**Abstract**—The characterization of single gene disorders has provided important insights into the molecular pathogenesis of cardiac arrhythmias. Primary electrical diseases including long-QT syndrome, short-QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia have been associated with mutations in a variety of ion channel subunit genes that promote arrhythmogenesis. Pathological remodeling of ionic currents and network properties of the heart critical for normal electrical propagation plays a critical role in the initiation and maintenance of acquired arrhythmias. This review focuses on the molecular and cellular basis of electrical activity in the heart under normal and pathophysiological conditions to provide insights into the fundamental mechanisms of inherited and acquired cardiac arrhythmias. Improved understanding of the basic biology of cardiac arrhythmias holds the promise of identifying new molecular targets for the treatment of cardiac arrhythmias. *(Circulation. 2005;112:2517-2529.)*

**Key Words:** arrhythmia • electrophysiology • genetics • ion channels • molecular biology

Normal heart rhythm requires the finely orchestrated activity of a number of ion channels and transporters and the orderly propagation of electrical impulses throughout the myocardium; disruption of either can have severe consequences, resulting in potentially lethal heart rhythm disturbances. Indeed, it is surprising that arrhythmias do not occur more frequently in the setting of structural heart disease, which results in a host of electrophysiological changes that render the heart more vulnerable to electrical instability. This review focuses on the molecular and cellular basis of excitability, conduction, and electrical recovery in the heart under normal and pathophysiological conditions, with the goal of providing insights into the fundamental mechanisms of cardiac arrhythmias and the identification of appropriate targets for antiarrhythmic therapy.

**Molecular and Cellular Basis of Cardiac Excitability**

Ion channels are multisubunit transmembrane protein complexes that perform the seemingly paradoxical task of mediating the exquisitely selective flux of millions of ions per second across cell membranes. These macromolecules are the fundamental functional units of biological electricity in all excitable cells. In the past 2 decades most of the relevant ion channel genes encoding the major or pore-forming (α) subunits and many of the ancillary (β) subunits corresponding to ionic currents in the heart have been cloned, sequenced, and functionally characterized (Figure 1). A growing number of inherited arrhythmias have been linked to mutations in ion channel subunit genes. Other heritable cardiac diseases that alter the structure of the heart may change the level of expression or function of 1 or more of these ion channel genes, enhancing the risk of arrhythmias. Many of these ion channel subunits serve as molecular targets for drugs used in the treatment of cardiovascular diseases. We are just beginning to discover that subtle variations in gene sequences that occur in a significant proportion of the population (ie, polymorphisms) may dramatically and potentially lethally alter the response to drugs that act on ion channels.1,2

Myocardial cells have a characteristically long action potential that is sculpted by the orchestrated activity of multiple ion channels and transporters (Figure 2). Depolarizing currents, primarily sodium and calcium, are responsible for the action potential upstroke and maintenance of the action potential plateau, and repolarizing currents, primarily potassium, in concert with a reduction in depolarizing currents are responsible for restoration of the resting membrane potential (∼−80 mV). A number of electrogenic transporters contribute to the action potential profile; the magnitude and direction of the current depend on the transmembrane voltage and concentration gradient of the ions being transported.

**Rare Disease Paradigm: Monogenic Electric Diseases**

Primary electrical diseases of the heart refer to rare inherited cardiac arrhythmias in the absence of structural abnormalities of the heart that are associated with mutations in ion channel genes. The long-QT syndrome (LQTS), short-QT syndrome (SQTS), Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT) are primary electrical diseases and constitute a significant minority of cases of sudden cardiac death (SCD) in the young (Table). Important insights into the pathogenesis of cardiac arrhythmias have been gleaned from the molecular characterization of monogenic inherited arrhythmia syndromes. The ion channel basis of congenital LQTS was verified with the discovery of

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disease-causing mutations in KCNH2 (hERG) and SCN5A (Nav1.5), the genes encoding the cardiac delayed rectifier ($I_{Kr}$) and sodium ($I_{Na}$) currents, respectively. The recent identification of overlap syndromes with mutations in a single gene producing distinct inherited arrhythmias (eg, mutations in SCN5A producing LQTS and Brugada syndrome) further adds to the phenotype complexity of the rare monogenic arrhythmia syndromes. This may be the result of interactions of the expressed genes with the environment or the effect of other “modifier genes” that alter the susceptibility of an individual to the expression of a specific phenotype.

Mutations in ion channels have also been implicated in multisystem disorders associated with abnormal ventricular repolarization and an enhanced risk of SCD, such as Andersen and Timothy syndromes. Heritable forms of structural ventricular disease may be associated with atrial arrhythmias and an increased risk of SCD. These disorders include hypertrophic and dilated cardiomyopathies and arrhythmogenic right ventricular dysplasia, which have been linked to mutations in sarcomeric, cytoskeletal, and intercellular junction proteins, respectively. Linking these syndromes to their genetic and molecular basis not only offers the practitioner tools to accurately diagnose rare disorders but also provides novel markers for assessing risk of SCD. Unfortunately, more far-reaching screening strategies, risk stratification schemes, and molecular therapeutics have been limited by the unexpectedly wide spectrum of clinical phenotypes associated with even single gene abnormalities.

