Published in final edited form as:
Card Electrophysiol Clin. 2011 March 1; 3(1): 23–45. doi:10.1016/j.ccep.2010.10.012.

Overview of Basic Mechanisms of Cardiac Arrhythmia

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Keywords

Electrophysiology; Pharmacology; Ventricular tachycardia; Ventricular fibrillation

A cardiac arrhythmia simply defined is a variation from the normal heart rate and/or rhythm that is not physiologically justified. Recent years have witnessed important advances in our understanding of the electrophysiologic mechanisms underlying the development of a variety of cardiac arrhythmias. The mechanisms responsible for cardiac arrhythmias are generally divided into 2 major categories: (1) enhanced or abnormal impulse formation (ie, focal activity) and (2) conduction disturbances (ie, reentry) (Fig. 1).

ABNORMAL IMPULSE FORMATION

Normal Automaticity

Automaticity is the property of cardiac cells to generate spontaneous action potentials. Spontaneous activity is the result of diastolic depolarization caused by a net inward current during phase 4 of the action potential, which progressively brings the membrane potential to threshold. The sinoatrial (SA) node normally displays the highest intrinsic rate. All other pacemakers are referred to as subsidiary or latent pacemakers because they take over the function of initiating excitation of the heart only when the SA node is unable to generate impulses or when these impulses fail to propagate.

The Voltage and Calcium Clocks

The terms sarcolemma voltage or Ca clocks have been used by Maltsev and colleagues[1] and Lakatta[2] to describe the mechanisms of SA node automaticity. The voltage clock refers to voltage-sensitive membrane currents, such as the hyperpolarization-activated pacemaker current (I_f).[3] This current is also referred to as a “funny” current because, unlike most voltage-sensitive currents, it is activated by hyperpolarization rather than depolarization. At the end of the action potential, the I_f is activated and depolarizes the sarcolemmal membrane.[3] I_f is a mixed Na-K inward current modulated by the autonomic nervous system through cAMP. The depolarization activates $I_{Ca,L}$, which provides Ca to activate the cardiac ryanodine receptor (RyR2). The activation of RyR2 initiates sarcoplasmic reticulum (SR) Ca release (Ca-induced Ca release), leading to contraction of the heart, a process known as EC coupling. Intracellular Ca (Ca_i) is then pumped back into SR by the SR Ca-ATPase (SERCA2a) and completes this Ca cycle. In addition to I_f, multiple time- and voltage-dependent ionic currents have been identified in cardiac pacemaker cells, which contribute to diastolic depolarization. These currents include (but are not limited to) $I_{Ca\text{-}L}$, $I_{Ca\text{-}T}$, I_{ST}, and various types of delayed rectifier K currents.[2] Many of these membrane currents are

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Conflict of interest: None.

known to respond to β-adrenergic stimulation. All these membrane ionic currents contribute to the regulation of SA node automaticity by altering membrane potential.

Another important ionic current capable of depolarizing the cell is the sodium-calcium exchanger current (I_{NCx}). In its forward mode, I_{NCx} exchanges 3 extracellular Na^+ with 1 intracellular Ca^{2+}, resulting in a net intracellular charge gain. This electrogenic current is active during late phase 3 and phase 4 because the Ca_i decline outlasts the SA node action potential duration. Recent studies showed that I_{NCx} may participate in normal pacemaker activity.[4] The sequence of events includes spontaneous rhythmic SR Ca release, Ca_i elevation, the activation of I_{NCx}, and membrane depolarization. This process is highly regulated by cAMP and the autonomic nervous system.[2] These studies suggest that sympathetic stimulation accelerates heart rate by phosphorylation of proteins that regulate Ca_i balance and spontaneous SR Ca cycling. These proteins include phospholamban (PLB, an SR membrane protein regulator of SERCA2a), L-type Ca channels, and RyR2. Phosphorylation of these proteins controls the phase and extent of subsarcolemmal SR Ca releases.

Subsidiary Pacemakers

In addition to the SA node, the atrioventicular (AV) node and Purkinje system are also capable of generating automatic activity. The contribution of I_f and I_K differs in SA node/AV nodes and Purkinje fiber because of the different potential ranges of these two pacemaker types (ie, −70 to −35 mV and −90 to −65 mV, respectively). The contribution of other voltage-dependent currents can also differ among the different cardiac cell types. Whether or not the Ca clock plays a role in pacemaking of AV node and Purkinje cells remains unclear.

SA nodal cells possess the fastest intrinsic rates, making them the primary pacemakers in the normal heart. When impulse generation or conduction in the SA node is impaired, latent or subsidiary pacemakers within the atria or ventricles take control of pacing the heart. The intrinsically slower rates of these latent pacemakers generally result in bradycardia. Both atrial and AV junctional subsidiary pacemakers are under autonomic control, with the sympathetic system increasing and parasympathetic system slowing the pacing rate. Although acetylcholine produces little in the way of a direct effect, it can significantly reduce Purkinje automaticity by means of the inhibition of the sympathetic influence, a phenomenon termed *accentuated antagonism*.[5] Simultaneous recording of cardiac sympathetic and parasympathetic activity in ambulatory dogs confirmed that sympathetic activation followed by vagal activation may be associated with significant bradycardia.[6,7]

AUTOMATICITY AS A MECHANISM OF CARDIAC ARRHYTHMIAS

Abnormal automaticity includes both reduced automaticity, which causes bradycardia, and increased automaticity, which causes tachycardia. Arrhythmias caused by abnormal automaticity can result from diverse mechanisms (see Fig. 1). Alterations in sinus rate can be accompanied by shifts of the origin of the dominant pacemaker within the sinus node or to subsidiary pacemaker sites elsewhere in the atria. Impulse conduction out of the SA mode can be impaired or blocked as a result of disease or increased vagal activity leading to development of bradycardia. AV junctional rhythms occur when AV junctional pacemakers located either in the AV node or in the His bundle accelerate to exceed the rate of SA node, or when the SA nodal activation rate was too slow to suppress the AV junctional pacemaker.

Bradycardia can occur in structurally normal hearts because of genetic mutations that result in abnormalities of either membrane clock or Ca clock mechanisms of automaticity. One example is the mutation of hyperpolarization-activated nucleotide-gated channel (HCN4),

which is part of the channels that carry I_f. Mutations of the HCN4 may cause familial bradycardia as well.[8,9]

Secondary SA Node Dysfunction

Common diseases, such as heart failure and atrial fibrillation, may be associated with significant SA node dysfunction. Malfunction of both membrane voltage and Ca clocks might be associated with both of these common diseases. Zicha and colleagues[10] reported that down-regulation of HCN4 expression contributes to heart failure-induced sinus node dysfunction. An A450 V missense loss of function mutation in *HCN4* has recently been shown to underlie familial sinus bradycardia in several unrelated probands of Moroccan Jewish descent.[9,11–13]

Enhanced Automaticity

Atrial and ventricular myocardial cells do not display spontaneous diastolic depolarization or automaticity under normal conditions, but can develop these characteristics when depolarized, resulting in the development of repetitive impulse initiation, a phenomenon termed *depolarization-induced automaticity*.[14] The membrane potential at which abnormal automaticity develops ranges between −70 and −30 mV. The rate of abnormal automaticity is substantially higher than that of normal automaticity and is a sensitive function of resting membrane potential (ie, the more depolarized resting potential the faster the rate). Similar to normal automaticity, abnormal automaticity is enhanced by β-adrenergic agonists and by reduction of external potassium.

Depolarization of membrane potential associated with disease states is most commonly a result of (1) an increase in extracellular potassium, which reduces the reversal potential for I_{K1}, the outward current that largely determines the resting membrane or maximum diastolic potential; (2) a reduced number of I_{K1} channels; (3) a reduced ability of the I_{K1} channel to conduct potassium ions; or (4) electrotonic influence of neighboring cells in the depolarized zone. Because the conductance of I_{K1} channels is sensitive to extra-cellular potassium concentration, hypokalemia can lead to major reduction in I_{K1}, leading to depolarization and the development of enhanced or abnormal automaticity, particularly in Purkinje pacemakers. A reduction in I_{K1} can also occur secondary to a mutation in *KCNJ2*, the gene that encodes for this channel, leading to increased automaticity and extrasystolic activity presumably arising from the Purkinje system.[15,16] Loss of function KCNJ2 mutation gives rise to Andersen-Tawil syndrome, which is characterized among other things by a marked increase in extrasystolic activity.[17–20]

Overdrive Suppression of Automaticity

Automatic activity of most pacemakers within the heart is inhibited when they are overdrive paced,[21] owing to a mechanism termed *overdrive suppression*. Under normal conditions, all subsidiary pacemakers are overdrive-suppressed by SA nodal activity. A possible mechanism of overdrive suppression is intracellular accumulation of Na leading to enhanced activity of the sodium pump (sodium-potassium adenosine triphosphatase [Na^+-K^+ ATPase]), which generates a hyperpolarizing electrogenic current that opposes phase 4 depolarization.[22] The faster the overdrive rate or the longer the duration of overdrive, the greater the enhancement of sodium pump activity, so that the period of quiescence after cessation of overdrive is directly related to the rate and duration of overdrive.

