Cellular Arrhythmogenic Effects of Congenital and Acquired Long-QT Syndrome in the Heterogeneous Myocardium

Prakash C. Viswanathan, PhD; Yoram Rudy, PhD

Background—Certain alterations by mutations or drugs of the potassium currents $I_{K_s}$ and $I_{Kr}$ and the sodium current $I_{Na}$ give rise to several types of the long-QT syndrome. $I_{Kr}$ is heterogeneously distributed across the ventricular wall.

Methods and Results—We investigated the effects of reducing $I_{K_s}$ or $I_{Kr}$ or enhancing late $I_{Na}$ (to simulate the 3 forms of long-QT syndrome) on action potential duration (APD) in the context of $I_{K_s}$ heterogeneity. We introduced $I_{K_s}$ heterogeneity in the Luo-Rudy dynamic cell model to simulate epicardial, endocardial, and midmyocardial (M) cells. Results demonstrated higher susceptibility of M cells to the development of arrhythmogenic early afterdepolarizations (EADs) in isolated cells and poorly coupled tissue. An important observation is that $I_{K_s}$ block or late $I_{Na}$ acts to increase APD differences between the cell types, whereas $I_{K_s}$ block minimizes such differences. Also, for normal transverse coupling, EADs develop in the endocardial region rather than in the M region as the result of strong electrotonic interaction.

Conclusions—$I_{K_s}$ heterogeneity and intercellular coupling strongly influence EAD development during interventions or disorders that prolong APD. M cells in isolation or in poorly coupled tissue are more susceptible to EAD development than epicardial or endocardial cells. In well-coupled myocardium, EAD formation in the subendocardium can be the source of focal arrhythmias or provide the trigger for reentrant excitation. The efficacy of $I_{K_s}$ block in minimizing APD dispersion could have important implications for antiarrhythmic therapy. (Circulation. 2000;101:1192-1198.)

Key Words: action potentials ▪ cells ▪ long-QT syndrome ▪ arrhythmia

A subpopulation of cells (midmyocardial [M] cells) has been described1–2 in the ventricular wall. These cells display a longer action potential duration (APD) and a steeper dependence of APD on rate than epicardial or endocardial cells. M cells display greater responsiveness to interventions that prolong APD (eg, agents with class III antiarrhythmic action) and a higher susceptibility to the development of arrhythmogenic early afterdepolarizations (EADs).3 These properties suggest that M cells play an important role in arrhythmias associated with abnormal repolarization such as the congenital or acquired long-QT syndrome (LQTS). We recently showed that differences in $I_{K_s}$ densities result in heterogeneity of the repolarization properties of cells.4 A smaller density of $I_{K_s}$ results in longer APD and its greater prolongation with slowing of rate, an experimentally observed behavior typical of M cells.5

The density of functional channels can be altered by disease, as occurs in the congenital LQTS, in which mutations in the genes that encode $I_{K_s}$ (KvLQT1 or MinK) or $I_{Kr}$ (HERG) act through a dominant negative mechanism to cause a loss of function of $I_{K_s}$ (LQT1) or $I_{Kr}$ (LQT2), thereby slowing action potential repolarization. LQT3 involves mutations in the SCN5A gene that cause incomplete inactivation of $I_{Na}$ and a persistent inward current that prolongs APD. Prolonged repolarization also can be acquired. Methanesulfonanilides (E-4031) block $I_{K_s}$ and chromanol 293B blocks $I_{Kr}$, whereas the neurotoxin anthopleurin A slows $I_{Na}$ inactivation, resulting in a sustained inward current during the action potential (AP) plateau. All these interventions prolong APD.

The different $I_{K_s}$/$I_{Kr}$ density ratios in different cell types and the fact that these currents are affected in the LQTS and by antiarrhythmic agents necessitates characterization of the cellular responses to such pathologies and interventions. In this study we used theoretical models of isolated cells and multicellular fibers to investigate the effects of heterogeneities of $I_{K_s}$ on steady-state APD and EAD formation during prolonged repolarization caused by the different LQTS types or antiarrhythmic agents that block $I_{Kr}$ or $I_{K_s}$.

Methods

The theoretical Luo-Rudy model of a mammalian ventricular action potential provides the basis for the simulations in this study (Figure

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From the Cardiac Bioelectricity Research and Training Center, Department of Physiology and Biophysics (P.C.V., Y.R.), and the Department of Biomedical Engineering (Y.R.), Case Western Reserve University, Cleveland, Ohio.