The mechanisms of arrhythmias associated with mutations in ion channel genes are relatively straightforward compared with rhythm disturbances that occur in the context of acquired structural heart disease. Altered functional expression of ionic currents, often referred to as electrical remodeling, is prominently associated with arrhythmias in complex polygenic disorders such as atrial fibrillation (AF) and ventricular arrhythmias associated with heart failure (HF) and myocardial ischemia/infarction. For example, the electrical remodeling characteristic of the failing heart enhances the predis-

**Figure 1.** $I_{Kr}$ channel assembly. a, Four $Kv_\alpha$-subunits (each with 6 transmembrane domains). b, $\beta$-Subunit proteins may be cytoplasmic proteins or transmembrane spanning proteins that interact with $\alpha$-subunits. c, $\alpha$-Subunits tetramerize to form a $K^+$-selective holochannel. $\beta$-Subunit proteins interact with $\alpha$-subunits in various stoichiometric ratios to modulate channel function.

**Figure 2.** Depolarizing and repolarizing ionic currents that underlie ventricular and atrial action potentials (AP) in human heart. Each phase of the action potential is labeled. A schematic of the time course of each current is shown, and the gene/gene product that underlies the current is indicated.
position to both atrial and ventricular arrhythmias and increases the risk of lethal proarrhythmic complications of antiarrhythmic drugs.

**LQTS and Other Syndromes That Alter Repolarization**

Congenital LQTS is an inherited disorder characterized by prolonged ventricular repolarization on the ECG (ie, QT prolongation) and a predisposition for ventricular tachyarrhythmias. Syncope and sudden death in LQTS patients may result from a distinctive polymorphic ventricular tachycardia (VT) called torsades de pointes (TdP). This polymorphic VT has a characteristic undulating axis that can degenerate into ventricular fibrillation (VF), culminating in death. TdP is commonly initiated with abrupt increases in sympathetic tone as might occur with fright, emotional distress, or physical activity. It has been suggested that triggers may be genotype specific.

The prevalence of LQTS is estimated to be between 1 in 3000 to 5000 individuals, with onset of symptoms typically occurring within the first 2 decades of life. LQTS has a wide spectrum of presentations, ranging from marked prolongation of the QT interval and recurrent syncope to subclinical forms with borderline QT prolongation and no arrhythmias. Perhaps the most difficult challenge in managing patients with LQTS is assessing their risk for SCD. Even now in the postgenomic era, clinical features such as congenital deafness, a prior history of syncope and/or tachyarrhythmia, female gender, family history of SCD, and the degree of QT prolongation are important determinants of the risk of SCD.8

In 1995, through a combination of positional cloning and candidate gene approaches, Keating and colleagues described mutations in ion channel genes in the autosomal dominant form of LQTS. Over the last decade, hundreds of distinct mutations in disease genes at 6 additional loci have been linked to the LQTS. Of the 6 disease genes that have been identified, 2 encode K⁺ channel β-subunits, 2 encode K⁺ channel α-subunits, 2 encode K⁺ channel β-subunits, and 1 encodes the voltage-gated Na⁺ channel. Recently, a mutation in ankyrin B (ANK2), a scaffolding protein, has been described in LQTS4, the only nonchannel disease gene described, although this protein clearly influences the functional expression of a number of ion channel and transporter proteins.

LQTS is characterized by genetic heterogeneity. Altered expression and/or function of ion channel subunits could result in action potential prolongation by either enhancing depolarizing or reducing repolarizing currents. The details of the changes depend on the specific genotype, but the final common pathway is action potential prolongation and decreased repolarizing reserve, resulting in a diminished capacity of the ventricular cell to respond to additional stresses that impair repolarization such as hypokalemia, hypomagnesemia, and drugs with class III antiarrhythmic action.

Na⁺ and K⁺ currents have disparate effects on the action potential duration: increases in I_

\[I_{Na} \text{ and } I_K\]

tend to depolarize the myocyte and therefore lengthen the action potential; alternatively, reduced K current also lengthens the action potential. The molecular genetics of LQTS are consistent with the functional effects on the ion channel genes; mutations in SCN5A tend to increase function (gain-of-function mutations), whereas mutations in K⁺ channel genes reduce or eliminate the function of the gene product or alter its trafficking to the cell membrane. In some cases, mutant channels retain the ability to combine with normal subunits and in doing so render the holochannel nonfunctional and therefore reduce the pool of functional subunits from which intact functional K⁺ channels can be synthesized (dominant negative effect). In fact, as predicted by the autosomal dominant inheritance, only 1 copy of the mutated gene is necessary to produce the clinical syndrome.

The rapid and slow components of the delayed rectifier potassium current I_

\[I_{Ks}\]

and I_

\[I_{Kr}\]

are critical to phase 3 (Figure 2) of the ventricular action potential and are mutated in different forms of LQTS. I_

\[I_{Kr}\]

is formed by the coassembly of the

<p>| Primary Electric Diseases Producing Ventricular Arrhythmias |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>Protein</th>
<th>Frequency</th>
<th>SCD Incidence</th>
<th>Inheritance Pattern</th>
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<tr>
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<td>11p15</td>
<td>KCNQ1</td>
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<td>7q35</td>
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<td>Na channel</td>
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<td>Ankyrin B</td>
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<td>21q22</td>
<td>KCNE1</td>
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<tr>
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<tr>
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<td>KCNH2</td>
<td>hERG (I(_K))</td>
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<td>11</td>
<td>KCNQ1</td>
<td>KvLQT1 (I(_K))</td>
<td>Rare</td>
<td>AD</td>
</tr>
<tr>
<td>Idiopathic VF (Brugada syndrome)</td>
<td>3</td>
<td>SCN5A (&gt;30)</td>
<td>Na channel</td>
<td></td>
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<td>CASQ2</td>
<td>Calsequestrin</td>
<td></td>
<td>AR</td>
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</tbody>
</table>

AD indicates autosomal dominant; AR, autosomal recessive.
**KCNQ1** (KVLQT1) and the **KCN1** (minK accessory subunit) gene products. **KCN1** is one of 2 genes on chromosome 21 mutated in LQTS. Mutations in **KCNQ1** and **KCN2** are also associated with the Jervell Lange-Nielsen (autosomal recessive) variants of LQTS.