Parasystole and Modulated Parasystole

Latent pacemakers throughout the heart are generally reset by the propagating wavefront initiated by the dominant pacemaker. An exception to this rule occurs when the pacemaking

tissue is protected from the impulse of sinus nodal origin. A region of entrance block arises when cells exhibiting automaticity are surrounded by ischemic, infarcted, or otherwise compromised cardiac tissues that prevent the propagating wave from invading the focus, but which permit the spontaneous beat generated within the automatic focus to exit and activate the rest of the myocardium. A pacemaker region exhibiting entrance block, and exit conduction is referred to as a parasystolic focus. The ectopic activity generated by a parasystolic focus is characterized by premature ventricular complexes with variable coupling intervals, fusion beats, and inter-ectopic intervals that are multiples of a common denominator. This rhythm is relatively rare and is usually considered benign, although a premature ventricular activation of parasystolic origin can induce malignant ventricular rhythms in the ischemic myocardium or in the presence of a suitable myocardial substrate.

Modulated parasystole, a variant of classical parasystole, was described by Jalife and colleagues.[23,24] This variant of the arrhythmia results from incomplete entrance block of the parasystolic focus. Electrotonic influences arriving early in the pacemaker cycle delayed and those arriving late in the cycle accelerated the firing of the parasystolic pacemaker, so that ventricular activity could entrain the partially protected pacemaker. As a consequence, at select heart rate, extrasystolic activity generated by the entrained parasystolic pacemaker can mimic reentry, generating extrasystolic activity with fixed coupling.[23–27]

AFTERDEPOLARIZATION AND TRIGGERED ACTIVITY

Depolarizations that attend or follow the cardiac action potential and depend on preceding transmembrane activity for their manifestation are referred to as afterdepolarizations (Fig. 2). Two subclasses are traditionally recognized: (1) early, and (2) delayed. Early afterdepolarization (EAD) interrupts or retards repolarization during phase 2 and/or phase 3 of the cardiac action potential, whereas delayed afterdepolarization (DAD) occurs after full repolarization. When EAD or DAD amplitude suffices to bring the membrane to its threshold potential, a spontaneous action potential referred to as a triggered response is the result (see Fig. 2). These triggered events give rise to extrasystoles, which can precipitate tachyarrhythmias.

Early Afterdepolarizations and Triggered Activity

EADs are typically observed in cardiac tissues exposed to injury, altered electrolytes, hypoxia, acidosis, catecholamines, and pharmacologic agents, including antiarrhythmic drugs. Ventricular hypertrophy and heart failure also predispose to the development of EADs.[28] EAD characteristics vary as a function of animal species, tissue or cell type, and the method by which the EAD is elicited. Although specific mechanisms of EAD induction can differ, a critical prolongation of repolarization accompanies most, but not all, EADs. Drugs that inhibit potassium currents or which augment inward currents predispose to the development of EADs.[29] Phase 2 and phase 3 EADs sometimes appear in the same preparation.

EAD-induced triggered activity is sensitive to stimulation rate. Antiarrhythmic drugs with class III action generally induce EAD activity at slow stimulation rates.[14] In contrast, β-adrenergic agonist–induced EADs are fast rate-dependent.[30] In the presence of rapidly activating delayed rectifier current (rapid outward potassium current [I_{Kr}]) blockers, β-adrenergic agonists, and/or acceleration from an initially slow rate transiently facilitate the induction of EAD activity in ventricular M cells, but not in epicardium or endocardium and rarely in Purkinje fibers.[31]

Cellular Origin of Early Afterdepolarizations

EADs develop more commonly in midmyocardial M cells and Purkinje fibers than in epicardial or endocardial cells when exposed to action potential duration (APD)-prolonging agents. This is because of the presence of a weaker I_{Ks} and stronger late I_{Na} in M cells.[32,33] Block of I_{Ks} with chromanol 293B permits the induction of EADs in canine epicardial and endocardial tissues in response to I_{Kr} blockers such as E-4031 or sotalol.[34] The predisposition of cardiac cells to the development of EADs depends principally on the reduced availability of I_{Kr} and I_{Ks} as occurs in many forms of cardiomyopathy. Under these conditions, EADs can appear in any part of the ventricular myocardium.[35]

Ionic Mechanisms Responsible for the EAD

EADs develop when the balance of current active during phase 2 and/or 3 of the action potential shifts in the inward direction. If the change in current-voltage relation results in a region of net inward current during the plateau range of membrane potentials, it leads to a depolarization or EAD. Most pharmacologic interventions or pathophysiological conditions associated with EADs can be categorized as acting predominantly through 1 of 4 different mechanisms: (1) A reduction of repolarizing potassium currents (I_{Kr}, class IA and III antiarrhythmic agents; I_{Ks}, chromanol 293B or I_{K1}); (2) an increase in the availability of calcium current (Bay K 8644, catecholamines); (3) an increase in the sodium-calcium exchange current (I_{NCx}) caused by augmentation of Ca_i activity or upregulation of the I_{NCx}; and (4) an increase in late sodium current (late I_{Na}) (aconitine, anthopleurin-A, and ATX-II). Combinations of these interventions (ie, calcium loading and I_{Kr} reduction) or pathophysiological states can act synergistically to facilitate the development of EADs.

Delayed Afterdepolarization-Induced Triggered Activity

DADs and DAD-induced triggered activity are observed under conditions that augment intracellular calcium, $[Ca^{2+}]_i$, such as after exposure to toxic levels of cardiac glycosides (digitalis)[36–38] or catecholamines.[30,39,40] This activity is also manifest in hypertrophied and failing hearts[41,42] as well as in Purkinje fibers surviving myocardial infarction.[43] In contrast to EADs, DADs are always induced at relatively rapid rates.

Role of Delayed Afterdepolarization-Induced Triggered Activity in the Development of Cardiac Arrhythmias

An example of DAD-induced arrhythmia is the catecholaminergic polymorphic ventricular tachycardia (CPVT), which may be caused by the mutation of either the type 2 ryanodine receptor (RyR2) or the calsequestrin (CSQ2).[44] The principal mechanism underlying these arrhythmias is the “leaky” ryanodine receptor, which is aggravated during catecholamine stimulation. A typical clinical phenotype of CPVT is bidirectional ventricular tachycardia, which is also seen in digitalis toxicity. Wehrens and colleagues[45] demonstrated that heterozygous mutation of FKBP12.6 leads to leaky RyR2 and exercise-induced VT and VF, simulating the human CPVT phenotype. RyR2 stabilization with a derivative of 1,4-benzothiazepine (JTV519) increased the affinity of calstabin2 for RyR2, which stabilized the closed state of RyR2 and prevented the Ca leak that triggers arrhythmias. Other studies indicate that delayed afterdepolarization-induced extrasystoles serve to trigger catecholamine-induced VT/VF, but that the epicardial origin of these ectopic beats increases transmural dispersion of repolarization, thus providing the substrate for the development of reentrant tachyarrhythmias, which underlie the rapid polymorphic VT/VF.[46] Heart failure is associated with structural and electrophysiological remodeling, leading to tissue heterogeneity that enhances arrhythmogenesis and the propensity of sudden cardiac death.[47]

Late Phase 3 Early Afterdepolarizations and Their Role in the Initiation of Fibrillation

In 2003, Burashnikov and Antzelevitch[48,49] described a novel mechanism giving rise to triggered activity, termed "late phase 3 EAD," which combines properties of both EAD and DAD, but has its own unique character (see Fig. 2). Late phase 3 EAD-induced triggered extrasystoles represent a new concept of arrhythmogenesis in which abbreviated repolarization permits "normal SR calcium release" to induce an EAD-mediated closely coupled triggered response, particularly under conditions permitting intracellular calcium loading.[48,49] These EADs are distinguished by the fact that they interrupt the final phase of repolarization of the action potential (late phase 3). In contrast to previously described DAD or Ca_i-dependent EAD, it is *normal*, not spontaneous SR calcium release that is responsible for the generation of the EAD. Two principal conditions are required for the appearance of late phase 3 EAD: an APD abbreviation and a strong SR calcium release.[48] Such conditions may occur when both parasympathetic and sympathetic influences are combined. Simultaneous sympathovagal activation is also known to be the primary trigger of paroxysmal atrial tachycardia and AF episodes in dogs with intermittent rapid pacing.[6]

Late phase 3 EAD-induced extrasystoles have been shown to initiate AF in canine atria, particularly following spontaneous termination of the arrhythmia (IRAF, immediate reinduction of AF).[48] The appearance of late phase 3 EAD immediately following termination of AF or rapid pacing has been reported by in the canine atria in vivo[50] and pulmonary veins in vitro.[51] In addition to the atrial arrhythmias, late phase 3 EAD may also be responsible for the development recurrent VF in failing hearts.[52]

REENTRANT ARRHYTHMIAS

Reentry is fundamentally different from automaticity or triggered activity in the mechanism by which it initiates and sustains cardiac arrhythmias. Circus movement reentry occurs when an activation wavefront propagates around an anatomic or functional obstacle or core, and reexcites the site of origin (Fig. 3). In this type of reentry, all cells take turns in recovering from excitation so that they are ready to be excited again when the next wavefront arrives. In contrast, reflection and phase 2 reentry occur in a setting in which large differences of recovery from refractoriness exist between one site and another. The site with delayed recovery serves as a virtual electrode that excites its already recovered neighbor, resulting in a reentrant reexcitation. In addition, reentry can also be classified as anatomic and functional, although there is a gray zone in which both functional and anatomic factors are important in determining the characteristics of reentrant excitation.

