Ionic Current Basis of Electrocardiographic Waveforms
A Model Study
Kazutaka Gima, Yoram Rudy

Abstract—Body surface electrocardiograms and electrograms recorded from the surfaces of the heart provide information for diagnosis and treatment of cardiac electrophysiological disorders and arrhythmias. Recent advances in understanding the molecular mechanisms of arrhythmia, it is important to relate these electrocardiographic waveforms to cellular electrophysiological processes. This modeling study establishes the following principles: (1) voltage gradients created by heterogeneities of the slow-delayed rectifier (\(I_{Ks}\)) and transient outward (\(I_{Na}\)) potassium current inscribe the T wave and J wave, respectively; T-wave polarity and width are strongly influenced by the degree of intercellular coupling through gap-junctions. (2) Changes in \([K^+]_o\) modulate the T wave through their effect on the rapid-delayed rectifier, \(I_{Kr}\). (3) Alterations of \(I_{Ks}\), \(I_{Kr}\), and \(I_{Na}\) (fast sodium current) in long-QT syndrome (LQT1, LQT2, and LQT3, respectively) are reflected in characteristic QT-interval and T-wave changes; LQT1 prolongs QT without widening the T wave. (4) Accelerated inactivation of \(I_{Na}\) on the background of large epicardial \(I_{Na}\) results in ST elevation (Brugada phenotype) that reflects the degree of severity. (5) Activation of the ATP-sensitive potassium current, \(I_{KATP}\), is sufficient to cause ST elevation during acute ischemia. These principles provide a mechanistic cellular basis for interpretation of electrocardiographic waveforms. (Circ Res. 2002;90:889-896.)

Key Words: electrocardiography ■ mathematical modeling ■ long-QT syndrome ■ Brugada syndrome ■ ischemia

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Materials and Methods
AP propagation was reconstructed as described previously\(^4\) in a 1-dimensional fiber of Luo-Rudy dynamic (LRd) model cells.\(^6\)–\(^9\) This reconstruction represents the broad planar wavefront that propagates from endocardium to epicardium during normal ventricular excitation\(^9\) resulting from Purkinje network participation. The model also represents AP propagation in the arterially perfused transmural wedge preparation, used by Antzelevitch and colleagues in experimental studies of ECG waveforms.\(^1\)–\(^4\) The fiber formulation takes into account heterogeneities of ion channel expression,\(^6\)\(^,\)\(^8\)\(^,\)\(^11\) with additional modifications described in the following section. The source program code (in C++) for a single LRd model cell can be downloaded from http://www.cwru.edu/med/CBRTC.

Multicellular 1-Dimensional Fiber Model
The theoretical fiber, of length 1.65 cm, is composed of 165 LRd model cells connected through gap junctions. Transmural heterogeneities of ion channel densities are introduced to represent the 3 ventricular cell types: endocardial (cells 1 to 60), midmyocardial (M cells, cells 61 to 105), and epicardial (cells 106 to 165). Density of \(I_{Na}\) (slow-delayed rectifier potassium current) is varied as described previously,\(^8\)\(^,\)\(^11\) with the lowest in the M cells (density ratios between the slow- and rapid-delayed rectifiers are \(I_{Na}\) to \(I_{Ks}\) = 11:1 endocardial, 4:1 midmyocardial, 35:1 epicardial). The transient outward potassium current (\(I_{Na}\)) is introduced in epicardial and M cells after the formulation of Dumaine et al.\(^12\) The maximum conductance of \(I_{Na}\) is
Long-QT and Brugada Syndromes

As described previously, LQT syndromes are simulated by reducing the membrane conductance of $I_{Ks}$ (LQT1), of $I_{le}$ (LQT2), or by altering the steady-state inactivation of the fast sodium current $I_{Na}$ to generate a late (persistent) current during the AP plateau (LQT3). The Brugada syndrome is simulated by increasing the rate of fast inactivation of $I_{Ks}$, as described by Dumaine et al. Acute Myocardial Ischemia

The major change of AP morphology during acute ischemia is caused by activation of the normally dormant ATP-sensitive potassium current, $I_{KATP}$. To simulate the associated ECG changes, we incorporate $I_{KATP}$ into the model using the formulation derived previously. Greater sensitivity of $I_{KATP}$ to ATP changes in the epicardium is accounted for by decreasing the half-maximal saturation point, $k_{sat}$, of channel activity of endocardial cells by 75% and of M cells by 50%.