LQTS2 is caused by mutations in a potassium channel known as the human ether a-go-go–related gene (hERG), which is encoded by **KCNH2** after the effects of the gene on *Drosophila*. hERG putatively combines with MiRP-1 encoded by **KCN2** to generate I<sub>Ks</sub>; mutations in **KCNH2** may also produce LQTS. I<sub>Ks</sub> is the target of a number of clinically important antiarrhythmic drugs with so-called class III (QT-interval prolonging) action, such as sotalol, dofetilide, and amiiodarone. The hERG channel also has a cyclic nucleotide binding domain in its C-terminus providing a link to the adrenergically mediated triggering of arrhythmic events. Mutations or polymorphisms in **KCNQ1**, **KCN1**, **KCN2**, and **KCNH2** have been associated with autosomal dominant and recessive forms of LQTS<sup>13</sup> and apparently acquired, drug-induced TdP.

Andersen syndrome is a rare sporadic or autosomal dominant disorder characterized by periodic paralysis, cardiac arrhythmias, short stature, scoliosis, clinodactyly, and dysmorphic facies.<sup>14</sup> Patients with Andersen syndrome exhibit a number of ventricular arrhythmias including TdP and bidirectional VT, thus sharing an electrophysiological functional defect with the canonical forms of LQTS. Mutations in **KCNJ2**, the gene that encodes the α-subunit of the inward rectifier K<sup>+</sup> channel (Kir2.1), have been identified in several families with this syndrome.<sup>3</sup> Hence, an ion channel that is essential for normal cardiac excitability also appears to play a critical role in development.

Timothy syndrome is a rare sporadic disorder characterized by multiorgan dysfunction, including cardiac arrhythmias, congenital heart disease, syndactyly, immune deficiency, and autism. Patients with Timothy syndrome exhibit severe prolongation of QT interval and have a predilection for life-threatening ventricular arrhythmias. De novo missense mutations in the L-type Ca<sup>2+</sup> channel α-subunit, Cav1.2, that have been described in Timothy syndrome result in maintained inward Ca<sup>2+</sup> currents by causing nearly complete loss of voltage-dependent channel inactivation.<sup>4</sup> This gain-of-function mutation results in prolongation of the cardiac action potential and likely serves as the mechanism for arrhythmia susceptibility.

The importance of correlating protein function with specific mutations and clinical phenotype is illustrated by the **KCNQ1** gene mutation resulting in a gain of function of I<sub>Ks</sub>, leading to accelerated repolarization, short QT intervals, and SCD.<sup>15</sup> Mutations in the **KCNQ1** gene have now been associated with 3 diseases including LQTS, SQTS, and familial AF. To add to the complexity of genotype-phenotype correlation is the description of a single large family with nocturnal death, ECG features of LQTS, and familial idiopathic VF. Genetic analysis revealed an identical mutation in the cardiac Na<sup>+</sup> channel in affected individuals that was associated with an overlap syndrome exhibiting features of both LQTS and idiopathic VF.<sup>16</sup> Experimental and simulation studies of this **SCN5A** mutation suggest mechanisms that may produce both electrophysiological phenotypes.<sup>16,17</sup> Such studies highlight the hazards of predicting phenotype on the basis of grouping of mutations by genetic loci or by association with a single gene mutation.

TdP leading to SCD remains the most feared manifestation of LQTS. Reduced repolarization reserve due to previously described ion channel mutations contributes to action potential prolongation. The extended plateau phase results in repolarization instability; thus, slight increases in depolarizing current can generate secondary depolarizations during the plateau or early repolarization phases of the action potential known as early afterdepolarizations (EADs).<sup>18</sup> The resulting EADs may initiate polymorphic VTs.<sup>19</sup> Well-described spatial differences in action potential duration or dispersion of repolarization have been proposed as a mechanism for TdP resulting from functional reentry (Figure 3). Spatial differences in action potential duration create pockets of excitable myocardium (secondary to extended refractory periods) that form regions of block and promote reentrant arrhythmias. Pharmacological models of LQTS have shown exaggerated dispersion of repolarization across the transmural wall, leading to local block and polymorphic reentrant arrhythmias.<sup>19,20</sup> EAD-mediated triggered activity and functional reentry are not mutually exclusive mechanisms, and both may contribute to the genesis of TdP.