Circus Movement Reentry Around an Anatomic Obstacle

The ring model is the prototypical example of reentry around an anatomic obstacle (see Fig. 3). It first emerged as a concept shortly after the turn of the last century when Mayer[53] reported the results of experiments involving the subumbrella tissue of a jellyfish (*Sychomedusa cassiopeia*). The muscular disk did not contract until ringlike cuts were made and pressure and a stimulus applied. This caused the disc to "spring into rapid rhythmic pulsation so regular and sustained as to recall the movement of clockwork."(p25) Mayer demonstrated similar circus movement excitation in rings cut from the ventricles of turtle hearts, but he did not consider this to be a plausible mechanism for the development of cardiac arrhythmias. His experiments proved valuable in identifying 2 fundamental conditions necessary for the initiation and maintenance of circus movement excitation: (1) unidirectional block—the impulse initiating the circulating wave must travel in one direction only; and (2) for the circus movement to continue, the circuit must be long enough to allow each site in the circuit to recover before the return of the circulating wave. G. R. Mines[54] was the first to develop the concept of circus movement reentry as a mechanism responsible

for cardiac arrhythmias. He confirmed Mayer's observations and suggested that the recirculating wave could be responsible for clinical cases of tachycardia.[55] The following 3 criteria developed by Mines for identification of circus movement reentry remains in use today:

1. An area of unidirectional block must exist.
2. The excitatory wave progresses along a distinct pathway, returning to its point of origin and then following the same path again.
3. Interruption of the reentrant circuit at any point along its path should terminate the circus movement.

It was recognized that successful reentry could occur only when the impulse was sufficiently delayed in an alternate pathway to allow for expiration of the refractory period in the tissue proximal to the site of unidirectional block. Both conduction velocity and refractoriness determine the success or failure of reentry, and the general rule is that the length of the circuit (path length) must exceed or equal that of the wavelength, the wavelength being defined as the product of the conduction velocity and the refractory period or that part of the path length occupied by the impulse and refractory to reexcitation. The theoretical minimum path length required for development of reentry was therefore dependent on both the conduction velocity and the refractory period. Reduction of conduction velocity or APD can both significantly reduce the theoretical limit of the path length required for the development or maintenance of reentry.

Circus Movement Reentry without an Anatomic Obstacle

In 1914, Garrey[56] suggested that reentry could be initiated without the involvement of anatomic obstacles and that "natural rings are not essential for the maintenance of circus contractions."(p409) Nearly 50 years later, Allessie and coworkers[57] provided direct evidence in support of this hypothesis in experiments in which they induced a tachycardia in isolated preparations of rabbit left atria by applying properly timed premature extra-stimuli. Using multiple intracellular electrodes, they showed that although the basic beats elicited by stimuli applied near the center of the tissue spread normally throughout the preparation, premature impulses propagate only in the direction of shorter refractory periods. An arc of block thus develops around which the impulse is able to circulate and reexcite its site of origin. Recordings near the center of the circus movement showed only subthreshold responses. The investigators proposed the term "leading circle" to explain their observation.[58] They argued that the functionally refractory region that develops at the vortex of the circulating wavefront prevents the centripetal waves from short circuiting the circus movement and thus serves to maintain the reentry. The investigators also proposed that the refractory core was maintained by centripetal wavelets that collide with each other. Because the head of the circulating wavefront usually travels on relatively refractory tissue, a fully excitable gap of tissue may not be present; unlike other forms of reentry, the leading circle model may not be readily influenced by extraneous impulses initiated in areas outside the reentrant circuit and thus may not be easily entrained. Although the leading circle reentry for a while was widely accepted as a mechanism of functional reentry, there is significant conceptual limitation to this model of reentry. For example, the centripetal wavelet was difficult to demonstrate either by experimental studies with high-resolution mapping or with computer simulation studies.

Weiner and Rosenblueth[59] in 1946 introduced the concept of spiral waves (rotors) to describe reentry around an anatomic obstacle; the term *spiral wave reentry* was later adopted to describe circulating waves in the absence of an anatomic obstacle.[60] Spiral wave theory has advanced our understanding of the mechanisms responsible for the functional form of

reentry. Although leading circle and spiral wave reentry are considered by some to be similar, a number of distinctions have been suggested. The curvature of the spiral wave is the key to the formation of the core.[61] The term *spiral wave* is usually used to describe reentrant activity in 2 dimensions. The center of the spiral wave is called the *core* and the distribution of the core in 3 dimensions is referred to as the *filament*. The 3-dimensional form of the spiral wave forms a scroll wave. In its simplest form, the scroll wave has a straight filament spanning the ventricular wall (ie, from epicardium to endocardium). Theoretical studies have described 3 major scroll wave configurations with curved filaments (L-, U-, and O-shaped), although numerous variations of these 3-dimensional filaments in space and time are assumed to exist during cardiac arrhythmias.

Spiral wave activity has been used to explain the electrocardiographic patterns observed during monomorphic and polymorphic cardiac arrhythmias as well as during fibrillation. Monomorphic VT results when the spiral wave is anchored and not able to drift within the ventricular myocardium. In contrast, a meandering or drifting spiral wave causes polymorphic VT- and VF-like activity.[62] VF seems to be the most complex representation of rotating spiral waves in the heart. VF is often preceded by VT. One of the theories suggests that VF develops when a single spiral wave responsible for VT breaks up, leading to the development of multiple spirals that are continuously extinguished and re-created.[63]

Figure 8 Reentry

In the late 1980s, El-Sherif and coworkers[64] delineated a figure 8 reentry in the surviving epicardial layer overlying an area of infarction produced by occlusion of the left anterior descending artery in canine hearts. The same patterns of activation can also be induced by creating artificial anatomic obstacles in the ventricles,[65] or during functional reentry induced by a single premature ventricular stimulation.[66] In the figure 8 model, the reentrant beat produces a wavefront that circulates in both directions around a line of conduction block rejoining on the distal side of the block. The wavefront then breaks through the arc of block to reexcite the tissue proximal to the block. The reentrant activation continues as 2 circulating wavefronts that travel in clockwise and counterclockwise directions around the 2 arcs in a pretzellike configuration.

Reflection

Reentry can occur without circus movement. Reflection and phase 2 reentry are 2 examples of non–circus movement reentry. The concept of reflection was first suggested by studies of the propagation characteristics of slow action potential responses in K^+-depolarized Purkinje fibers.[67] In strands of Purkinje fiber, Wit and coworkers[67] demonstrated a phenomenon similar to that observed by Schmitt and Erlanger[68] in which slow anterograde conduction of the impulse was at times followed by a retrograde wavefront that produced a “return extrasystole.” They proposed that the nonstimulated impulse was caused by circuitous reentry at the level of the syncytial interconnections, made possible by longitudinal dissociation of the bundle, as the most likely explanation for the phenomenon but also suggested the possibility of reflection. Direct evidence in support of reflection as a mechanism of arrhythmogenesis was provided by Antzelevitch and colleagues[69,70] in the early 1980s. A number of models of reflection have been developed. The first of these involves use of *ion-free* isotonic sucrose solution to create a narrow (1.5 to 2 mm) central inexcitable zone (gap) in unbranched Purkinje fibers mounted in a 3-chamber tissue bath (Fig. 4).[71] In the sucrose-gap model, stimulation of the proximal (P) segment elicits an action potential that propagates to the proximal border of the sucrose gap. Active propagation across the sucrose gap is not possible because of the ion-depleted extracellular milieu, but local circuit current continues to flow through the intercellular low-resistance pathways (an Ag/AgCl extracellular shunt pathway is provided). This local circuit or

electrotonic current, very much reduced on emerging from the gap, gradually discharges the capacity of the distal (D) tissue, thus giving rise to a depolarization that manifests as a either a subthreshold response (last distal response) or a foot-potential that brings the distal excitable tissue to its threshold potential. Active impulse propagation stops and then resumes after a delay that can be as long as several hundred milliseconds. When anterograde (P to D) transmission time is sufficiently delayed to permit recovery of refractoriness at the proximal end, electrotonic transmission of the impulse in the retrograde direction is able to reexcite the proximal tissue, thus generating a closely coupled reflected reentry. Reflection therefore results from the to-and-fro electrotonically mediated transmission of the impulse across the same inexcitable segment; neither longitudinal dissociation nor circus movement need be invoked to explain the phenomenon.