Results

Effects of $I_{Ks}$ and $I_{le}$ Heterogeneities on AP Morphology and ECG Waveforms

Figure 1 relates normal (physiological) transmural AP heterogeneities and their underlying ionic currents to the ECG waveforms. In the normal myocardium, $I_{Ks}$ is uniformly distributed across the ventricular wall, $I_{Ks}$ density is much lower in the midmyocardium than in either the epicardium or the endocardium, and $I_{le}$ density increases from endocardium to epicardium. This situation is shown in Figure 1, left column (control), where the small $I_{Ks}$ of M cells results in longer APD ($APD_{endo}=187$ ms and $APD_{epi}=148$ ms), and $I_{le}$ produces a notch in the AP during the early repolarization phase (phase 1) in the epicardial and M cells (arrows). Complete repolarization of the epicardium corresponds to the peak of the T wave, whereas repolarization of the midmyocardium corresponds to the end of the T wave. These results are consistent with corresponding experimental observations in the arterially perfused wedge preparation. Despite the opposite polarity of depolarization and repolarization, the
QRS and T wave are both positive (upright). This is because the spatial $V_m$ gradient ($\nabla V_m$ in Equation 1) is determined by the intrinsic APD heterogeneity with only minor modulation by the sequence of activation, because conduction time between inhomogeneous regions (e.g., M to epicardium) is small compared with the intrinsic APD differences. Because the transmural APD heterogeneity reflects mostly the heterogeneity of $I_{Ks}$ expression, it can be hypothesized that $I_{Ks}$ plays a major role in determining the T-wave morphology. To verify this hypothesis (Figure 1, middle column), $I_{Ks}$ density in the entire fiber is set equal to the endocardial $I_{Ks}$ density under control conditions. For such homogeneous conditions, the sequence of repolarization follows the sequence of activation with the epicardium (rather than midmyocardium) repolarizing last and determining the end of the T wave. This inversion of the repolarization sequence relative to control results in an inversion of the transmural $\nabla V_m$ and, therefore, in an inversion of the T wave.

Figure 1, right column, explores the ionic basis of the J wave (Osborn wave) that appears after the QRS complex. The J wave, present under control conditions, coincides with the J wave (Osborn wave) that appears after the QRS complex. The spatial gradient of the membrane potential ($\nabla V_m$) is directed from epicardium to midmyocardium and generates a positive T wave. The smaller $\nabla V_m$ (in comparison with enhanced coupling) results in a smaller T-wave amplitude. Right, Slow conduction, resulting from reduced coupling, overrides the intrinsic repolarization differences in the 3 cell types. This results in an inversion of the repolarization sequence and, consequently, inverts $\nabla V_m$ and the T wave.

**Effects of Varying the Degree of Cell-to-Cell Coupling**

Figure 2 examines the effects of varying the degree of intercellular coupling on the ECG. Three degrees of gap-junction coupling are modeled: enhanced ($g_j=17.3 \mu S$, left), control ($g_j=1.73 \mu S$, middle), and reduced ($g_j=0.192 \mu S$, right). A gap junction conductance of 1.73 $\mu S$ (control) results in propagation velocity of 44 cm/s and conduction time of 30 ms that are in close agreement with the experimental observations of Yan et al. A gap junction conductance of 1.73 $\mu S$ (control) results in propagation velocity of 44 cm/s and conduction time of 30 ms that are in close agreement with the experimental observations of Yan et al. A gap junction conductance of 0.192 $\mu S$ (control) results in propagation velocity of 14 cm/s and conduction time of 95 ms.

