voltage-gated ion channels. The transmembrane segments are hydrophobic and have an alpha-helical 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.

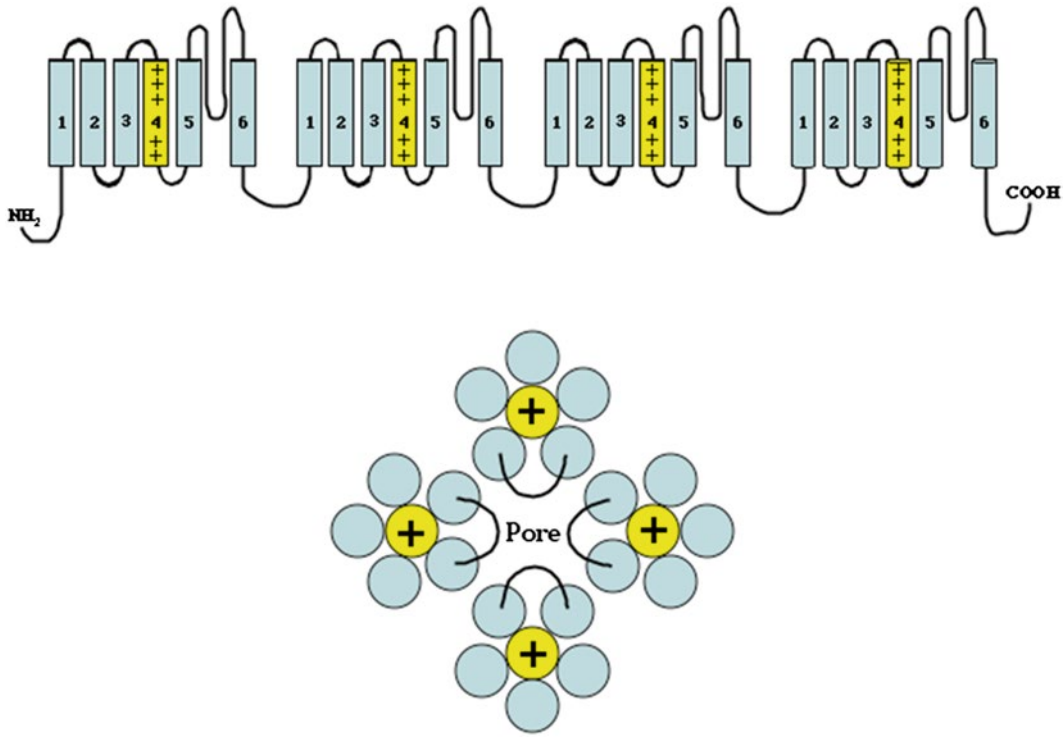

Fig. 2.1 *Top*: Drawing of a voltage-gated sodium channel. The channel is composed of four domains, each of which has six membrane-spanning hydrophobic helical segments. The fourth transmembrane segment is highly charged and acts as the voltage sensor for the channel. The linker segment between the fifth and sixth 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

The function of the β-subunit continues to be investigated. In addition to modulating channel-gating properties, the subunit serves as a cell adhesion molecule that interacts with the extracellular matrix serving an anchoring function. The β-subunits also regulate both the level of channel expression and the trafficking of the completed protein to the plasma membrane. In the last few years, genetic mutations leading to errors in ion channel trafficking have been linked to arrhythmogenesis. A mutation in the Nav1.5 gene (gene encoding the sodium channel) associated with Brugada Syndrome has been demonstrated to result from poor subunit trafficking. Interestingly, the class Ia antiarrhythmic drug quinidine's efficacy has been linked, in part, to increased Na-channel endocytosis (the energy-using process by which cells absorb molecules by engulfing them).

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 result from the linker sequences between S5 and S6 in each domain bending back into the pore of the channel and occluding it (Fig. 2.1).

The *SCN5A* gene located on chromosome 3 encodes the cardiac sodium channel, Nav 1.5. Several genetically mediated arrhythmias in humans resulting from cardiac sodium channel gene mutations have been identified (Chap. 18).