A second model of reflection involved the creation of an inexcitable zone permitting delayed conduction by superfusion of a central segment of a Purkinje bundle with a solution designed to mimic the extracellular milieu at a site of ischemia.[70] The gap was shown to be largely composed of an inexcitable cable across which conduction of impulses was electrotonically mediated. Reflected reentry has been demonstrated in isolated atrial and ventricular myocardial tissues as well.[72–74] Reflection has also been demonstrated in Purkinje fibers in which a functionally in-excitable zone is created by focal depolarization of the preparation with long duration constant current pulses.[75] Reflection is also observed in isolated canine Purkinje fibers homogeneously depressed with high K^+ solution as well as in branched preparations of *normal* Purkinje fibers.[76]

Phase 2 Reentry

Another reentrant mechanism that does not depend on circus movement and can appear to be of focal origin is Phase 2 reentry.[77–79] Phase 2 reentry occurs when the dome of the action potential, most commonly epicardial, propagates from sites at which it is maintained to sites at which it is abolished, causing local reexcitation of the epicardium and the generation of a closely coupled extra-systole. Severe spatial dispersion of repolarization is needed for phase 2 reentry to occur.

Phase 2 reentry has been proposed as the mechanism responsible for the closely coupled extrasystole that precipitates ventricular tachycardia/ventricular fibrillation (VT/VF) associated with Brugada and early repolarization syndromes.[80,81]

Spatial Dispersion of Repolarization

Studies conducted over the past 20 years have established that ventricular myocardium is electrically heterogeneous and composed of at least 3 electrophysiologically and functionally distinct cell types: epicardial, M, and endocardial cells.[82,83] These 3 principal ventricular myocardial cell types differ with respect to phase 1 and phase 3 repolarization characteristics (Fig. 5). Ventricular epicardial and M, but not endocardial, cells generally display a prominent phase 1, because of a large 4-aminopyridine (4-AP)-sensitive transient outward current (I_{to}), giving the action potential a spike and dome or notched configuration. These regional differences in I_{to}, first suggested on the basis of action potential data,[84] have now been directly demonstrated in ventricular myocytes from a wide variety of species including canine,[85] feline,[86] guinea pig,[87] swine,[88] rabbit,[89] and humans.[90,91] Differences in the magnitude of the action potential notch and corresponding differences in I_{to} have also been described between right and left ventricular (LV) epicardium.[92] Similar inter-ventricular differences in I_{to} have also been described for canine ventricular M cells.[93] This distinction is thought to form the basis for why the Brugada syndrome is a right ventricular disease.

Myocytes isolated from the epicardial region of the LV wall of the rabbit show a higher density of cAMP-activated chloride current when compared with endocardial myocytes.[94] I_{to2}, initially ascribed to a K^+ current, is now thought to be largely composed of a calcium-activated chloride current ($I_{Cl(Ca)}$) that contributes to the action potential notch, but it is not known whether this current differs among the 3 ventricular myocardial cell types.[95]

Between the surface epicardial and endocardial layers are transitional cells and M cells. M cells are distinguished by the ability of their action potential to prolong disproportionately relative to the action potential of other ventricular myocardial cells in response to a slowing of rate and/or in response to APD-prolonging agents.[82,96,97] In the dog, the ionic basis for these features of the M cell includes the presence of a smaller slowly activating delayed rectifier current (I_{Ks}),[32] a larger late sodium current (late I_{Na}),[33] and a larger Na-Ca exchange current (I_{NCx}).[98] In the canine heart, the rapidly activating delayed rectifier (I_{Kr}) and inward rectifier (I_{K1}) currents are similar in the 3 transmural cell types. Transmural and apical-basal differences in the density of I_{Kr} channels have been described in the ferret heart.[99] Amplification of transmural heterogeneities normally present in the early and late phases of the action potential can lead to the development of a variety of arrhythmias, including Brugada, long QT, and short QT syndromes, as well as catecholaminergic VT. The genetic mutations associated with these inherited channelopathies are listed in Table 1. The resulting gain or loss of function underlies the development of the arrhythmogenic substrate and triggers.

MECHANISMS UNDERLYING CHANNELOPATHIES

In the following sections we briefly discuss how the reentrant and triggered mechanisms described previously contribute to development of VT/VF associated with the long QT, short QT, and J wave syndromes.

J Wave Syndromes

Because they share a common arrhythmic platform related to amplification of I_{to}-mediated J waves, and because of similarities in ECG characteristics, clinical outcomes and risk factors, congenital and acquired forms of Brugada syndrome (BrS) and early repolarization syndrome (ERS) have been grouped together under the heading of J wave syndromes.[80]

Brugada syndrome—In 1992, Pedro and Josep Brugada[100] reported a new syndrome associated with ST elevation in ECG leads V1-V3, right bundle branch appearance during sinus rhythm, and a high incidence of VF and sudden cardiac death. BrS has been associated with mutations in 7 different genes. Mutations in *SCN5A* ($Na_v1.5$, BrS1) have been reported in 11% to 28% of BrS probands, *CACNA1C* ($Ca_v1.2$, BrS3) in 6.7%, *CACNB2b* ($Ca_v\beta2b$, BrS4) in 4.8%, and mutations in Glycerol-3-phophate dehydrogenase 1–like enzyme gene (*GPD1L*, BrS2), *SCN1B* (β_1-subunit of sodium channel, BrS5), *KCNE3* (MiRP2; BrS6), and *SCN3B* (β3-subunit of sodium channel, BrS7) are much more rare.[101–105] The newest gene associated with BrS is *CACNA2D1* (*$Ca_v\alpha2\delta$, BrS8)*.[106]

The mechanisms of arrhythmogenesis in BrS can be explained by the heterogeneous shortening of the APD on the right ventricular epicardium (Fig. 6).[81]

In regions of the myocardium exhibiting a prominent I_{to}, such as the right ventricular outflow tract epicardium, accentuation of the action potential notch secondary to a reduction of calcium or sodium channel current or an increase in outward current, results in a transmural voltage gradient that leads to coved ST segment elevation, which is the only form of ST segment elevation diagnostic of BrS (see Fig. 6B). Under these conditions, there is little in the way of an arrhythmogenic substrate. However, a further outward shift of the

currents active during the early phase of the action potential can lead to loss of the action potential dome, thus creating a dispersion of repolarization between epicardium and endocardium as well as within epicardium, between regions at which the dome is maintained and regions where it is lost (see Fig. 6C). The extent to which the action potential notch is accentuated leading to loss of the dome depends on the initial level of I_{to}.[107–109] When I_{to} is prominent, as it is in the right ventricular epicardium,[92,107,109] an outward shift of current causes phase 1 of the action potential to progress to more negative potentials at which the L-type calcium current ($I_{Ca,L}$) fails to activate, leading to an *all-or-none* repolarization and loss of the dome (see Fig. 6C). Because loss of the action potential dome is usually heterogeneous, the result is a marked abbreviation of action potential at some sites but not others. The epicardial action potential dome can then propagate from regions where it is maintained to regions where it is lost, giving rise to a very closely coupled extrasystole via phase 2 reentry (see Fig. 6D).[77] The extrasystole produced via phase 2 reentry often occurs on the preceding T wave resulting in an R-on-T phenomenon. This in turn can initiate polymorphic VT or VF (see Fig. 6E, F).