Correspondence to Yoram Rudy, PhD, Cardiac Bioelectricity Research and Training Center, 505 Wickenden Bldg, Case Western Reserve University, Cleveland, OH 44106-7207. E-mail yxr@po.cwru.edu

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1). The action potential is numerically reconstructed from ionic processes that are formulated on the basis of experimental data obtained mostly from the guinea pig. The model also accounts for processes that regulate dynamic concentration changes of Na\(^{1+}\), K\(^{+}\), and Ca\(^{2+}\). References 6 and 7 provide a detailed description of the cell model and a list of equations governing its behavior. The 3 different cell types (epicardial, midmyocardial, and endocardial) are formulated by altering \(I_{\text{Ks}}\) density while keeping \(I_{\text{Kr}}\) density constant. Heterogeneity of \(I_{\text{Ks}}\) density is introduced by altering its maximum conductance, \(G_{\text{Ks}}\).

**Acquired and Congenital Long-QT Syndrome**

Evidence suggests that congenital long-QT syndromes (LQTS) LQT1 and LQT2 involve reduction in the density of functional \(I_{\text{Ks}}\) or \(I_{\text{Kr}}\) channels, respectively, through a dominant negative mechanism. Acquired LQTS results from drugs that prolong action potential duration (APD) by blocking \(I_{\text{Ks}}\) or \(I_{\text{Kr}}\). In our studies we reduced the maximum conductance of \(I_{\text{Ks}}\) or \(I_{\text{Kr}}\) to represent the effects of the congenital or acquired LQTS. We simulated LQT3 by altering the steady-state inactivation of the \(h\) (fast) and \(j\) (slow) inactivation gates of \(I_{\text{Na}}\). This results in a persistent late current that is 0.2% of peak \(I_{\text{Na}}\) during a voltage clamp protocol (step from \(-120\) to \(-30\) mV). The overall behavior of the current is in good agreement with whole cell recordings of mutant \(I_{\text{Na}}\) channels.

**Protocols**

Cells were paced for 5 minutes at each cycle length (CL) to reach steady state. The effects of drugs were simulated by reducing \(I_{\text{Ks}}\) or \(I_{\text{Kr}}\) at steady state. Results are reported for CL=300 ms (rapid pacing) and CL=2000 ms (slow pacing). These CLs are in the range of clinically observed heart rates. APD was measured from stimulus onset to 90% repolarization (APD\(_{90}\)). Simulations were performed for 37°C.

**1D Fiber**

The theoretical fiber\(^{12}\) (Figure 1B) is composed of 190 Luo-Rudy cells. It contains an endocardial region (cells 1 to 80), M-cell region (81 to 110), and epicardial region (111 to 190). Gap-junction conductance (g\(_{\text{J}}\)) is homogeneous throughout the fiber and for different simulations varies from 2.5 \(\mu\)S (normal longitudinal coupling) to 0.025 \(\mu\)S (poor coupling). A stimulus is applied to cell 1 to simulate normal endocardial to epicardial activation. Pacing studies were conducted by stimulating cell 1 at CL=300 ms (3.3 Hz) or 2000 ms (0.5 Hz) for 90 seconds.

**Results**

**Reduction of \(I_{\text{Kr}}\) or Presence of Late \(I_{\text{Na}}\) Enhances APD Differences Between Isolated Cells of the Different Types. Reduction of \(I_{\text{Ks}}\) Eliminates Such Differences**

Figure 2 shows the effects of \(I_{\text{Ks}}\) or \(I_{\text{Kr}}\) block, simulating the effects of congenital or acquired LQT1 and LQT2, respectively, on APD during rapid pacing. \(I_{\text{Kr}}\) block prolongs M-cell APD more than that of epicardial or endocardial cells. In contrast, \(I_{\text{Ks}}\) block has a smaller effect on the M cell than on the other cell types. At a cycle length (CL)=300 ms, 100% \(I_{\text{Kr}}\) block prolongs APD by 20%, 36%, and 25% in epicardial cells, M cells, and endocardial cells, respectively, whereas 100% \(I_{\text{Ks}}\) block prolongs the respective APDs by 43%, 26%,