**Brugada Syndrome**

Idiopathic VF in the setting of right ventricular ECG abnormalities and the absence of structural heart disease is often referred to as Brugada syndrome. The syndrome of sudden unexpected right precordial ECG abnormalities was described as early as the 1950s.<sup>21</sup> In the 1990s, Brugada and Brugada<sup>22</sup> described a cohort of patients that had no apparent structural heart disease, right ventricular ECG abnormalities, and a propensity to die suddenly. It is now recognized that idiopathic VF with right precordial ECG abnormalities is worldwide in distribution, with a high prevalence in Southeast Asia,<sup>23,24</sup> where it exhibits a striking male predominance (8:1),<sup>25</sup> distinct from that in Western cohorts.<sup>25,26</sup> Idiopathic VF is a highly lethal disease with a 40% survival at 5 years in high-risk patients.<sup>25–27</sup>

Patients with Brugada syndrome exhibit a spectrum of right precordial ST abnormalities in leads V<sub>1</sub> through V<sub>3</sub> from most (type I) to least (type III) severe in both appearance and prognosis. An ST-segment pattern is referred to as spontaneous if it is present on the resting ECG; however, the ECG changes are dynamic, and patterns may vary in the same patient. Thus, repeated recordings may be required to make the diagnosis. Antiarrhythmic drugs with class I action (flecainide, procainamide, ajmaline) have been used to unmask and exaggerate the ST-segment changes in IVF.

The Brugada syndrome has been linked to mutations in the Na<sup>+</sup> channel α-subunit, **SCN5A**,<sup>28</sup> but the syndrome is genetically heterogeneous. In the largest genotyped cohort reported to date, only 42% of 200 subjects (proband and family members) and only 20% of probands harbored **SCN5A** mutations.<sup>25</sup> There have been >30 different mutations in **SCN5A** that have been associated with Brugada syndrome. A consistent theme has been the functional reduction in peak
Na⁺ current; however, mutations have been described that produce overlap syndromes of Brugada syndrome and LQTS associated with multiple defects in channel function.16 The proposed mechanisms of the ECG abnormalities and arrhythmia induction in the SCN5A-linked forms of Brugada syndrome involve the imbalance of ionic currents during phase 1 repolarization. The deep phase 1 notch in the epicardial action potential, particularly prominent in the right ventricle, renders it susceptible to the effects of a reduction in the Na⁺ current. The reduction in Na⁺ current establishes a steep voltage gradient across the right ventricular wall (J-point elevation and ST-segment changes) due to short-circuiting of the epicardial action potential with extreme shortening. The imbalance of currents allows for reactivation of the right ventricular epicardium by neighboring regions of myocardium, with longer action potentials producing functional reentry, commonly referred to as phase 2 reentry.29 Support for this hypothesis in humans comes from a small study of monophasic action potential recordings in patients with Brugada syndrome during chest surgery.30

Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT is a heritable disorder that presents as exercise- or stress-induced ventricular arrhythmias, syncope, or sudden death. Originally described in children,31 more recent studies suggest that ventricular arrhythmias may begin in adulthood.32–34 In patients with CPVT who have been monitored during exercise, several types of malignant ventricular arrhythmias have been described, including polymorphic VT, bidirectional VT (exhibiting a beat-to-beat alternation of the QRS axis), and VF. This syndrome is genetically heterogeneous, with both autosomal dominant and autosomal recessive transmission. Disease-causing mutations in RYR232–34 and calsequestrin (CSQ)35 have been identified, the former segregating as dominant and the latter as recessive traits. More than 20 different mutations in functionally important domains of RYR2 have already been described in CPVT.32–34 There are a number of families with mutations that do not map to either the RYR2 or CSQ loci; thus, there is at least 1 and probably several additional disease genes associated with this disorder. RYR2 and CSQ are molecules that are central to normal Ca²⁺ homeostasis of the cardiac myocyte. Mutations that produce functional abnormalities in either of these molecules can produce cellular Ca²⁺ overload and lead to arrhythmias induced by abnormalities of repolarization known as delayed afterdepolarizations (DADs). DADs occur at the completion of the cardiac action potential and are initiated by abnormal Ca²⁺ release from the sarcoplasmic reticulum and subsequent activation of a transient inward depolarizing current, which drives the transmembrane potential toward 0 mV (Figure 4). Inherited abnormalities in the ryanodine receptor or associated proteins have been shown to result in a leaky sarcoplasmic reticulum and cytosolic calcium overload, thus providing a link between abnormal calcium handling and triggered arrhythmias.36 Notably, HF is characterized by abnormalities of calcium handling and increased sympathetic tone and may also exhibit DAD-induced triggered ventricular arrhythmias.37

Familial Supraventricular Arrhythmias and Conduction System Disease

Familial forms of AF were first described over 6 decades ago.38,39 Since then, a number of families with heritable AF have been described. Linkage analysis of 4 families with autosomal dominant AF identified 2 genetic loci, 10q22-q24 and 6q14-q16; however, candidate gene approaches have yet to identify specific gene(s).40,41 Recently, several Chinese kindreds with autosomal dominant AF have been linked to mutations in KCNQ1 and KCNE2.42,43 In contrast to LQTS1,
both mutations are associated with a gain of function in a background current composed of KCNQ1 and KCNE2 in cell expression systems, predicting shortening of the atrial action potential, which is consistent with the electrical remodeling observed in rapid atrial pacing–induced AF.\textsuperscript{44–46}

Patients with KCNQ1-associated familial AF did not exhibit QT shortening but instead had modest prolongation of the QT interval consistent with a divergent effect of KCNQ1 mutations on \( I_{Ks} \) and the background K\(^+\) current, highlighting the importance of additional genetic and/or environmental contributors to the electrophysiological phenotype.\textsuperscript{42} Shortening of the atrial action potential leads to a reduction in the wavelength of conduction through atrial tissue and, in the setting of inhomogeneous shortening, the possibility for functional reentry and or rapid conduction in the setting of a primary driver (so-called mother rotor\textsuperscript{47}) for AF.