Potent sodium channel blockers like procainamide, pilsicainide, propafenone, and flecainide can be used to induce or unmask ST segment elevation in patients with concealed J-wave syndromes because they facilitate an outward shift of currents active in the early phases of the action potential.[110–112] Sodium channel blockers like quinidine, which also inhibits I_{to}, reduce the magnitude of the J wave and normalize ST segment elevation.[107,113]

Recent studies point to a prominent role of depolarization impairment resulting in local conduction delay in the RV[114]; however, the role of conduction delay in the RV in the electrocardiographic and arrhythmic manifestations of BrS remains a matter of debate.[115]

Early repolarization syndrome—An early repolarization (ER) pattern, consisting of a J point elevation, a notch or slur on the QRS (J wave), and tall/symmetric T waves, is commonly found in healthy young males and has traditionally been regarded as totally benign.[116,117] A report in 2000 that an ER pattern in the coronary-perfused wedge preparation can easily convert to one in which phase 2 reentry gives rise to polymorphic VT/VF, prompted the suggestion that ER may in some cases predispose to malignant arrhythmias in the clinic.[80,118] Many case reports and experimental studies have long suggested a critical role for the J wave in the pathogenesis of idiopathic ventricular fibrillation (IVF).[119–127] Several recent studies have provided a definitive association between ER and IVF.[128–132]

The high prevalence of ER in the general population suggests that it is not a sensitive marker for sudden cardiac death (SCD), but that it is a marker of a genetic predisposition for the development of VT/VF via an ERS. Thus, when observed in patients with syncope or malignant family history of sudden cardiac death, ER may be prognostic of risk. We recently proposed a classification scheme for ERS based on the available data pointing to an association of risk with spatial localization of the ER pattern.[80] In this scheme, Type 1 is associated with ER pattern predominantly in the lateral precordial leads; this form is very prevalent among healthy male athletes and is thought to be largely benign. Type 2, displaying an ER pattern predominantly in the inferior or inferolateral leads, is associated with a moderate level of risk and Type 3, displaying an ER pattern globally in the inferior, lateral, and right precordial leads, appears to be associated with the highest level of risk and is often associated with electrical storms.[80] Of note, BrS represents a fourth variant in which ER is limited to the right precordial leads.

In ERS, as in BrS, the dynamic nature of J wave manifestation is well recognized. The amplitude of J waves, which may be barely noticeable during sinus rhythm, may become

progressively accentuated with increased vagal tone and bradycardia and still further accentuated following successive extrasystoles and compensatory pauses giving rise to short long short sequences that precipitate VT/VF.[80,129,133]

Studies examining the genetic and molecular basis for ERS are few and data are very limited (see Table 1). Haissaguerre and colleagues[134] were the first to associate *KCNJ8* with ERS. Functional expression of the S422L missense mutation in *KCNJ8* was not available at the time but was recently reported by Medeiros-Domingo and colleagues.[135] The investigators genetically screened 101 probands with BrS and ERS and found one BrS and one ERS proband with an S422L-*KCNJ8* (Kir6.1) mutation; the variation was absent in 600 controls. The investigators co-expressed the *KCNJ8* mutation with ATP regulatory subunit *SUR2A* in COS-1 cells and measured $I_{K\text{-}ATP}$ using whole cell patch clamp techniques. A significantly larger $I_{K\text{-}ATP}$ was recorded for the mutant versus wild type in response to a high concentration of pinacidil (100 μM). The presumption is that the S422L-*KCNJ8* mutant channels fail to close properly at normal intracellular ATP concentrations, thus resulting in a gain of function. The prospect of a gain of function in $I_{K\text{-}ATP}$ as the basis for ERS is supported by the observation that pinacidil, an $I_{K\text{-}ATP}$ opener, has been shown to induce both the electrocardiographic and arrhythmic manifestation of ERS in LV wedge preparations.[80]

Recent studies from our group have identified 4 probands in whom mutations in highly conserved residues of *CACNA1C*, *CACNB2*, and *CACNA2D1* were found to be associated with ERS.[106] Preliminary studies involving heterologous expression of these genes in HEK293 cells indicate that these mutations are associated with a loss of function of I_{Ca}, supporting the thesis that all 3 are ERS-susceptibility genes (Barajas, unpublished observation, 2010).

The ECG and arrhythmic manifestations of ERS are thought to be attributable to mechanisms similar to those operative in BrS. In ERS, the outward shift of current may extend beyond the action potential notch, thus leading to an elevation of the ST segment akin to early repolarization. Activation of the ATP-sensitive potassium current ($I_{K\text{-}ATP}$) or depression of inward calcium channel current (I_{Ca}) can effect such a change.[106] Transmural gradients generated in response to I_{Ca} loss of function or $I_{K\text{-}ATP}$ gain of function could manifest in the ECG as a diversity of ER patterns including J point elevation, slurring of the terminal part of the QRS, and mild ST segment elevation. The ER pattern could facilitate loss of the dome because of other factors and thus lead to the development of ST segment elevation, phase 2 reentry, and VT/VF.

The Long QT Syndrome

The long QT syndromes (LQTS) are phenotypically and genotypically diverse, but have in common the appearance of long QT interval in the ECG, an atypical polymorphic ventricular tachycardia known as Torsade de Pointes (TdP), and, in many but not all cases, a relatively high risk for sudden cardiac death.[136–138] Congenital LQTS has been associated with 13 genes in at least 7 different ion genes and a structural anchoring protein located on chromosomes 3, 4, 6, 7, 11, 17, 20, and 21 (see Table 1).[139–146] Timothy syndrome, also referred to as LQT8, is a rare congenital disorder characterized by multiorgan dysfunction including prolongation of the QT interval, lethal arrhythmias, webbing of fingers and toes, congenital heart disease, immune deficiency, intermittent hypoglycemia, cognitive abnormalities, and autism. Timothy syndrome has been linked to loss of voltage-dependent inactivation owing to mutations in $Ca_v1.2$, the gene that encodes for an α subunit of the calcium channel.[147] The most recent gene associated with LQTS is *KCNJ5*, which encodes Kir3.4 protein, the protein that encodes the α subunit of the $I_{K\text{-}ACh}$ channel. Mutations in

this gene produce a loss of function that produces an LQT phenotype via a mechanism that is not clearly understood.[148]

Two patterns of inheritance have been identified in LQTS: (1) a rare autosomal recessive disease associated with deafness (Jervell and Lange-Nielsen), caused by 2 genes that encode for the slowly activating delayed rectifier potassium channel (KCNQ1 and KCNE1); and (2) a much more common autosomal dominant form known a the Romano Ward syndrome, caused by mutations in 13 different genes (see Table 1).

Acquired LQTS refers to a syndrome similar to the congenital form but caused by exposure to drugs that prolong the duration of the ventricular action potential[149] or QT prolongation secondary to cardiomyopathies, such as dilated or hypertrophic cardiomyopathy, as well as to abnormal QT prolongation associated with bradycardia or electrolyte imbalance.[150–154] The acquired form of the disease is far more prevalent than the congenital form, and in some cases may have a genetic predisposition.

Amplification of spatial dispersion of repolarization within the ventricular myocardium has been identified as the principal arrhythmogenic substrate in both acquired and congenital LQTS. The accentuation of spatial dispersion, typically secondary to an increase of transmural, trans-septal, or apico-basal dispersion of repolarization, and the development of early afterdepolarization (EAD)-induced triggered activity underlie the substrate and trigger for the development of TdP arrhythmias observed under LQTS conditions.[155,156] Models of the LQT1, LQT2, and LQT3, and LQT7 forms of the long QT syndrome have been developed using the canine arterially perfused left ventricular wedge preparation (Fig. 7).[16,157,158] Data from these studies suggest that in LQTS, preferential prolongation of the M cell APD leads to an increase in the QT interval as well as an increase in transmural dispersion of repolarization (TDR), which contributes to the development of spontaneous as well as stimulation-induced TdP.[159–161] The unique characteristics of the M cells, ie, the ability of their action potential to prolong more than that of epicardium or endocardium in response to a slowing of rate,[96,162,163] is at the heart of this mechanism.-Fig. 7 presents our working hypothesis for our understanding of the mechanisms underlying LQTS-related TdP based on available data. The hypothesis presumes the presence of electrical heterogeneity in the form of transmural dispersion of repolarization under baseline conditions and the amplification of TDR by agents that reduce net repolarizing current via a reduction in I_{Kr} or I_{Ks} or augmentation of I_{Ca} or late I_{Na}. Conditions leading to a reduction in I_{Kr} or augmentation of late I_{Na} lead to a preferential prolongation of the M cell action potential. As a consequence, the QT interval prolongs and is accompanied by a dramatic increase in transmural dispersion of repolarization, thus creating a vulnerable window for the development of reentry. The reduction in net repolarizing current also predisposes to the development of EAD-induced triggered activity in M and Purkinje cells, which provide the extrasystole that triggers TdP when it falls within the vulnerable period. β adrenergic agonists further amplify transmural heterogeneity (transiently) in the case of I_{Kr} block, but reduce it in the case of I_{Na} agonists.[161,164]

Short QT Syndrome

The short QT syndrome (SQTS), first proposed as a clinical entity by Gussak and colleagues[165] in 2000, is an inherited syndrome characterized by a QTc of 360 msec or less and high incidence of VT/VF in infants, children, and young adults.[166,167] The familial nature of this sudden death syndrome was highlighted by Gaita and colleagues[168] in 2003. Mutations in 5 genes have been associated with SQTS: *KCNH2*, *KCNJ2*, *KCNQ1*, *CACNA1c*, and *CACNB2b*.[102,169–171] Mutations in these genes cause either a gain of function in outward potassium channel currents (I_{Kr}, I_{Ks} and I_{K1}) or a loss of function in inward calcium channel current (I_{Ca}).