Potassium Channels

Potassium channels are major components in the establishment of the resting membrane potential (see above) and, as will be discussed, cardiac myocyte automaticity. These channels are more numerous and diverse than any other type of ion channel in the heart. In mammals, over 75 genes have been identified that code for potassium channels. The channels may be categorized by their (1) voltage, (2) time, and (3) molecular structure, dependent properties, as well as their response to pharmacological agents. 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. In addition to the natural variability in the expression of potassium channels, many disease processes such as congestive heart failure and persistent tachyarrhythmias, such as chronic atrial fibrillation, 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."

Voltage-Gated Channels

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 (Fig. 2.2). 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 delin-

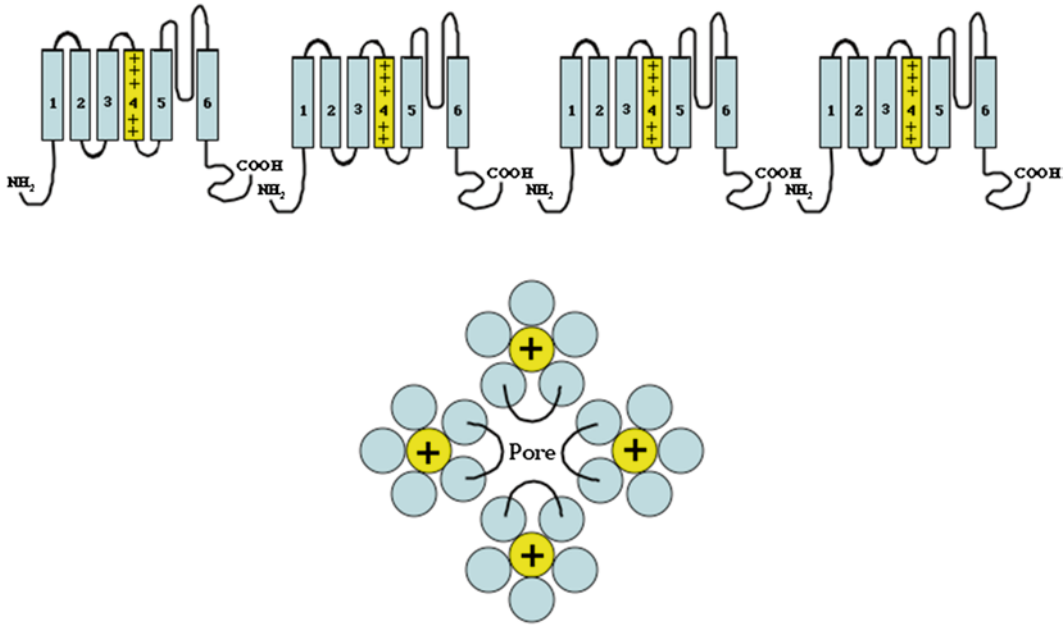

Fig. 2.2 Similar to the voltage-gated sodium channels, the voltage-gated potassium channels are composed of four domains (α-subunits) composed of six membrane-spanning segments. Unlike the sodium channels, the potassium channel domains are separate subunits that co-assemble to form a functional channel (compared with the sodium channel, which is a single large α-subunit composed of four domains. These four α-subunits assemble to form a single pore (structurally similar to the sodium channel, Fig. 2.1) 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

eated 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 subfamilies of potassium channel α-subunits exist, only closely related subfamilies of α-subunits are capable of co-assembling to form functioning channels.

Inwardly Rectifying Channels

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 (Fig. 2.3). The ATP-gated channel ($I_{K\text{-}ATP}$) 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} is the dominant resting conductance current 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.