Enhanced coupling increases conduction velocity to 69 cm/s and decreases the conduction time across the fiber (conduction time = 20 ms) as reflected in the narrow QRS in Figure 2, left column. The short conduction time reduces the effect of the activation sequence on repolarization gradients. The T-wave morphology, therefore, reflects primarily the effect of the intrinsic transmural AP heterogeneity and its orientation is upright (positive) as under conditions of control coupling. Enhanced electrotonic interaction between the well-coupled cells acts to reduce APD differences. This, together with the short transmural conduction time, reduces TDR to 19 ms.

Decreased coupling ($g_j=0.192 \mu S$) decreases velocity to 14 cm/s and prolongs transmural conduction time to 95 ms (reflected in widening of the QRS). Consequently, the activation sequence rather than intrinsic APD heterogeneities determines the sequence of repolarization and the direction of $\nabla V_m$ is reversed compared with control, resulting in an inverted T wave. APD dispersion is increased (TDR = 39 ms).

**Effects of Changes in Extracellular Potassium Concentration**

Figure 3 illustrates the effects of changes in extracellular potassium concentration, $[K^+]_o$, on the ECG waveform. $[K^+]_o$
affects repolarization mostly through its effect on \( I_K \) conductance (conductance is proportional to \((\left[K^+\right]_o)^{1/2}\)). At \([K^+]_o=2\) mmol/L, \( I_K \) is reduced relative to control (\([K^+]_o=4\) mmol/L). This reduction in repolarizing \( I_K \) causes APD prolongation in all cell types. However, the effect is quantitatively greater in M cells, where \( I_K \) is small, because the \( I_K \) change constitutes a greater percent change of the total repolarizing current (principally, \( I_{Kr} \) and \( I_K \)) in these cells. This results in prolongation of the QT interval (QT-control=196 ms and QT-hypokalemia=236 ms) and flattening of the T wave relative to control (maximum T-wave amplitude is 0.33 mV and 0.26 mV for control and hypokalemia, respectively), in agreement with experimental and clinical observations. High \([K^+]_o\) (occurring clinically during acute ischemia) has an opposite effect. At \([K^+]_o=6\) mmol/L, the QT interval (177 ms) is abbreviated, reflecting a shorter epicardial APD, and the T-wave amplitude is increased (\( V_m \)). These morphological alterations are observed experimentally as well. With respect to control, \([K^+]_o=6\) mmol/L results in a slightly narrower QRS, reflecting an increased velocity (“supernormal conduction”). At higher levels of hyperkalemia, velocity is decreased and the QRS is widened (not shown). It should be noted that conductance of \( I_K \), the inward rectifier current, is also proportional to \((\left[K^+\right]_o)^{1/2}\). However, \( I_K \) has a small effect on the time course of AP repolarization and its modulation by \([K^+]_o\), changes does not affect the ECG waveform significantly.

Effects of Ion Channel Mutations: LQT and Brugada Syndromes

Figure 4 shows computed ECG changes caused by 3 types of the LQT syndrome. Reducing \( I_K \) or \( I_{Kr} \) models LQT1 and LQT2, respectively. LQT3 is modeled by slowed \( I_{Kr} \) inactivation, leading to the presence of a late \( I_{Kr} \). Several degrees of severity (degree of ionic current modification) are simulated for each LQT type. In all cases, the QT interval is prolonged by the mutation, and the prolongation increases with severity.

Reducing \( I_K \) simulates LQT1 (Figure 4, left column). Because \( I_K \) is inherently smaller in M cells than in epicardial and endocardial cells, an equal percent reduction of \( I_K \) prolongs APD to a lesser extent in M cells than in the other cell types. The net result is a prolongation of the APD of all cell types with decreased APD dispersion. On the ECG, this is reflected in QT-interval prolongation with reduction of TDR (TDR: control=23 ms, 50% \( I_K=21 \) ms, 25% \( I_K=18 \) ms, and 0% \( I_K=17 \) ms).