Experimental studies suggest that the abbreviation of the action potential in SQTS is heterogeneous with preferential abbreviation of either ventricular epicardium or endocardium, giving rise to an increase in TDR.[172,173] In the atria, the I_{Kr} agonist PD118057 causes a much greater abbreviation of the action potential in epicardium when compared with cristae terminalis, thus creating a marked dispersion of repolarization in the right atrium.[174] Dispersion of repolarization and refractoriness serve as substrates for reentry by promoting unidirectional block. The marked abbreviation of wavelength (product of refractory period and conduction velocity) is an additional factor promoting the maintenance of reentry. T_{peak}-T_{end} interval and T_{peak}-T_{end} /QT ratio, an electrocardiographic index of spatial dispersion of ventricular repolarization, and perhaps TDR, have been reported to be significantly augmented in cases of SQTS.[175,176] Interestingly, this ratio is more amplified in patients who are symptomatic.[177]

Evidence supporting the role of augmented TDR in atrial and ventricular arrhythmogenesis in SQTS derives from experimental studies involving the canine left ventricular wedge and atrial preparations.[172–174,178]

The Role of Spatial Dispersion of Repolarization in Channelopathy-Mediated Sudden Death

The inherited and acquired sudden death syndromes discussed previously differ with respect to the behavior of the QT interval (Fig. 8). In the long QT syndrome, QT increases as a function of disease or drug concentration. In the Brugada and early repolarization syndromes, it remains largely unchanged or is abbreviated, and in the short QT syndrome, QT interval decreases as a function of disease or drug. What these syndromes have in common is an amplification of TDR, which results in the development of polymorphic VT when TDR reaches the threshold for reentry. In the setting of a prolonged QT, we refer to it as TdP. It is noteworthy that the threshold for reentry decreases as APD and refractoriness are reduced, thus requiring a shorter path length for reentry, making it easier to induce.

Acknowledgments

Financial support: Supported by grant HL47678 from the National Heart, Lung, and Blood Institute (CA) and NYS and Florida Masons.

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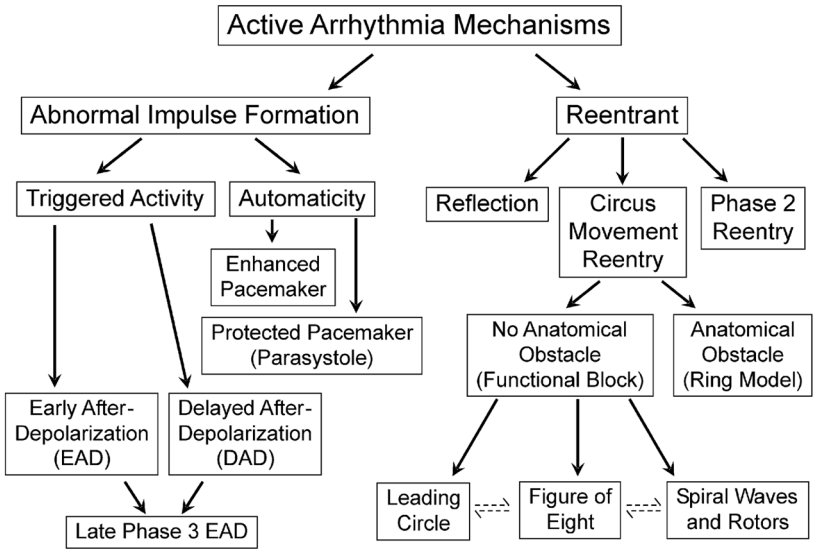

Fig. 1.
Classification of active cardiac arrhythmias.

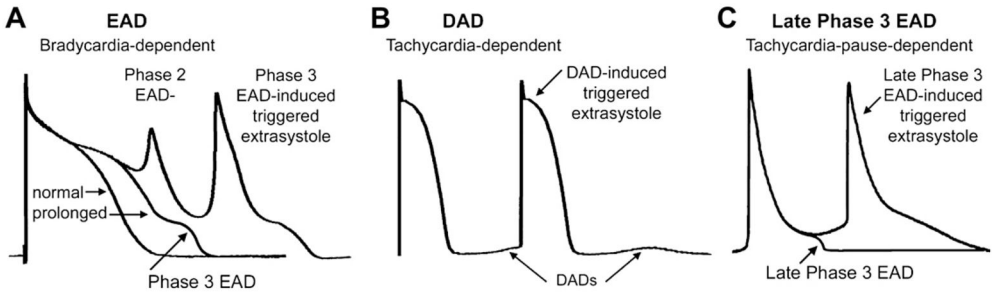

Fig. 2.

Examples of early afterdepolarization (EAD) (*A*), delayed afterdepolarization (DAD) (*B*), and late phase 3 EAD (*C*). (*Modified from* Burashnikov A, Antzelevitch C. Late-phase 3 EAD. A unique mechanism contributing to initiation of atrial fibrillation. Pacing Clin Electrophysiol 2006;29:290–5; with permission.)

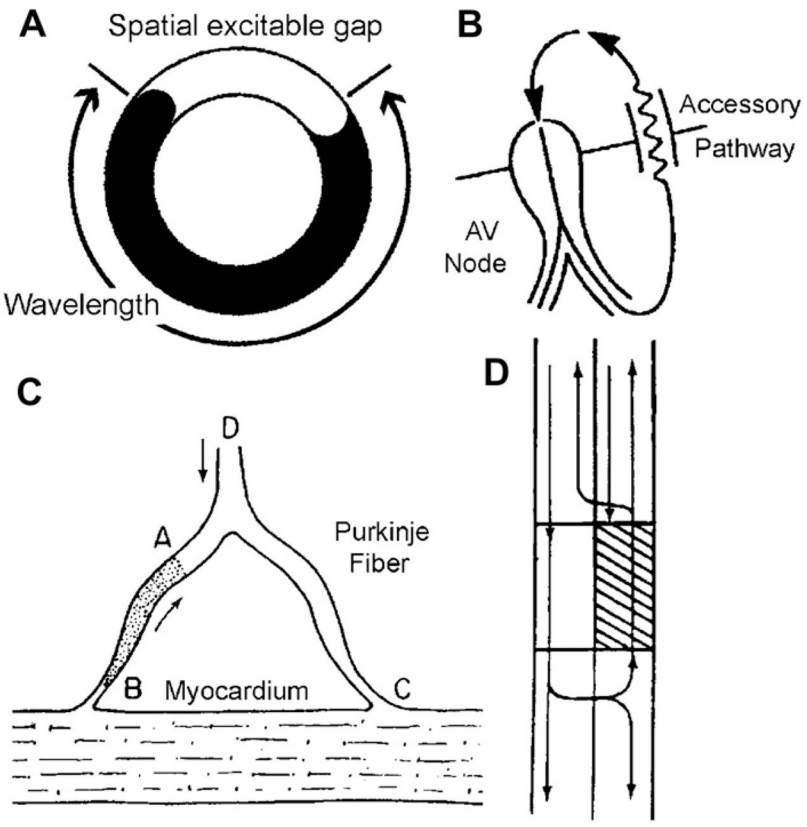

Fig. 3.

Ring models of reentry. (*A*) Schematic of a ring model of reentry. (*B*) Mechanism of reentry in the Wolf-Parkinson-White syndrome involving the AV node and an atrioventricular accessory pathway (AP). (*C*) A mechanism for reentry in a Purkinje-muscle loop proposed by Schmitt and Erlanger. The diagram shows a Purkinje bundle (D) that divides into 2 branches, both connected distally to ventricular muscle. Circus movement was considered possible if the stippled segment, A → B, showed unidirectional block. An impulse advancing from D would be blocked at A, but would reach and stimulate the ventricular muscle at C by way of the other terminal branch. The wavefront would then reenter the Purkinje system at B traversing the depressed region slowly so as to arrive at A following expiration of refractoriness. (*D*) Schematic representation of circus movement reentry in a linear bundle of tissue as proposed by Schmitt and Erlanger. The upper pathway contains a depressed zone (shaded) that serves as a site of unidirectional block and slow conduction. Anterograde conduction of the impulse is blocked in the upper pathway but succeeds along the lower pathway. Once beyond the zone of depression, the impulse crosses over through lateral connections and reenters through the upper pathway. (*C* and *D from* Schmitt FO, Erlanger J. Directional differences in the conduction of the impulse through heart muscle and their possible relation to extrasystolic and fibrillary contractions. Am J Physiol 1928;87:326–47.)