**Acquired Arrhythmias: AF**

In contrast to rare monogenic arrhythmias, the most frequent cardiac rhythm disorders commonly occur in the context of structural heart disease. Acquired arrhythmias are dependent on complex interactions between the myocardial substrate and triggers that define the overall risk of arrhythmia susceptibility (Figure 5). The risk of cardiac arrhythmias is in part genetically determined; population-based studies of sudden death demonstrate an increased risk of SCD among patients who have a parental history of cardiac arrest.\textsuperscript{48,49} The genetic basis for this increased risk is not limited to variations in the disease genes implicated in rare inherited arrhythmia syndromes. Polymorphisms of genes that alter the structure or excitability of the arrhythmic myocardial substrate, as well as those that generate triggers (eg, metabolism and energy utilization, thrombosis, and inflammation), will influence arrhythmic risk.

The single most important factor contributing to the risk of common acquired arrhythmias is the presence of structural heart disease. For example, myocardial infarction with scar formation and left ventricular dysfunction are both associated with dramatic increases in arrhythmia susceptibility. Structural and electrical remodeling in response to myocardial injury, altered hemodynamic loads, and changes in neurohormonal signaling can lead to alterations in ion channel function, intracellular calcium handling, intercellular communication, and the composition of the extracellular matrix, all of
which conspire to create a substrate for both atrial and ventricular arrhythmias. A number of other concomitant factors, including electrolyte imbalance, neurohumoral activation, pharmacological therapy, and ischemia, can serve as triggers for arrhythmia initiation.

AF is associated with multiple cellular and tissue electrophysiological changes that promote the maintenance and recurrence of the arrhythmia after cardioversion.50,51 The progressive nature of AF lends support to the hypothesis that electrical and structural remodeling are key components of arrhythmogenesis. Several distinct types of remodeling have been associated with AF. Atrial tachycardia–induced remodeling is associated with shortening of atrial refractoriness. In contrast, atrial remodeling in the aged and failing heart is associated with prominent fibrosis, producing heterogeneous slowing of conduction velocity in the heart and prolongation of atrial refractoriness. In either case, there is a reduction in the cardiac wavelength (\(\lambda\)), which is defined as the physical distance traveled by an electrical impulse in one refractory period and mathematically is the product of the conduction velocity and refractory period (or action potential duration). Reentry is critically dependent on the wavelength being shorter than the total length of the reentrant pathway (path length). If the wavelength exceeds the path length, reentry cannot be established because as the wavelength approaches the path length, the wave head encroaches on the refractory tail, resulting in termination of reentrant activation. A reduction in wavelength improves the stability of a reentrant circuit and increases the allowable number of independent reentrant circuits in a given area of tissue, thereby promoting the conditions necessary for existence of multiple reentrant circuits.

Three main mechanisms have been proposed for the initiation and maintenance of AF. Rapid firing from a single ectopic focus (eg, pulmonary veins) can produce atrial tachycardia, AF, and atrial electrophysiological remodeling that serves to perpetuate AF (“AF begets AF”).51 A single reentrant circuit or motor rotor may drive activation of the atria with fibrillatory conduction, with the result of interaction of the high-frequency activation wave fronts with heterogeneous atrial tissue generating random propagation of the activation wave(s), producing characteristically irregular rhythm. Ectopic activation and single reentry circuits may both be mechanistically linked through remodeling of the atria to the multiple wavelet mechanism of AF.32 The latter is the result of a number of distinct electrical circuits activating the atria. Indeed, these mechanisms are not mutually exclusive. In fact, the multiple wavelet reentry hypothesis has been proposed as a final common pathway for AF.

Reduced functional expression of L-type Ca\(^{2+}\) channels43 is thought to underlie the shortening of action potential duration associated with tachycardia remodeling of the atria. Reductions in the transient outward current (\(I_{to}\)) and alterations in the inward rectifier current (\(I_{Ki}\)) and acetylcholine-sensitive K\(^{+}\) channels (\(I_{KACO}\))53 have been noted in AF models; however, their electrophysiological significance remains unclear.44,46 The altered functional expression of these ionic currents is spatially inhomogeneous, tending to further exaggerate the electrophysiological heterogeneity of the atria.50,54 Atrial tachycardia may also influence currents that hasten refractoriness in pulmonary vein myocytes and serve as a trigger or source of AF.55 Disparities in the time course of shortening of atrial refractoriness and susceptibility to AF suggest that other factors may be important in tachycardia-induced atrial remodeling. The importance of alterations in intracellular Ca\(^{2+}\) homeostasis in atrial myocyte remodeling has recently been demonstrated. In a mouse atrial cell line, rapid stimulation in vitro led to reduction of sarcosommal L-type Ca\(^{2+}\) channel expression and structural changes (myolysis and nuclear condensation).56 Studies in humans suggest that atrial tachycardia remodeling may be clinically significant and to some degree reversible, with both acute and chronic normalization of atrial refractoriness and improvement in sinus node function.