Acetylcholine, which is released from the cardiac parasympathetic nerves, acts on type 2 muscarinic receptors to open $I_{K\text{-}Ach}$ channels via a G-protein-dependent mechanism. The channels are localized primarily in nodal cells and atrial myocytes. The presence of $I_{K\text{-}Ach}$ channels in the ventricle has been identified, although the sensitivity to ACh is less than in the nodal cells and atrial myocytes. Activation of the channels

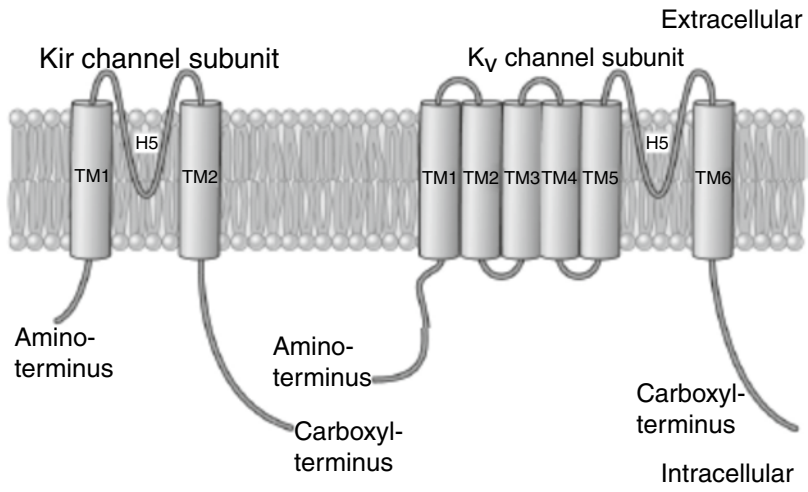

Fig. 2.3 Basic structure and Kir channel phylogenetic tree. A: primary structure of the Kir channel subunit (*left*). Each Kir subunit contains two transmembrane (TM1 and TM2) regions, a pore-forming (H5) loop, and cytosolic NH_2 and COOH termini. As a comparison, the structure of voltage-gated K^+ (K_v) channel subunit, which possesses six transmembrane (TM1–TM6) regions, is shown on the *right*

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.

Molecularly Active Channels

$I_{K\text{-}ATP}$ 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 $I_{K\text{-}ATP}$ have been described in the heart: one existing in the sarcolemma and the other in the inner mitochondrial membrane. *IK-ATP*, and in particular, the mitochondrial channel, has been demonstrated to be important in ischemic preconditioning.

Calcium Channels

Calcium channels share the same basic structural motif as the voltage-gated potassium channels and the voltage-gated sodium channels. The channels are composed of a single large pore-forming α-subunit, with two regulatory subunits (β, α_2/δ). 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 (Fig. 2.4). 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 calcium channels embedded in the sarcolemma which are differentiated by their conductance, activation/inactivation, and their response to pharmacological agents. 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, and has a larger single channel conductance. L-type calcium channel blocker drugs are used as cardiac antiarrhythmics or antihypertensives, depending on whether the drugs have higher affinity for the