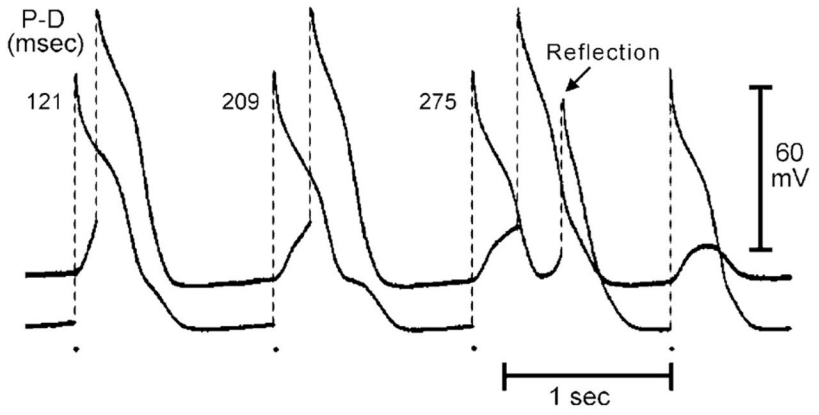

Fig. 4.

Delayed transmission and reflection across an inexcitable gap created by superfusion of the central segment of a Purkinje fiber with an *ion-free* isotonic sucrose solution. The 2 traces were recorded from proximal (P) and distal (D) active segments. P–D conduction time (indicated in the upper portion of the figure, in ms) increased progressively with a 4:3 Wenckebach periodicity. The third stimulated proximal response was followed by a reflection. (*From* Antzelevitch C. Clinical applications of new concepts of parasystole, reflection, and tachycardia. Cardiol Clin 1983;1:39–50; with permission.)

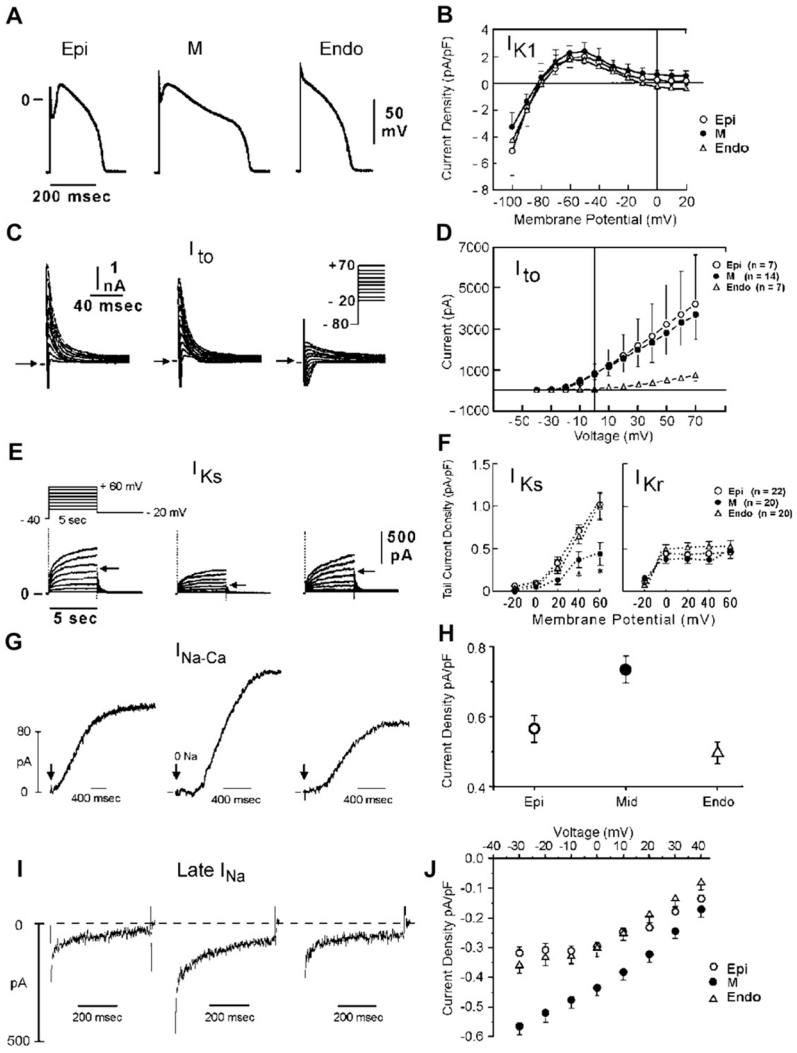

Fig. 5.

(*A*) Ionic distinctions among epicardial, M, and endocardial cells. Action potentials recorded from myocytes isolated from the epicardial, endocardial, and M regions of the canine left ventricle. (*B*) I-V relations for I_{K1} in epicardial, endocardial, and M region myocytes. Values are mean ± SD. (*C*) Transient outward current (I_{to}) recorded from the 3 cell types (current traces recorded during depolarizing steps from a holding potential of −80 mV to test potentials ranging between −20 and +70 mV). (*D*) The average peak current-voltage relationship for I_{to} for each of the 3 cell types. Values are mean ± SD. (*E*) Voltage-dependent activation of the slowly activating component of the delayed rectifier K^+ current (I_{Ks}) (currents were elicited by the voltage pulse protocol shown in the inset; Na^+-, K^+-, and Ca^{2+}- free solution). (*F*) Voltage dependence of I_{Ks} (current remaining after exposure to E-4031) and I_{Kr} (E-4031-sensitive current). Values are mean ± SE. **P* < .05 compared with Epi or Endo. (*G*) Reverse-mode sodium-calcium exchange currents recorded in potassium- and chloride-free solutions at a voltage of −80 mV. I_{Na-Ca} was maximally activated by switching to sodium-free external solution at the time indicated by the arrow. (*H*) Midmyocardial sodium-calcium exchanger density is 30% greater than endocardial density, calculated as the peak outward I_{Na-Ca} normalized by cell capacitance. Endocardial and epicardial densities were not significantly different. (*I*) TTX-sensitive late sodium current.

Cells were held at −80 mV and briefly pulsed to −45 mV to inactivate fast sodium current before stepping to −10 mV. (*J*) Normalized late sodium current measured 300 msec into the test pulse was plotted as a function of test pulse potential. (*Data from* Zygmunt AC, Goodrow RJ, Antzelevitch C. INaCa contributes to electrical heterogeneity within the canine ventricle. Am J Physiol Heart Circ Physiol 2000;278:H1671;8; and Refs.[32,84,97])

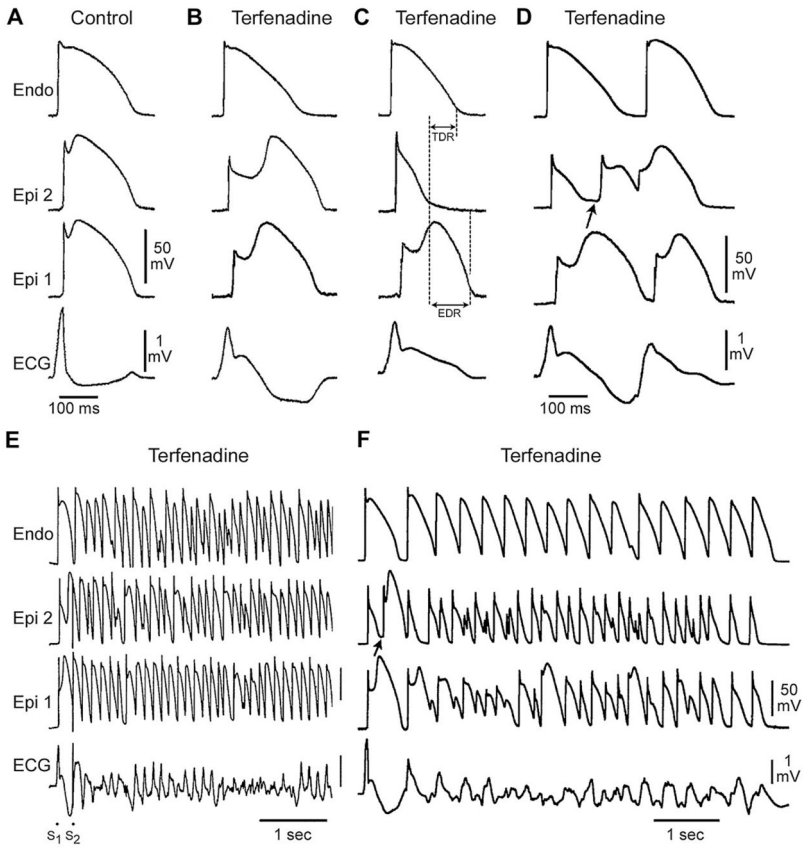

Fig. 6.