The type of atrial remodeling that predisposes to AF is context dependent. For example, experimental congestive HF models that promote AF are associated with atrial action potential prolongation and prominent alterations in conduction, arguing for structural or intercellular ion channel remodeling as a prominent feature of AF in HF. Fibrosis interspersed between myocyte bundles is a prominent feature of HF-induced AF models. In animal models of AF associated with HF, quantitative and qualitative changes in the interstium have been documented. Atrial collagen synthesis is increased and matrix metalloproteinases are activated in HF.59,60 In fact, in the pacing tachycardia HF model, the atria exhibit a more intense inflammatory and fibrotic phenotype than the ventricles.61 Intercellular ion channels or connexins at gap junctions are major determinants of conduction velocity and directional differences in wave front propagation (referred to as anisotropy). In AF they have been shown to be more heterogeneously distributed and in some studies decreased. These spatial heterogeneities in connexin expression may contribute to wave front fragmentation and increased dispersion of repolarization. Some studies have shown that connexin40, an isoform prominently expressed in the atrium, is decreased and more heterogeneously distributed in animal models of AF,62 although this is not a universal finding.63 In a recent study, 2 polymorphisms of the human connexin40 gene have been linked to indices of increased spatial dispersion of atrial refractoriness and an increased risk of AF.64 Such changes in tissue architecture and heterogeneities in cell coupling produce slowed and heterogeneous conduction and may act to increase dispersion of repolarization, thus creating a substrate ripe for reentry (Figure 6). Reversal of HF in animal models has been associated with resolution of ionic remodeling in atrium but persistence of atrial fibrosis and susceptibility to induced AF.65 Thus, fibrosis appears to be sufficient to generate a profibrillatory substrate in the atrium.

The pulmonary veins contain myocytes that are a source of ectopic activity that may trigger or maintain atrial arrhythmias in humans. Indeed, isolation of the pulmonary veins from the body of the left atrium has proven to be curative in some patients with AF.66 The diseased atrium is associated with both structural and functional remodeling of the pulmonary veins. Animal models of tachycardia-induced HF are characterized by enhanced susceptibility to atrial tachycardia, with a focal origin often in the pulmonary veins.67 DADs
have been recorded in pulmonary vein myocytes, suggesting triggered activity related to Ca$^{2+}$ overload as a mechanism of pulmonary vein ectopic activity$^{68}$; a relevant molecular correlate of DAD-mediated triggered activity is upregulation of the electrogenic Na$^+$-Ca$^{2+}$ exchanger in atrial myocytes isolated from failing hearts.$^{69}$

Several studies support the relevance of the electrophysiological remodeling in experimental AF to human arrhythmia. Action potential shortening with downregulation of Ca$^{2+}$ currents has been demonstrated in cells isolated from human atria.$^{45}$ Altered atrial refractory period dynamics have been demonstrated in patients who have undergone induction of AF under controlled conditions in the electrophysiology laboratory.$^{57}$ Patients with HF undergoing electroanatomic mapping exhibit regional conduction disturbances and enhanced susceptibility to AF.$^{70}$ Atrial extracellular matrix remodeling in the explanted hearts of patients undergoing cardiac transplantation reveals increased atrial fibrosis, downregulation of tissue inhibitor of matrix metalloproteinase-2, upregulation of matrix metalloproteinase-2, and an increased level of collagen type I.$^{71}$ These data suggest that remodeling of tissue structure may constitute a promising target with antifibrillatory action. Angiotensin-converting enzyme inhibitors will reduce atrial fibrosis and AF inducibility in animal models, and post hoc analysis of HF treatment trials suggests that angiotensin-converting enzyme inhibitor treatment is associated with a lower incidence of AF. The utility of inhibiting the renin-angiotensin-aldosterone pathway awaits testing in randomized clinical trials.

**Acquired Ventricular Arrhythmias**

Action potential prolongation is an electrophysiological hallmark of ventricular myocytes isolated from failing or hypertrophied hearts, independent of etiology. It is not surprising, however, that different models of ventricular dysfunction are associated with distinct patterns of remodeling of ion channel functional expression. There are at least 2 mechanisms that serve to explain the prolongation in action potential duration and alteration of action potential dynamics in the hypertrophied and failing heart, downregulation of repolarizing K$^+$ currents, and alterations in intracellular calcium handling (for review, see Tomaselli and Marban$^6$).

Functional downregulation of K$^+$ currents has been extensively documented in human and animal models of HF. The aggregate electrophysiological effect is a reduction in repolarization reserve, rendering the ventricular myocardium susceptible to EADs and functional reentry resulting from exaggerated temporal and spatial dispersion of repolarization. Downregulation of each of the major repolarizing K$^+$ currents, I$_{to}$, I$_{Kr}$, I$_{Ks}$, and I$_{K1}$, has been described in HF. The specific impact on the action potential duration and action potential dynamics as well as the molecular mechanisms of reduction in current density varies depending on the species and etiology of HF. I$_{to}$ is a rapidly activating and inactivating repolarizing current that occurs early in the plateau phase and is likely to have an indirect effect on action potential duration through its effects on ensuing plateau currents. Computer models of the cardiac action potential reveal impaired action potential duration rate adaptation in cells with diminished I$_{to}$, suggesting that sudden changes in heart rate as seen with premature ventricular contractions can result in enhanced spatial differences in action potential duration.$^{72}$ I$_{to}$ and I$_{Kr}$ are prominent repolarizing currents active during the plateau phase of the action potential and are altered in HF. Downregulation of both components of the delayed rectifier has been reported in models of cardiac hypertrophy and HF.$^{73-75}$ The inward rectifier current, I$_{K1}$, is responsible for setting the resting membrane potential and contributes to the terminal phase of repolarization. Ventricular myocytes isolated from failing human hearts and some animal models of HF demonstrate reduced I$_{K1}$ density.$^{76,77}$ In addition to prolongation of the action potential duration, alterations in the resting membrane current that accompanies reduced I$_{K1}$ density may enhance automaticity in failing ventricular myocytes.$^{78}$

Minor perturbations in depolarizing currents during the plateau phase of the action potential, a period of low current flow and high membrane resistance, can tilt the balance in favor of secondary depolarizations that result in triggered arrhythmias. In fact, animal studies of HF in which action potential duration prolongation is provoked with pharmaco-
logical agents demonstrate enhanced susceptibility to afterdepolarization-mediated ventricular tachyarrhythmias. 