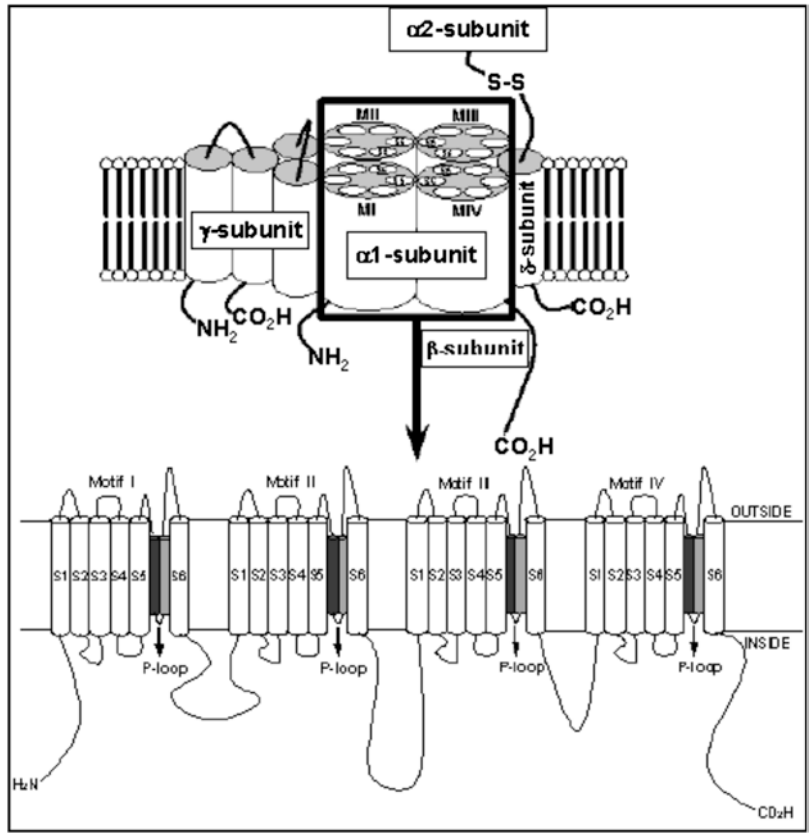

Fig. 2.4 L (transient) type calcium channel (voltage-gated). Molecular structure of the VGCC complex with zoom of the proposed transmembrane arrangement of the VGCC α 1-subunit. The dark and light gray cylinders are the SS1 and SS2 segments, respectively

heart (the phenylalkylamines, like verapamil), or for the vessels (the dihydropyridines, like nifedipine). $I_{Ca,L}$ is expressed abundantly in all myocytes responsible for bringing calcium into working myocytes and leading to calcium-dependent calcium release from the sarcoplasmic reticulum. The expression of $I_{Ca,T}$ is more heterogeneous, being most prominent 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 channel that participates in early repolarization, 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 despite having a clear effect on action potential duration.

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. These

channels allow the rapid spread of the electrical signal from cell to cell. They are produced by the non-covalent interaction of two hemichannels (connexins) that are embedded in the plasma membranes of adjacent cells. A connexin is formed by the association of six connexin subunits, each of which has four transmembrane-spanning domains and two extracellular loops. There are greater than 12 types of connexins expressed in myocardium. The transmembrane 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 connexins are named by their molecular weight, e.g., Cx40 weighs 40 kDa. The distribution of connexins within the heart is variable and changes between embryonic development and the adult heart. Connexins 40 and 43 predominate in the atria, 43 in the ventricle, and 40 and 45 in the specialized conduction tissue of the sinus node and His/Purkinje system. Heterogeneous placement in the heart as well as its location along the axis of the cardiomyocyte at the desmosome also facilitates sequential depolarization of the cell and propagation of the action potential. The embryologic differential expression of the connexins has been implicated as a possible etiology for some forms of congenital heart disease.

The Action Potential

The action potential is a time-dependent transcription of the change in voltage across the sarcolemma (cell membrane). It is divided into five phases, delineated by the dominant membrane conductance (Fig. 2.6). The action potential of fast response and slow response cells differ and will be addressed separately below:

Phase 0

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 sarcolemma as well as rapid conduction of the electrical signal between cells. 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 of +40 mV. The channel then 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.

This phase includes the rapid depolarization of the membrane. At rest, as discussed earlier, 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 (I_{Na} ~ +40 mV). The stimulus that generates the action potential elicits an all-or-nothing response. If the stimulus is subthreshold, the membrane is partially 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 greater 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 (less negative) relative to the normal value

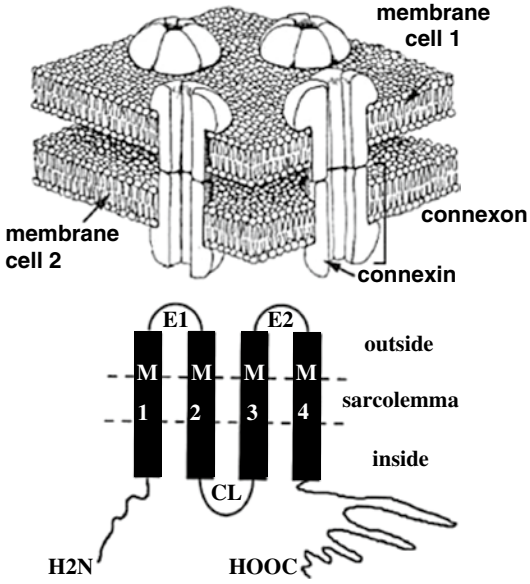

Fig. 2.5 Schematic representation of part of a gap junction. The individual gap junction channels consist of two connexins that are non-covalently attached. Each connexin is composed of six connexins. The individual connexins has four membrane-spanning regions (M1–M4), two extracellular loops (E1 and E2), and one cytoplasmic loop (CL) [Reprinted from van der Velden et al. Cardiac gap junctions and connexins: their role in atrial fibrillation and potential as therapeutic targets. Cardiovasc Res 2002;54: 270–279. With permission from Oxford University Press]