LQT2 (Figure 4, middle column) is caused by reduced \( I_{Kr} \), which causes greater APD prolongation in M cells (as a consequence of their smaller \( I_{Kr} \)) than in the other cell types. Because M cell repolarization determines the end of the T wave, this nonuniform AP change is reflected in QT-interval prolongation accompanied by widening of the T wave and an increased TDR on the ECG (TDR: control=23 ms, 50% \( I_{Kr}=41 \) ms, 25% \( I_{Kr}=58 \) ms, and 0% \( I_{Kr}=91 \) ms). The greater difference between the M cell AP and the ACPs of other cell types during the repolarization phase augments \( V_n \) and, consequently, the T-wave amplitude. When simulated hyperkalemia (\([K^+]_o=2.1\) mmol/L) is superimposed on the LQT2 with 50% \( I_{Kr} \) reduction (Figure 4, LQT2, inset), the T wave becomes notched, as indicated by the arrow. Shimizu et al. observed similar ECG changes experimentally (Figure 4, bottom row, inset). Superimposing this level of hypokalemia on LQT2 with 50% \( I_{Kr} \) translates into 36% \( I_{Kr} \). This is less severe than LQT2 with 25% and 0% \( I_{Kr} \), which do not manifest a notched T wave. Therefore, modification of an ionic current other than \( I_K \) by the reduced [K+]o must be involved in inscribing the T-wave notch. To test this hypothesis, the conductance of the inward rectifier potassium current (\( I_{Kr} \)) was decreased to account for its dependence on \((\left[K^+\right]_o)^{1/2}\).
The combined effects of reduced $I_{K1}$ and $I_{Kr}$ were sufficient to generate a notched T wave.

APD prolongation in LQT3 (Figure 4, right column) is caused by a late mutant $I_{Na}$ that shifts the balance of currents during the AP plateau in the inward (depolarizing) direction. As in LQT2, the effect is greater in the M cells. ECG changes caused by late $I_{Na}$ (magnitude 0.2% of peak) include widening of the T wave (control=63 ms and LQT3=100 ms), increased T-wave amplitude (control=0.33 mV and LQT3=0.72 mV), and increased TDR (control=23 ms and LQT3=62 ms). The QT-interval prolongation is partly due to late appearance of the T wave (Q- to T-wave onset is 141 ms in control, 157 ms in LQT1, 155 ms in LQT2, and 172 ms in LQT3). These results are consistent with experimental observations.23

Figure 5 illustrates the ECG manifestations of the Brugada syndrome. The T1620M mutation, which accelerates fast inactivation of $I_{Na}$, is introduced following the formulation of Dumaine et al.12 In addition, $I_{to}$ conductance is increased relative to control, to account for the high $I_{to}$ density.

The effects of channel block with mexiletine are shown in Figure 6. Left, Mexiletine reduces the peak of $I_{Na}$ by 50% (compare control with 50% mexiletine). Middle, Decreased $I_{Na}$ prolongs AP in M cells, leading to a broad-based T wave (control=60 ms and LQT3=110 ms). Right, The TDR is increased in LQT3 (control=23 ms and LQT3=62 ms).

Figure 5. Effects of ion channel mutations in Brugada syndrome. Accelerating the fast inactivation rate of $I_{Na}$ by decreasing its time constant $t_\text{h}$ simulates 3 levels of Brugada syndrome severity. Left, 3-fold increase in $I_{to}$ density (to simulate the high $I_{to}$ density in the right ventricle) superimposed with 1.5 times decrease of $t_\text{h}$ results in ST-segment elevation with an accompanying pronounced J wave (“saddleback” morphology). Center, Further accentuation (5-fold increase in $I_{to}$ density with 2.5 times decrease of $t_\text{h}$) results in a prolonged AP beyond midmyocardial and endocardial repolarization, leading to an inverted T wave and a coved ECG. Right, In the most severe case (7-fold increase in $I_{to}$ density with 3.5 times decrease of $t_\text{h}$), the outward shift in transmembrane current results in loss of the epicardial plateau and in a triangular ECG.
Acute Myocardial Ischemia

Figure 6. Acute myocardial ischemia and the effect of $I_{\text{KATP}}$ activation during hypoxia. Activation of $I_{\text{KATP}}$ (dashed gray lines) results in a heterogeneous suppression of the AP plateau and APD shortening (thin gray lines). This leads to ST-segment elevation (arrow; dashed line in the ECG indicates the isoelectric line).