Abnormalities in intracellular Ca\(^{2+}\) handling that characterize failing myocardium are responsible for altered ventricular mechanics and increased electrical instability. The ventricular action potential and intracellular Ca\(^{2+}\) homeostasis are linked through a number of mechanisms, including Ca\(^{2+}\)-mediated inactivation of the L-type Ca\(^{2+}\) channel, activation of a variety of Ca\(^{2+}\)-sensitive transporters, and the Na\(^+\)-Ca\(^{2+}\) exchanger. Cells isolated from failing human hearts exhibit no change or a slight decrease in L-type Ca\(^{2+}\) current density. Increased Na\(^+\)-Ca\(^{2+}\) exchanger current density and protein expression have been reported in the ventricles in some models of HF. Increased Na\(^+\)-Ca\(^{2+}\) exchanger current may contribute to the production of arrhythmias by altering the action potential profile or contributing to the generation of DADs and triggered arrhythmias. Indeed, human HF studies have correlated increased expression of Na\(^+\)-Ca\(^{2+}\) exchanger with increased incidence of DAD-mediated ventricular arrhythmias. Preliminary evidence suggests that selective pharmacological inhibition of the Na\(^+\)-Ca\(^{2+}\) exchanger may be a promising target for correcting cellular excitation-contraction coupling defects and reducing triggered activity in HF.

Alterations in ionic currents that accompany structural heart disease affect the steady state as well as the dynamic behavior of the action potential. In response to increased heart rates, myocardial cells dynamically adapt (shorten) their action potential duration. Electric restitution refers to the dependence of the action potential duration on the previous diastolic interval. This dependence is exaggerated in HF such that subtle changes in diastolic interval produce marked differences in action potential duration, accounting for large beat-to-beat changes in action potential duration or enhanced temporal lability of repolarization. Abnormal electrical restitution properties have been hypothesized to account for the transition from stable reentrant monomorphic VT to VF. Pharmacological treatment with Ca\(^{2+}\) channel blockers and bretylium have been shown to flatten the restitution slope (<1), reduce wave break, and prevent VF.

Cellular electrophysiological abnormalities are prominent in the structurally diseased heart and are complicated by the presence of abnormalities of the electrical network properties of the heart. The altered composition of the interstitium and intercellular coupling reduce conduction velocity in the failing heart. Slowed conduction velocity leading to shortened wavelengths and reduced cellular coupling may be an important contributor to the production of reentrant ventricular arrhythmias in HF. Electrophysiological indices of depressed conduction velocity, including delayed paced ventricular activation and fractionated electrograms, are observed in diseased hearts at risk for SCD. The molecular determinants of conduction velocity in myocardial tissue include the quantity and pattern of fibrous tissue, the density and distribution of gap junctions, and the availability of Na\(^+\) current, all of which are altered in some models of HF. In histological studies of failing human hearts, increased density and patterns of tissue fibrosis correlate with depressed conduction velocity and increased directional differences in wave front propagation (tissue anisotropy). Areas of patchy fibrosis with long, dense groups of strands create isolating barriers and discontinuities that may cause unidirectional block, wave break, and reentry.

In addition to fibrosis, the speed and direction of wave front propagation are significantly influenced by the location and density of gap junctions. Alterations in the density and distribution of gap junction channel proteins have been described in ischemic, hypertrophic, and dilated hearts. Connexin43, the major gap junction protein in the ventricle, is redistributed from the intercalated disk to the lateral cell border, accounting in part for abnormal conduction in HF. Such a change in connexin expression may promote reentry by slowing conduction velocity and/or uncoupling myocytes. Poor electrotonic coupling between adjacent cells in the diseased heart contributes to regional inhomogeneities of action potential duration, predisposing to local conduction block and reentrant excitation. Alterations in Na\(^+\) current may also contribute to conduction slowing in the diseased heart. Myocardial infarction models have shown slow conduction and reduced expression of Na\(^+\) current in regions adjacent to the infarcted tissue shortly after coronary artery ligation. Several chronic infarction models have been associated with a reduction in Na\(^+\) current density. Further functional and molecular studies will be required to elucidate the relative contribution of interstitial changes, ionic remodeling, and cell-to-cell coupling to conduction velocity and arrhythmogenesis.

The manifestations of coronary artery disease create distinct and time-varying changes in the myocardium that enhance the risk of arrhythmias. The time course of cellular electrophysiological changes after coronary artery ligation has been characterized in infarcted tissue and in areas remote from the infarct. Clearly, scar formation after myocardial infarction is a major contributor to arrhythmia susceptibility. However, the healing phase preceding scar formation is also associated with an increased risk of sustained ventricular tachyarrhythmias. The acute electrophysiological response of cells adjacent to the infarcted territory is progressive shortening of action potential duration, followed by a return to near-normal action potential duration by 2 months. Cells isolated from noninfarcted regions demonstrate cellular hypertrophy and action potential duration prolongation. Action potential duration prolongation is thought to be secondary to downregulation of repolarizing currents and upregulation of depolarizing calcium currents (L-type Ca\(^{2+}\) current). Studies of paired myocytes isolated from the epicardial border zone of a myocardial infarction have shown decreased side-to-side coupling with no change in overall connexin43 expression. Heterogeneities in action potential duration and altered coupling between infarct border zone tissue and surrounding myocardium create a region of conduction slowing susceptible to local conduction block necessary for reentrant excitation.