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**Figure 1. A, Schematic of the Luo-Rudy mammalian ventricular cell model. Details are provided in References 6 and 7. \(I_{\text{Ks}}, I_{\text{Kr}},\) and \(I_{\text{Na}}\) are highlighted to indicate their participation in congenital or acquired LQT1, LQT2, and LQT3. B, Multicellular fiber composed of Luo-Rudy cells interconnected by gap junctions. Spatial heterogeneity in the density of \(I_{\text{Ks}}\) is introduced to simulate the different cell types found in the myocardium.**

**Figure 2. Effect of \(I_{\text{Ks}}\) and \(I_{\text{Kr}}\) block on APD during fast pacing of isolated cells. Thick lines indicate control conditions; thin lines, conditions of block. Left, APs during 100% \(I_{\text{Ks}}\) block. Right, APs during 100% \(I_{\text{Kr}}\) block. APs are from epicardial cells (A), M cells (B), and endocardial cells (C). \(I_{\text{Ks}}\) block prolongs APD most in M cells, thereby increasing APD differences between cell types, whereas \(I_{\text{Kr}}\) block prolongs APD least in M cells, thereby reducing APD differences. Cells are paced at CL=300 ms. APD difference between M and epicardial cells under control conditions is 27 ms.**
and 37%. Figure 3 shows the effect of persistent $I_{\text{Na}}$ on APD of the 3 cell types at CL=300 ms. Late $I_{\text{Na}}$ prolongs APD of M cells more than that of epicardial or endocardial cells and increases APD differences between cell types.

Figure 3. Effect of late $I_{\text{Na}}$ on APD during fast pacing of isolated cells. APs are from different cell types for control (thick lines) and in presence of late $I_{\text{Na}}$ (thin lines) at CL=300 ms. Late $I_{\text{Na}}$ prolongs APD of M cells more than that of epicardial or endocardial cells and increases APD differences between cell types.

An important observation from Figures 2 and 3 is that $I_{\text{Kr}}$ block and late $I_{\text{Na}}$ act to increase APD differences between the cell types. In contrast, $I_{\text{Ks}}$ block acts to reduce such APD differences. Figure 4 shows APDs from the 3 cell types during different interventions (complete $I_{\text{Ks}}$ block, complete $I_{\text{Kr}}$ block, and in presence of late $I_{\text{Na}}$) at CL=300 ms. $I_{\text{Ks}}$ block decreases $D_{\text{APD}}$ ($D_{\text{APD}}_{\text{Epi}}-D_{\text{APD}}_{\text{M}}$), whereas $I_{\text{Kr}}$ block or presence of late $I_{\text{Na}}$ increases $D_{\text{APD}}$. In the absence of intervention, $D_{\text{APD}}$=27 ms. $I_{\text{Ks}}$ block or late $I_{\text{Na}}$ increases $D_{\text{APD}}$ to 53 or 55 ms, respectively; $I_{\text{Kr}}$ block reduces $D_{\text{APD}}$ to 17 ms.

Figure 5 shows the effect of 50% $I_{\text{Kr}}$ or $I_{\text{Ks}}$ block during slow pacing of isolated cells. Same format as Figure 2. CL=2000 ms. $I_{\text{Kr}}$ block but not $I_{\text{Ks}}$ block results in EADs in M cells. APD difference between M and epicardial cells under control conditions is 60 ms. AP with EAD repolarizes outside scale shown.

Effect of Gap-Junction Coupling on APD and Development of EADs

In the previous section we focused on the effects of $I_{\text{Ks}}$ and $I_{\text{Kr}}$ reduction and of late $I_{\text{Na}}$ on APD and the development of EADs in isolated cells. In the intact heart, cells are coupled through gap junctions and are subject to electrotonic interactions. In this section, we study the effects of intercellular coupling on the development of EADs during simulated LQTS.

Figure 7 shows APs (aligned for comparison) from the middle of each region of the multicellular fiber for CL=300 ms.
ms and gap-junctional conductance $g_j = 0.43 \mu S$ (corresponding to a velocity of 30 cm/s, typical of transmural propagation transverse to fibers). During control conditions, M-cell APD is longest (panel A), and the difference in APD between M and epi cells ($D_{APD} = APD_M - APD_{Epi}$) is $\approx 20$ ms. APD at $CL = 2000$ ms is $30$ ms (not shown). This suggests that baseline level of APD differences exists in the normal myocardium. On block of $I_{Kr}$ (panel B), APD differences are greatly reduced. For 100% $I_{Ks}$ block, $D_{APD}$ decreases to 6 ms. In contrast, complete $I_{Kr}$ block (panel C) or late $I_{Na}$ (panel D) increases $D_{APD}$ from 20 to 32 or 33 ms, respectively. This behavior is similar to that observed in isolated cells (Figure 6) in which $I_{Kr}$ block and late $I_{Na}$ enhanced the differences of APD between cell types, whereas $I_{Ks}$ block eliminated it.