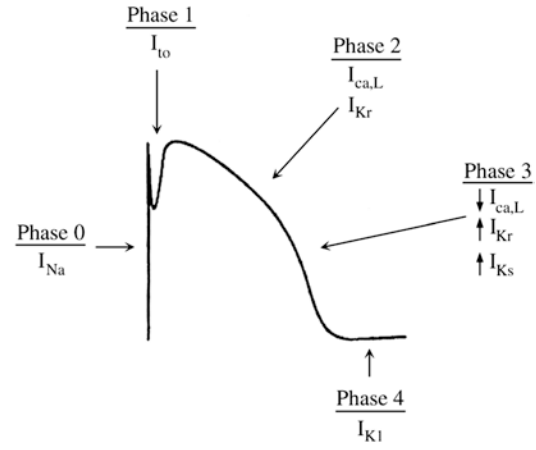

Fig. 2.6 Shown is a typical action potential recorded from an epicardial ventricular myocyte. Phase 0 is the rapid depolarization of the membrane driven by opening of the voltage-gated sodium channel. Phase 1 is rapid initial repolarization resulting from closing of the sodium channel and opening of 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

(i.e., ~−90 mV), 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. Sodium channel blocking antiarrhythmic drugs produce a decrease in dV/dt_{max} (upstroke velocity of phase 0, Fig. 2.5) and result in a prolonged phase 0.

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 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 (Fig. 2.6). 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 fast and slow components. 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 density in the epicardium than in the endocardium (Fig. 2.7). 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,