Hibernating myocardium, defined as cardiac tissue with reduced baseline blood flow and contractile dysfunction that recovers viability on revascularization, is prevalent in patients with ischemic cardiomyopathy. In fact, it occurs in as many as 40% to 60% of patients with ischemic heart disease and contributes to their relatively high risk of SCD.
nating myocardium is a proarrhythmic substrate that is independent of myocardial necrosis or scar. Studies of electrical remodeling in models of hibernating myocardium have demonstrated prolonged action potential duration and impaired intracellular Ca\(^{2+}\) handling. Preliminary studies have noted an increase in the depolarizing L-type Ca current; however, evaluation of repolarizing K\(^+\) currents has not been reported. Reperfusion of ischemic myocardium, as may occur in patients with coronary artery disease, is associated with increased susceptibility to VF. Electrophysiological cell and tissue properties that characterize ischemic and reperfused myocardium help to rationalize the frequency of reperfusion arrhythmias. During ischemia there is increased intracellular resistance and shortened action potential durations in whole-tissue preparations. Additionally, high intracellular resistance, caused by gap junction uncoupling, results in poor cell-to-cell electrical coupling and conduction slowing. Soon after reperfusion there is a rapid restoration of action potential duration to near-normal durations; however, persistent cellular uncoupling enhances spatial differences in repolarization between the ischemic and nonischemic zones, thus promoting reentry. Consistent with this hypothesis, studies have shown multiple reentrant circuits in the ischemic area during reperfusion-related VF.

**Clinical Implications**

Novel strategies that leverage our understanding of molecular mechanisms to identify clinical predictors of SCD continue to rapidly evolve. Until recently, genetic screening for primary electrical diseases was not available to practitioners outside of specialized academic centers. In 2005, the FAMILION test was introduced to screen for selected mutations in Na\(^+\) and K\(^+\) channels (SCN5A, KCNQ1, KCNH2, KCNE1, KCNE2). Mutations in these genes are thought to account for 50 to 75\% of cases of congenital LQTS and 15\% to 30\% of Brugada syndrome cases. The most recent study to integrate LQTS genotype as a risk-stratifying parameter characterized 647 patients with mutations at the LQT51, LQT52, and LQT3 loci and followed them prospectively for their first cardiac event (syncope, cardiac arrest, or SCD before age 40 years). The incidence of a first cardiac event before age 40 years was lowest among those patients with mutations at the LQT51 locus (30\%) compared with those with mutations at the LQT52 (46\%) and LQT3 (42\%) locus.\(^{120}\) Prognosis was accurately assessed with the use of genotype, gender, and corrected QT interval in patients with LQTS. Although promising, the role of genotyping patients with suspected inherited cardiac arrhythmias remains controversial because patients with single gene mutations often exhibit large variability in phenotypic expressivity. Ultimately, genotyping patients and family members may be useful prognostically and in defining genotype-specific antiarrhythmic therapy.

Antiarrhythmic drugs have exhibited limited efficacy in the treatment of serious arrhythmias and have often been relegated to second-line therapy secondary to proarrhythmic side effects in patients with structural heart disease. Despite our improved understanding of the molecular basis of inherited cardiac arrhythmias, pharmacotherapeutic targets to specific channel proteins have both limited efficacy and liabilities that relate to the pharmacodynamic properties of the drugs and spatial/temporal heterogeneities in channel expression and therefore action potential profile and duration. Newer therapeutic agents may target multiple ion channels and use several modes of action. In HF, novel drug design will likely focus on ion channels, exchangers, and interacting subunits that regulate intracellular calcium as well as proteins and pathways that regulate the constitution of tissue structure.

The generation of cardiac arrhythmias requires the presence of a susceptible myocardial substrate and an appropriate trigger. Although any heart may serve as a substrate for the development of a potentially serious cardiac arrhythmia, in structurally normal hearts this is rare and requires highly potent triggers. Alterations of the cellular and tissue electrophysiological properties of the heart mediate enhanced susceptibility to cardiac arrhythmias. These changes include alterations in conduction and changes in the spatial and temporal features of electrical recovery reflected in the action potential. Changes in the functional expression of ionic currents and transporters mediate the changes in action potential profile and cellular excitability. Extracardiac influences (eg, neurohumoral activation) may modulate the cardiac substrate and serve as arrhythmia triggers in the setting of structural heart disease. An individual’s genetic makeup will influence one’s risk of development of an arrhythmia, and in rare cases mutations in genes that influence cardiac excitability are sufficient to cause life-threatening arrhythmias. Understanding the basic biology of arrhythmogenesis holds the promise of identifying novel targets for the treatment of arrhythmias, including prevention of the development of structural changes in the heart that form the substrate for cardiac rhythm disturbances.

**Disclosure**

Dr Tomaselli has served as a consultant to Pfizer.

**References**


42. Shah et al. Molecular Basis of Arrhythmias