Cellular basis for electrocardiographic and arrhythmic manifestation of BrS. Each panel shows transmembrane action potentials from 1 endocardial (*top*) and 2 epicardial sites together with a transmural ECG recorded from a canine coronary-perfused right ventricular wedge preparation. (*A*) Control (basic cycle length (BCL) 400 msec). (*B*) Combined sodium and calcium channel block with terfenadine (5 μM) accentuates the epicardial action potential notch creating a transmural voltage gradient that manifests as an ST segment elevation or exaggerated J wave in the ECG. (*C*) Continued exposure to terfenadine results in all-or-none repolarization at the end of phase 1 at some epicardial sites but not others, creating a local epicardial dispersion of repolarization (EDR) as well as a transmural dispersion of repolarization (TDR). (*D*) Phase 2 reentry occurs when the epicardial action potential dome propagates from a site where it is maintained to regions where it has been lost giving rise to a closely coupled extrasystole. (*E*) Extrastimulus (S1–S2 = 250 msec) applied to epicardium triggers a polymorphic VT. (*F*) Phase 2 reentrant extrasystole triggers a brief episode of polymorphic VT. (*Modified from* Fish JM, Antzele-vitch C. Role of sodium and calcium channel block in unmasking the Brugada syndrome. Heart Rhythm 2004;1:210–17; with permission.)

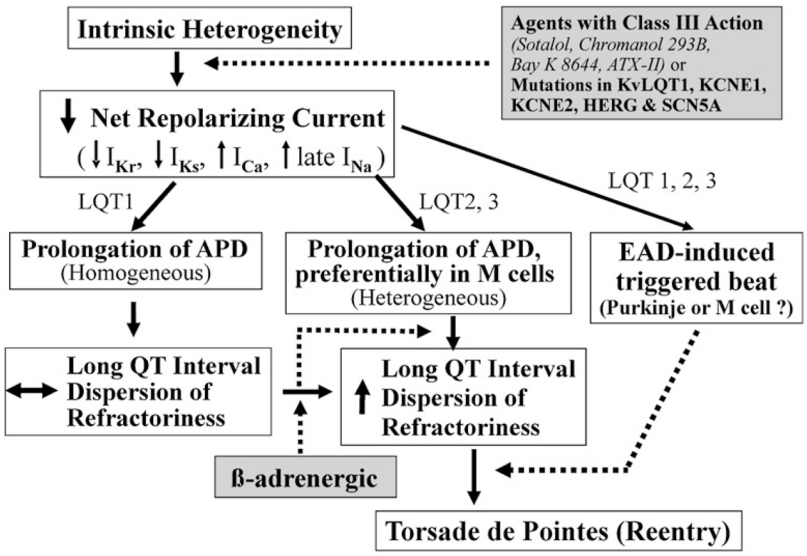

Fig. 7.
Proposed cellular and ionic mechanisms for the long QT syndrome.

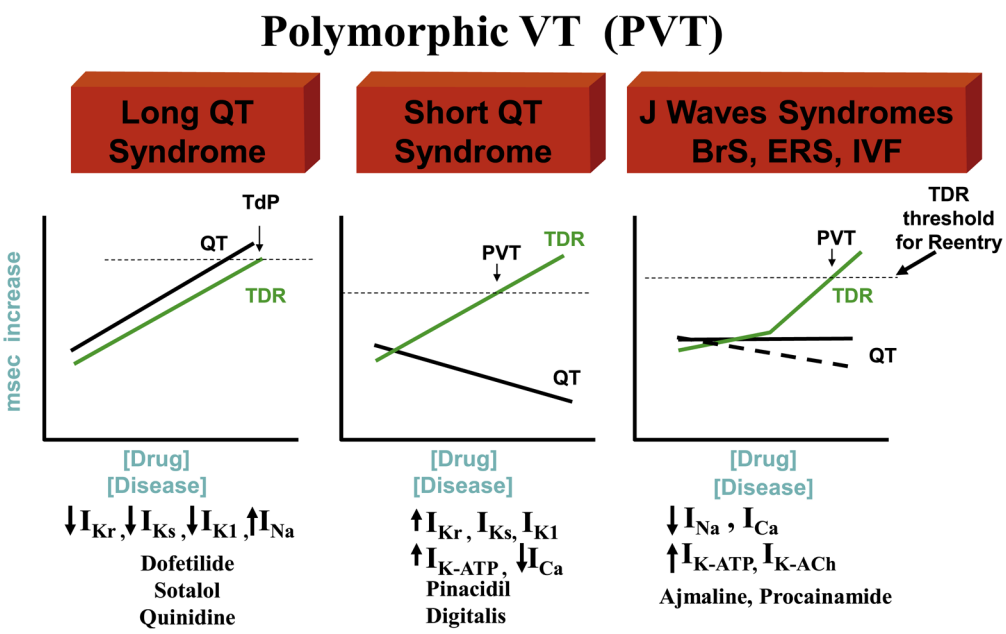

Fig. 8.

The role of transmural dispersion of repolarization (TDR) in channelopathy-induced sudden death. In the long QT syndrome, QT increases as a function of disease or drug concentration. In the J wave syndromes (Brugada and early repolarization syndromes), it remains largely unchanged or is moderately abbreviated, and in the short QT syndrome, QT interval decreases as a function of disease or drug. The 3 syndromes have in common the ability to amplify TDR, which results in the development of polymorphic VT (PVT) or Torsade de Pontes (TdP) when dispersion reaches the threshold for reentry.

Table 1

Genetic disorders causing cardiac arrhythmias in the absence of structural heart disease (Primary Electrical Disease)

		Rhythm	Inheritance	Locus	Ion Channel	Gene
LQTS	**(RW)**	**TdP**	**AD**			
	LQT1	(Andersen-Tawil Syndrome) (Timothy Syndrome)		11p15	I_{Ks}	*KCNQ1, KvLQT1*
	LQT2			7q35	I_{Kr}	*KCNH2, HERG*
	LQT3			3p21	I_{Na}	*SCN5A, $Na_v1.5$*
	LQT4			4q25		*ANKB, ANK2*
	LQT5			21q22	I_{Ks}	*KCNE1, minK*
	LQT6			21q22	I_{Kr}	*KCNE2, MiRP1*
	LQT7			17q23	I_{K1}	*KCNJ2, Kir 2.1*
	LQT8			6q8A	I_{Ca}	*CACNA1C, $Ca_v1.2$*
	LQT9			3p25	I_{Na}	*CAV3, Caveolin-3*
	LQT10			11q23.3	I_{Na}	*SCN4B. Na_vb4*
	LQT11			7q21-q22	I_{Ks}	*AKAP9, Yotiao*
	LQT12			20q11.2	I_{Na}	*SNTA1, α–1 Syntrophin*
	LQT13			11q24	IK-ACh	KCNJ5, Kir3.4
LQTS	(JLN)	TdP	AR	11p15	I_{Ks}	*KCNQ1, KvLQT1*
				21q22	I_{Ks}	*KCNE1, minK*
BrS	BrS1	PVT	AD	3p21	I_{Na}	*SCN5A, $Na_v1.5$*
	BrS2	PVT	AD	3p24	I_{Na}	*GPD1L*
	BrS3	PVT	AD	12p13.3	I_{Ca}	*CACNA1C, $Ca_V1.2$*
	BrS4	PVT	AD	10p12.33	I_{Ca}	*CACNB2b, $Ca_v\beta_{2b}$*
	BrS5	PVT	AD	19q13.1	I_{Na}	*SCN1B, $Na_v\beta1$*
	BrS6	PVT	AD	11q13–14	I_{Ca}	*KCNE3. MiRP2*
	BrS7	PVT	AD	11q23.3	I_{Na}	*SCN3B, Navb3*
	BrS8	PVT	AD	7q21.11	I_{Ca}	*CACNA2D1, $Ca_v\alpha2\delta$*
ERS	ERS1	PVT	AD	12p11.23	IK-ATP	*KCNJ8*, Kir6.1

		Rhythm	Inheritance	Locus	Ion Channel	Gene
LQTS	**(RW)**	**TdP**	**AD**			
	ERS2	PVT	AD	12p13.3	I_{Ca}	*CACNA1C, $Ca_V1.2$*
	ERS3	PVT	AD	10p12.33	I_{Ca}	*CACNB2b, $Ca_V\beta_{2b}$*
	ERS4	PVT	AD	7q21.11	I_{Ca}	*CACNA2D1, $Ca_V\alpha 2\delta$*
SQTS	SQT1	VT/VF	AD	7q35	I_{Kr}	*KCNH2, HERG*
	SQT2			11p15	I_{Ks}	*KCNQ1, KvLQT1*
	SQT3		AD	17q23.1–24.2	I_{K1}	*KCNJ2, Kir2.1*
	SQT4			12p13.3	I_{Ca}	*CACNA1C, $Ca_V1.2$*
	SQT5		AD	10p12.33	I_{Ca}	*CACNB2b, $Ca_V\beta_{2b}$*
Catecholaminergic Polymorphic VT						
	CPVT1	VT	AD	1q42–43		*RyR2*
	CPVT2	VT	AR	1p13–21		*CASQ2*

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; BrS, Brugada syndrome; ERS, early repolarization syndrome; JLN, Jervell and Lange –Nielsen; LQTS, long QT syndrome; RW, Romano-Ward; SQTS, short QT syndrome; TdP, Torsade de Pointes; VF, ventricular fibrillation; VT, ventricular tachycardia.