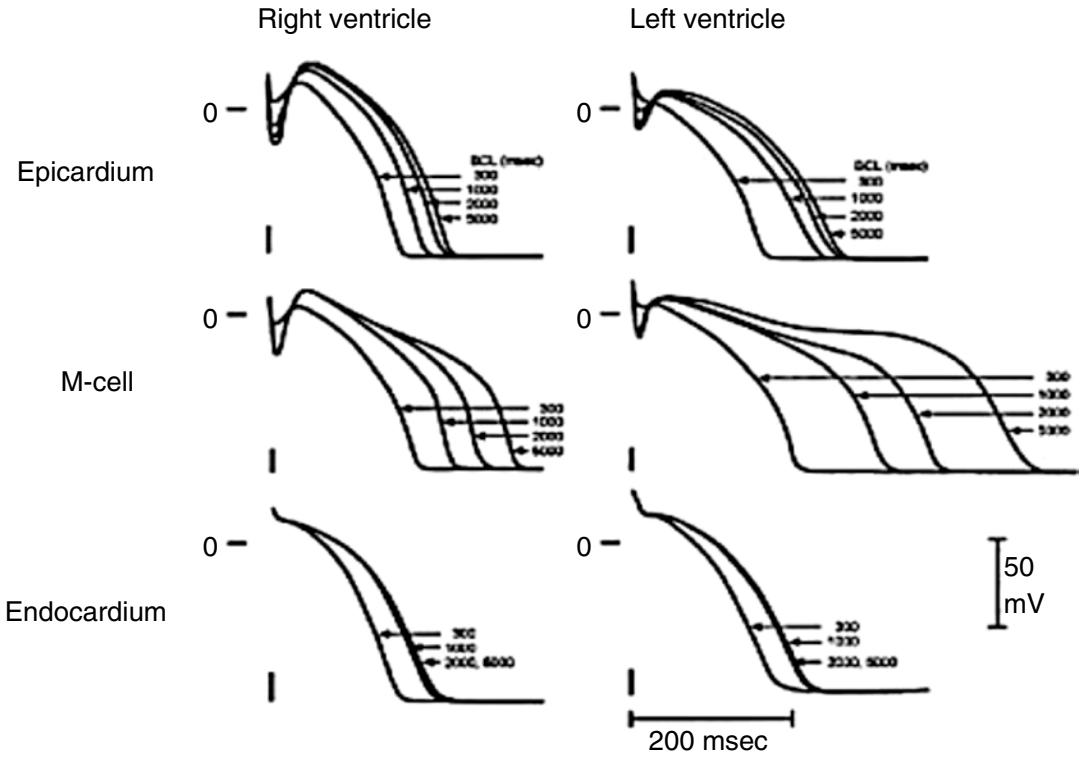

Fig. 2.7 Action potential heterogeneity. The action potentials in this figure were recorded from strips of ventricular myocardium isolated from canine right and left ventricle. The difference in the morphology of the action potentials across the ventricular wall is obvious with a longer action potential 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 [Reprinted from Antzelevitch C, Fish J. Electrical heterogeneity within the ventricular wall. Basic Res Cardiol 2001;96(6):517–527. With permission from Springer Science + Business Media, Inc.]

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. $I_{Ca,L}$ 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 of nodal cells.

Phase 3

At the completion of phase 2, the calcium channels close, leaving the effects of the potassium conductance unopposed. As noted above, the

potassium channels are major components in the establishment of the resting membrane potential, the plateau phase of the action potential, the repolarization (phase 3, Fig. 2.6) as well as automaticity. The membrane potential moves once again towards the equilibrium potential of potassium.

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 (I_{Kr}) and a slowly activating (I_{Ks}) portion. Both the I_{Kr} and I_{Ks} close during phase 3 and I_{K1} becomes the dominant conductance at the conclusion of phase 3. 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. Noncardiovascular 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 (Chap. 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 (Chap. 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 (tetraethyammonium) 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.

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. 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 midmyocardium, 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 the configuration of the T-wave in the surface electrocardiogram.

Chloride channels do appear to play an important role in maintaining the normal action potential. While chloride conductance 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.

Cardiac Excitation Characteristics

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] (Fig. 2.8). The action potentials of fast response cells are notable for having a rapid upstroke (large sharp V_{max}) generated by the large conductance voltage-gated sodium channel and the hyperpolarized resting membrane potentials (as just described above in detail). 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.

Slow Response Cells

The action potential of slow response cells is morphologically distinct from fast response cells (Fig. 2.8). 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 (slower upstroke) 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 ("funny" current, I_f). 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

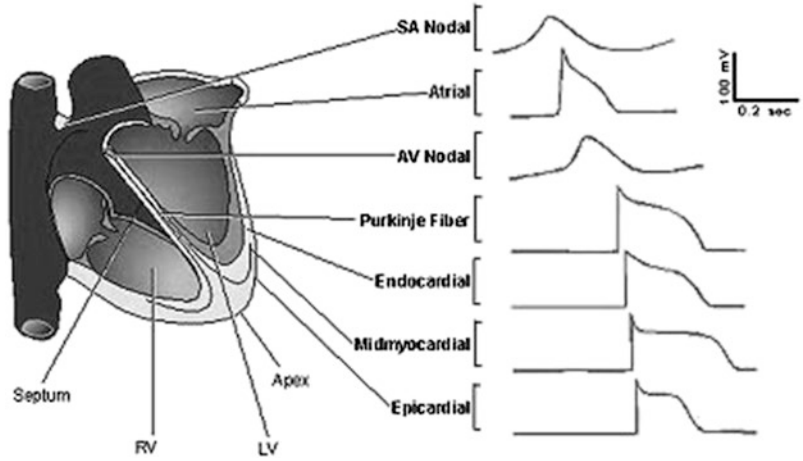

Fig. 2.8 Family of action potentials relative to tissue site in the heart

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 only 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. 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. Both the so-called funny current (I_f) and calcium clock, described below, are involved in forming the intrinsic cardiac pacemaker. The precise mechanism of sinoatrial (intrinsic pacemaker) activity and the centrality of one mechanism compared with the other remains a topic of spirited debate among electrophysiology researchers and clinicians.