Figure 8 shows APD along the multicellular fiber for longitudinal coupling (panel A, $g_j = 2.5 \mu S$, conduction velocity of 56 cm/s) and for transverse coupling as in Figure 7 (panel B, $g_j = 0.43 \mu S$). A 100% $I_{Ks}$ block or late $I_{Na}$ increases APD in the M region preferentially, thereby increasing APD differences between M and epi or endocardial cells (compared with control). A 100% $I_{Kr}$ block, on the other hand, decreases APD differences between M cells and other cell types.

The above studies were conducted at a short $CL$ of 300 ms. At this rate, APDs were significantly shorter than during slower pacing. At this fast rate, EADs did not develop during complete block of either $I_{Ks}$ or $I_{Kr}$ even during extreme gap-junctional uncoupling. Figure 9 shows APs of the middle cell from each region of the fiber for $CL = 2000$ ms with gap-junctional coupling of 0.43 $\mu S$ (panel A) or 0.025 $\mu S$ (corresponding to a slow velocity of 3.5 cm/s, observed during pathological conditions such as infarcition). For the normal transverse coupling ($g_j = 0.43 \mu S$), 85% reduction of $I_{Ks}$ results in the appearance of an EAD in the endocardial cell and not in the M cell, in contrast to the single cell behavior in which EADs developed in the M cell (Figure 5 and 6 and corresponding text). However, a similar degree of $I_{Ks}$ block on the background of pathologically reduced intercellular coupling resulted in the development of EADs in the M region (Figure 9B) similar to the isolated cell behavior. We also conducted simulations in which the pacing stimulus was applied epicardially or in the M region (not shown). In all cases, EADs develop in the endocardial region for 85% $I_{Ks}$ block when intercellular coupling is normal. This phenomenon highlights the importance of electrotonic influences in modulating the behavior of different cell types. During normal coupling, the epicardial region acts as a sink for axial current from the M region because of its shorter APD and earlier repolarization than that of the other regions. Note the existence of a large potential gradient between cells in the M and epicardial regions during the plateau and phase 3 of the AP (Figure 9A). This causes shortening of M-cell APD as axial current is lost to the epicardial region. Shortening of the APD prevents EAD development in the M region.

**Discussion**

We have demonstrated that changes in $I_{Ks}/I_{Kr}$ density ratios can explain heterogeneity of the repolarization properties of cells in the ventricular myocardium. Consistent with the experimentally observed behavior, simulated M cells could
be distinguished from epicardial and endocardial cells by their longer APD and greater APD prolongation with slowing of stimulation rate. In this study, we have investigated the rate-dependent effects of reduced \( I_{K_s} \) or \( I_{K_r} \), or the presence of late \( I_{K_s} \) or \( I_{K_r} \) to mimic the 3 forms of the LQTS and to simulate the effects of drugs with class III antiarrhythmic action. Effects on APD and the development of EADs were considered in isolated cells and in a multicellular fiber with varying degrees of gap-junctional coupling. Important findings of this study include the following: (1) At fast pacing, \( I_{K_s} \) block and late \( I_{K_s} \) prolong APD of isolated M cells more than that of isolated epicardial or endocardial cells. In contrast, \( I_{K_r} \) block prolongs APD of M cells less than that of the other cell types. (2) Greater prolongation of M-cell APD by \( I_{K_r} \) block or late \( I_{K_s} \) augments APD differences between the different cell types. In contrast, smaller prolongation of M-cell APD by \( I_{K_s} \) block acts to minimize such APD differences. (3) At slow pacing, M cells are highly susceptible to the development of plateau EADs upon \( I_{K_s} \) block or presence of late \( I_{K_s} \). A higher degree of \( I_{K_s} \) block is necessary for EAD development in the M cells. (4) When cells are electrotonically coupled through gap junctions, \( I_{K_s} \) block or late \( I_{K_s} \) enhances APD dispersion along the fiber during rapid pacing. In contrast, \( I_{K_s} \) block reduces APD dispersion, similar to the behavior observed in isolated cells. (5) At slow pacing and when cells are well coupled, \( I_{K_s} \) block results in the appearance of EADs in the endocardial region. However, in the presence of reduced coupling, EADs develop in the M region.