Discussion

The theoretical approach in this study allows us to establish a direct and specific relationship between cellular ionic processes, the AP, and the morphology of electrocardiographic waveforms. The results demonstrate how alteration of a particular ionic current modifies the transmembrane potential gradient across the ventricular wall ($\nabla V_m$ in Equation 1) and, consequently, the ECG waveforms. This study complements the experimental findings of Antzelevitch et al.1–4 and provides, through selected physiological and pathological examples, insights into the principles that relate electrocardiographic observations to underlying ion channel function. It should be emphasized that similar to the transmural wedge experiments,1–4 the simulations presented here only explore electrocardiographic waveforms at a site close to the epicardium during plane-wave propagation from endocardium to epicardium. This model simulates the situation during normal sinus rhythm, where the Purkinje system together with the anisotropic myocardial fiber structure establish a broad wavefront parallel to the endocardial surface that propagates toward the epicardium.10 Under such conditions, the experimental wedge preparation1–4 and the theoretical 1-dimensional fiber used here are adequate models for studying potentials generated by a section of the myocardium at an electrode positioned sufficiently close to the epicardium along the direction of wavefront propagation. Isolating a section of the ventricular wall in this manner facilitates establishing the relationships between the electrocardiographic waveforms, the morphology and properties of the propagating AP, and the underlying cellular ionic processes. However, an electrode sufficiently remote from the myocardium (eg, a body surface ECG electrode) is influenced not only by activity in a section of the myocardium closest to the electrode, but by the distribution of electrical sources in the entire heart. This can be seen clearly in Equation 1 where $-\nabla V_m$ (the source of electrophysiologic potentials) is integrated over the entire active tissue where $\nabla V_m$ is not zero. The term $\nabla(1/r)$ in this equation is a weight factor that acts to emphasize contribution of sources proximal to the electrode relative to those remote from the electrode (“proximity effect”). Under certain circumstances, a precordial electrode can record isolated activity from a proximal section of myocardium. An example in the context of this study is the Brugada syndrome where ST-segment elevation is observed in the right precordial leads.24 These leads are proximal to the right ventricular outflow tract where reduced mutant $I_{\text{Na}}$ on the background of large $I_{\text{Na}}$ suppresses the AP dome to generate a local $-\nabla V_m$ and right precordial ST elevation. Such “focusing” of the ECG requires both close proximity and small contribution from activity in other regions of the heart during the same phase of the cardiac cycle. In general, however, such conditions are not met and an ECG electrode
records potentials generated by sources in several regions of the heart. The principles established by our simulations and the transmural wedge experiments are derived in simplified models representing an isolated transmural section of the myocardium. However, these principles can be generalized and applied to electrogams and electrocardiograms measured in vivo and provide a mechanistic cellular basis for their interpretation. Recently, we demonstrated that a novel ECG imaging modality (ECGI) can reconstruct epicardial electrograms noninvasively from body surface ECG potentials. The results of this study are directly applicable to such noninvasive electrograms because, due to proximity, they mostly reflect local activity.