Spontaneous depolarization results from a net inward current resulting from the combination of several currents. The currents involved appear to include activation of several inward cation channels including (1) I_f, which is activated by hyperpolarization and closes shortly after the activation potential for the inward calcium channel is passed; (2) $I_{Ca\text{-}T}$, $I_{Ca\text{-}L}$ (mostly at the end of phase 4 depolarization as the activation potential is –40 mV for this current); and (3) 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, which are electrogenic, provide 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 evidence to support the central role of both mechanisms. The I_f current inhibitor ivabradine is a medication used to treat heart failure and inappropriate sinus tachycardia. Its mechanism of action has made it a good investigational drug for this question. It is effective in reducing pacemaker automaticity though does not terminate SA node activity. Definitive multicellular human cell experiments demonstrating Ca clock centrality, however, are lacking. Mechanistic interplay of the two has been suggested.

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 ($I_{K\text{-}Ach}$), 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 $I_{Ca\text{-}L}$ 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 $I_{Ca\text{-}L}$, 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 traversing a single myocyte, to cell-to-cell conduction, and finally conduction through the whole organ. The electrical signal passes along a myocyte by incrementally depolarizing the sarcolemma. At rest, an electrical gradient is maintained across the sarcolemma. When the local membrane potential is depolarized, sodium and calcium channels open (phase 0 of the action potential), establishing a small region of positive charge on the inner surface of the membrane and leaving a small zone of negative charge on the outer surface. 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 underscored 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. As noted previously, gap junctions form a low resistance passageway to allow for the rapid spread of excitation from cell to cell. It has also been noted that the tissue passes electrical current more rapidly along the long axis (length) of the myocytes than its short axis (width). 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 perpendicular 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 (see Chap. 8). 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 atrial septum 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 does not elicit a separate deflection on 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 as due to vasospasm following the delivery of radiofrequency energy in the postero-septal 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/s compared with 5 cm/s 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. Indeed, the macroscopic conduction system may be duplicated in L-looped hearts (Chap. 1).

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 that occurs in sick sinus syndrome, or failure of the signal to be conducted or propagated (SA node exit block, AV node block). Bradycardia is not amenable to chronic pharmacological therapy and when symptomatic requires an implantable pacemaker (Chaps. 14, 15, and 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 have this ability. Abnormally enhanced automaticity may result from hyperactivity of the autonomic nervous system (junctional tachycardia), 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 (Chap. 10), accelerated idioventricular rhythm, and some ischemic ventricular tachycardias (Chap. 13).

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 after depolarization or EAD) or following full repolarization of the action potential (delayed after depolarization or DAD). Mutations in the Ryanodine receptor (RyR2) and Calsequestrin (Casq2) have been identified as the cause of Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). Calcium dysregulation in the sarcoplasmic reticulum has been implicated as the mechanism for DAD activity and sustained VT during catecholamine stress.

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 nonspecific 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. To initiate re-entry, three conditions are required: (1) a continuous circuit, (2) unidirectional conduction block in part or limb of the circuit, and (3) conduction delay in the site of origin allowing tissue previously activated to regain its excitability by the time the advancing wave front returns. These conditions allow for a sustained circuit to be established.

Critical to the maintenance of reentrant arrhythmias are the (1) impulse conduction velocity and (2) 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.

$$\text{Conduction velocity (m/s)} \times \text{Refractory period } (s) = \text{Wavelength (m)}.$$

If the calculated wavelength of the arrhythmia exceeds the path length of the circuit, then reentry cannot occur. If the wavelength is less than the path length, 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 path length, an *excitable gap* exists, which is the time interval between the return of full excitability of the tissue following depolarization and the arrival of the returning electrical wave front 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 (Chap. 3), AV node reentrant tachycardia (Chap. 4), atrial flutter (intra-atrial reentrant tachycardia scar-mediated atrial flutter—Chap. 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 and rotor reentry" is thought to underlie atrial and ventricular 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.

Conclusion

Research into physiologic mechanisms of the cardiac conduction system continues to expand. Vigilance towards incorporating advances in the knowledge of the electrophysiologic mechanisms is crucial as this research paves the way for progress in arrhythmia management of the young.

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