Heterogeneity of APD and the resulting dispersion of repolarization provide a substrate for unidirectional block and reentry. This study demonstrates that at rapid rates, \( I_{K_s} \) block or late \( I_{K_s} \) enhances APD differences between different cell types not only in isolated cells (Figure 6) but also in the multicellular tissue (Figures 7 and 8). This is due to the greater effect of these interventions in prolonging the APD of M cells than epicardial or endocardial cells. \( I_{K_s} \) block or late \( I_{K_s} \) prolongs APD of the M cell most because of its smaller total repolarizing current (caused by a smaller \( I_{K_s} \)). Both these interventions have a similar effect on M cells because these currents are uniformly distributed in all cell types. In contrast, \( I_{K_r} \) block prolongs the APD of M cells less than that of epicardial or endocardial cells because of the smaller density of \( I_{K_s} \) in the M cells. This theoretical observation is consistent with experimental observations by Shimizu and Antzelevitch, who showed that the percentage of APD prolongation in epicardium or endocardium is greater than in the M cell upon application of chromanol 293B, a selective \( I_{K_s} \) blocker. This tends to minimize APD differences between the 3 cell types. It is therefore observed that \( I_{K_s} \) block or late \( I_{K_s} \) increases APD differences and dispersion, thereby creating a substrate for the development of unidirectional block and reentry, whereas \( I_{K_r} \) block tends to minimize APD differences and eliminate dispersion.

During slow pacing, \( I_{K_s} \) or \( I_{K_r} \) block and late \( I_{K_s} \) result in preferential EAD development in isolated M cells similar to experimental observations. A 50% \( I_{K_s} \) block was sufficient to cause EADs in the M cell, whereas EADs did not develop in epicardial or endocardial cells, even for complete \( I_{K_s} \) block. A higher percentage of \( I_{K_s} \) block (64%) was necessary to cause EADs in the M cell. In a multicellular fiber, EADs developed...
in the M region under conditions of reduced gap-junctional coupling. For example, when $g_{\text{j}}=0.025 \, \mu S$, EADs developed in the M region, which in turn prolonged APD and greatly enhanced APD dispersion. The higher likelihood of EADs in the M region suggests that M cells could become a source of triggered activity and focal arrhythmias when gap-junctional coupling is reduced. On the background of enhanced APD dispersion caused by greater APD prolongation in the M region, such EADs can provide the triggering event for the development of reentry.

Surprisingly, when cells are well coupled ($g_{\text{j}}=0.43 \, \mu S$), endocardial cells are more susceptible to APD prolongation and EAD development than M cells, which suggests their involvement in EAD-related arrhythmias. This behavior is consistent with experimental findings demonstrating that focal activity (possibly caused by EADs) in the subendocardium generates the initial beat of polymorphic tachycardias in the LQTS or in ventricular arrhythmias in patients with idiopathic dilated cardiomyopathy. Purkinje fibers are also known to be highly susceptible to interventions that prolong APD. It is possible that EADs generated in Purkinje fibers play an important role in these arrhythmias. The results of this study demonstrate the possibility that EADs in endocardial cells can also provide the trigger for ventricular arrhythmias associated with abnormal repolarization.

An important mechanistic observation is that in all cases (single cell or multicellular fiber), EAD depolarization is due to recovery from inactivation and reactivation of the L-type calcium channel current, $I_{\text{Ca,L}}$, as we have shown previously. Prolongation of the AP to provide sufficient time for recovery of outward repolarizing currents $I_{\text{Ks}}$ or $I_{\text{Kr}}$, respectively. In LQT1 and LQT2 it is achieved by reduction of outward repolarizing currents $I_{\text{K}}$, or $I_{\text{Ks}}$, respectively. In LQT3 it is achieved by an increase of an inward depolarizing current, late $I_{\text{K}}$. In a related study we showed that pause-induced EADs in the 3 types of LQTS also involve recovery and reactivation of $I_{\text{Ca,L}}$ during a prolonged AP plateau. These observations suggest a universal mechanism for EAD formation at plateau potentials, namely $I_{\text{Ca,L}}$ reactivation, whereas prolongation of the plateau that is necessary for $I_{\text{Ca,L}}$ recovery does not involve a specific mechanism, and its underlying ionic current is different in the different types of LQTS.