\[ \nabla V_m \] during repolarization is determined by 2 factors: the sequence of activation and local APD. In the (hypothetical) absence of intrinsic electrophysiological heterogeneity, the sequence of repolarization follows the sequence of activation, generating \( \nabla V_m \) in the opposite direction and a T wave of opposite polarity to the QRS (Figure 1, homogeneous \( I_{Ks} \)). In the normal myocardium, when AP propagates from endocardium to epicardium at normal velocity (normal sinus rhythm) transmural APD differences due to intrinsic heterogeneity of \( I_{Ks} \) expression are sufficient to reverse \( \nabla V_m \) during repolarization and consequently the T wave (Figure 1, control; QRS and T have same polarity). When conduction is sufficiently slow (Figure 2, reduced coupling), the activation sequence determines the sequence of repolarization (intrinsic APD differences are small compared with transmural conduction time). This situation approximates the homogeneous case, and the T-wave polarity is opposite to that of the QRS. Note that in all cases, the peak of the T wave coincides with the time of earliest repolarization (epicardial in control; endocardial for homogeneous \( I_{Ks} \) and for reduced coupling), whereas the end of the T wave corresponds to latest repolarization (midmyocardial in control; epicardial for homogeneous \( I_{Ks} \) and for reduced coupling). The results show that transmural \( I_{Ks} \) heterogeneity is the major determinant of T-wave morphology, whereas presence of \( I_{Ks} \) in epicardium generates the J wave. Transmural heterogeneity also exists in late \( I_{Ks} \) and in the \( Na^+/Ca^{2+} \) exchange current. Simulations of these heterogeneities (not shown), however, demonstrate only a minimal effect on the ECG waveforms. Another source of heterogeneity is different degrees of electrical loading on repolarizing cells across the transmural regions of the fiber. During endocardial to epicardial conduction, cells in the endocardial region repolarize when other cells are at depolarized potentials, which acts to prolong endocardial APD. The loading effect is opposite in the epicardial region and acts to shorten APD. Therefore, even in a homogeneous tissue, a gradient exists due to loading asymmetry introduced by the propagating AP. In our model, the effect of this functional heterogeneity (not shown) is minimal and does not contribute appreciably to the electrocardiographic waveforms. The pathological examples were chosen to illustrate important principles in situations where ion channel function is altered by disease. ST-segment elevation is generated by a \( -\nabla V_m \) directed toward the epicardium during the plateau phase of the AP. Such gradient develops when the epicardial AP plateau is preferentially suppressed. Because the plateau is maintained by a delicate balance between several inward and outward currents, the ionic basis of ST-segment elevation is not unique and can involve various combinations of processes that shift this balance in the outward (repolarizing) direction. In acute ischemia, we show that \( I_{K(ATP)} \) activation with greater ATP sensitivity in epicardial cells is sufficient to cause ST elevation. A similar mechanism has been suggested by recent experiments. In the Brugada syndrome, accelerated \( I_{Ks} \) inactivation on the background of a large epicardial \( I_{Ks} \) shifts the balance of currents to cause similar phenomenon and ECG phenotype. Of course, important ECG properties differ between the two pathologies, including sensitivity of specific ECG precordial leads, dependence on heart rate, \( \beta \)-adrenergic activity, and modulation by drugs. These properties are beyond the principles established here and will be investigated in future studies. The simulated ECG waveforms, however, have sufficient specificity to differentiate between different types of LQT. This is an important demonstration of the potential for using electrocardiographic waveforms to identify a specific channelopathy so that mechanism-based therapy can be administered. The different ECG phenotypes also have physiological and clinical relevance in the context of arrhythmogenesis. For example, LQT1 (\( I_{Ks} \) channelopathy) prolongs QT without increasing transmural dispersion of repolarization (TDR). This might explain its lower incidence of arrhythmogenesis compared with LQT2 and LQT3, where QT prolongation is associated with increased TDR. In the case of the Brugada syndrome (Figure 5), ECG waveforms are indicative of the severity of \( Na^+ \) channel abnormality. The different morphologies generated by the model as this severity is increased (saddleback, coved, triangular) support the predictions of Antzelevitch based on experimental observations in the transmural wedge preparation.

Acknowledgments
This study was supported by grants R01-HL-49054 and R37-HL-33343 (to Y. Rudy) from the National Heart, Lung, and Blood Institute.

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_Circ Res._ 2002;90:889-896; originally published online March 28, 2002;
doi: 10.1161/01.RES.000016960.61087.86
_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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