**Conclusions and Implications for Antiarrhythmic Therapy**

Electrophysiological heterogeneity is an important property of the myocardium that must be considered in the determination of arrhythmogenic mechanisms and the administration of antiarrhythmic drug therapy. Results from the multicellular fiber suggest that APD dispersion in the myocardium is greatly influenced by the degree of gap-junctional coupling and the type of intervention that prolongs APD. Substantial APD differences can exist in the myocardium when intercellular coupling is reduced, even in the absence of ion channel modification by drugs or disease. Conversely, the higher susceptibility of M cells to pathologies and interventions that prolong APD suggests that large APD dispersions can arise even in the normally coupled myocardium. A combination of reduced cellular coupling and enhanced cellular heterogeneity can result in extreme levels of APD dispersion, setting the stage for unidirectional block and reentry. Such a situation can arise when an antiarrhythmic drug that prolongs APD is administered in an aging or infarcted heart in which intercellular coupling is reduced. Studies (for review see Reference 17) have shown that antiarrhythmic drugs could become proarrhythmic when the substrate is altered by ischemia or infarction. Similar changes can occur during electrophysiological remodeling caused by various pathologies (eg, hypotrophic or dilated cardiomyopathy) or as a result of the fast rates associated with the arrhythmia itself (as can occur during atrial flutter and fibrillation). Our results show that drugs that prolong APD by blocking $I_{\text{Ks}}$ aggravate APD dispersion in the presence of reduced cellular coupling. Recent studies showed changes in the distribution and concentration of the gap-junctional protein connexin 43 during acute ischemia and infarction. It is likely that heterogeneity of gap junction distribution acts synergistically with ion channel heterogeneity to aggravate APD dispersion and EAD formation during administration of drugs that prolong APD or in the presence of disease that prolongs repolarization (eg, LQTS). A striking result of our simulations is that $I_{\text{Ks}}$ block minimized APD dispersion even in the presence of reduced cellular coupling. This is a very important observation because it could be a beneficial antiarrhythmic property that is not shared by drugs that block $I_{\text{Kr}}$.

**Limitations of the Study**

The role of gap-junctional coupling in APD heterogeneity and EAD formation during prolonged repolarization was studied in a 1D fiber. This is a simplified model that allowed us to investigate this phenomenon at the cellular and ion channel levels. Moreover, propagation that can be simulated in a 1-D model occurs frequently in the 3D heart when broad-plane waves are generated. Importantly, this is the situation during normal sinus rhythm in which planar waves created by the Purkinje network propagate from endocardium to epicardium. A similar situation occurs in the wedge preparation used extensively to study myocardial heterogeneity. It should be emphasized that local dispersion on a cellular scale is involved in the generation of unidirectional block and reentry. Even in the presence of complex 3D global wave fronts, local excitation can be 1D in nature. This is particularly true in the presence of pathological structural complexities such as narrow fibers connecting islands of surviving tissue in an infarct.

Clinically, LQT3 is usually associated with arrhythmias occurring at slow heart rates (during sleep), whereas arrhythmias in LQT1 often occur during exercise and/or excitement. It is likely that these different scenarios reflect different levels of sympathetic activity. A possible explanation for this behavior is that in LQT3, prolongation of APD is greater at slow rates, when the mutant late $I_{\text{K}}$ is opposed by a smaller repolarizing current as the result of greater deactivation of $I_{\text{Ks}}$ between APs. In the case of LQT1, the mutation results in reduced $I_{\text{K}}$. Sympathetic activity augments both $I_{\text{Ks}}$ and $I_{\text{Ca,L}}$ in addition to other effects on calcium cycling, $I_{\text{Na}}$, and the Na/K pump. The net effect on APD depends on the balance between $I_{\text{Ks}}$, reduction by the mutation and the
enhancement of $I_{\text{Kr}}$ and $I_{\text{Kf}}$ by $\beta$-adrenergic stimulation. This effect is likely to be nonuniform because of the heterogeneous distribution of $I_{\text{Kr}}$ in the myocardium, thereby increasing dispersion of repolarization and enhancing arrhythmogenesis. The multifactorial cellular effects of $\beta$-adrenergic stimulation can be simulated in the Luo-Rudy model. Their interactions with the different types of LQTS are complex and require extensive simulation protocols that are outside the scope of this study.

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