Generation of the T wave in the electrocardiogram: lessons to be learned from long-QT syndromes

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Abstract
T waves in the human electrocardiogram generally have the same sign as QRS complexes (T-wave concordance). Heterogeneity of the slow delayed rectifier current (\(I_{Ks}\)) is often held responsible for this. We demonstrate that this idea is in conflict with the observation of relatively large T-wave amplitudes in patients with the long-QT type I syndrome. Another current must be responsible for T-wave concordance.

Introduction
The electric potential fields generated by depolarization and repolarization waveformst have opposite sign. Therefore, if repolarization of the ventricles followed the same path as depolarization, QRS complex and T wave would have opposite signs. This is not the case in the normal electrocardiogram (ECG). On the contrary, most T waves are “concordant,” i.e., they have the same sign as the QRS complex. This is only possible if the order of repolarization is opposite to the order of depolarization. Generally, there must be a negative correlation between depolarization and repolarization times. This requires a large long-range heterogeneity of intrinsic action potential duration (APD). This theoretically inferred heterogeneity has been termed the “ventricular gradient”[6,11].

The necessity of heterogeneity of APD is thought to result from differences in the expression of ion channels and their subunits. Candidate channels include those responsible for the rapid and slow components of the delayed rectifier current (\(I_{Kr}\) and \(I_{Ks}\)) and the L-type calcium current (\(I_{Ca,L}\)). In rodents, the transient outward current plays an important role. It is less important for APD heterogeneity in human, due to the presence of \(I_{Kr}\) and \(I_{Ks}\).

Very few experimental data are available on ion-channel heterogeneity in human. The study of congenital T-wave abnormalities can place some of the pieces of this complicated puzzle.

Hypothesis
Following the discovery that \(I_{Ks}\) contributes importantly to the longer APD of M-cells [5, Gima and Rudy constructed a model in which \(I_{Ks}\) causes a concordant T wave [3]. This requires a difference between endocardial and epicardial \(I_{Ks}\) density that is not supported by experiments. Nevertheless, the role of \(I_{Ks}\) has been widely accepted. It is our purpose to refute the hypothesis that \(I_{Ks}\) can be responsible for the normal T wave in human. For this purpose we model concordant T waves using \(I_{Ks}\). We then compute the theoretically expected effects of a loss-of-function mutation in the channel responsible for \(I_{Ks}\), and compare them to what is actually observed in patients.

Methods
A reaction-diffusion model of the human ventricles was used to compute propagating depolarization and repolarization of membrane potentials [7,9]. Ionic currents were simulated with the TNFP model for the human ventricular myocyte [8]. The model had a resolution of 0.25 mm, a realistic cardiac anatomy, and anisotropic ventricles with transmural fiber orientation.

The heart model, here embedded in a thin layer of fluid (pink). The right circumflex artery is shown for orientation. The model has a heterogeneous myocardium; subendocardial tissue is shown in grey, the M region in blue, and subepicardial tissue in green.

Heterogeneity of ionic current density was implemented as in the original TNFP model [8], with an additional transmural gradient and left/right ventricular difference [2,10] in \(I_{Ks}\), as in the following table.

<table>
<thead>
<tr>
<th>Current</th>
<th>Left ((nA/cm^2))</th>
<th>Right ((nA/cm^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I_{Ks})</td>
<td>0.294</td>
<td>0.073</td>
</tr>
<tr>
<td>(I_{Kr})</td>
<td>0.400</td>
<td>0.096</td>
</tr>
</tbody>
</table>

APD90 ms: 278 330 281 309 251

Units are \(nA/cm^2\). The values are derived from normal values of the human ventricular myocyte.

Results
The experimentally observed heterogeneity of \(I_{Ks}\), alone (between M-cells and others), and between the two ventricles) led to T-wave concordance only in the right precordial leads. With the addition of an endocardial-to-epicardial gradient in \(I_{Ks}\) concordance was obtained in all 12 leads. Introduction of the L251P mutation, which decimates \(I_{Kr}\), globally, led to QT prolongation and reduction of T-wave amplitude. This observation is in conflict with clinical observations in LQT1 patients, and patients with the L251P mutation in particular [4]. Their T waves usually have normal or larger than normal amplitudes.

Discussion
T-wave concordance cannot exist without heterogeneity of \(APD\). A transmural \(APD\) gradient is often assumed. This hypothesis is attractive because transmural heterogeneity of cell types has been demonstrated. However, we have shown that the known ionic heterogeneities of \(I_{Kr}\) (between M-cells and others, and between the two ventricles) do not suffice to explain the normal T wave, which is concordant in all standard ECG leads. Only with an additional difference between endocardial and epicardial layers can this concordance be obtained. If this difference were due to \(I_{Kr}\) as proposed by Gima and Rudy [3], LQT1 syndromes would reduce the amplitude of the T wave. This is in disagreement with the observation that LQT1 syndromes are associated with normal or increased T-wave amplitude. To explain this observation, we must assume that

• heterogeneity in \(I_{Kr}\) opposes T-wave concordance, rather than causing it;

• other currents, such as \(I_{Kr}\) and \(I_{Ca,L}\), must play a role in the generation of the T wave.

Diagram of the TNFP model for the human ventricular myocyte. The heart model consists of a network of 22 million such elements, allowing it to be computationally simulated. The membrane potential was recorded using a realistic cardiac anatomy, and anisotropic ventricles with transmural fiber orientation. Simulations were repeated with a loss-of-function mutation (\(\Delta I_{Ks}\)) in \(KCNQ1\), which is associated with LQT1 syndrome [1]. When co-expressed with wild-type protein, the dominant-negative effect of \(\Delta I_{Ks}\) caused a decrease in current density and a shift of 8 mV in voltage dependence [1]. From the simulated membrane potentials, the ECG was computed using a boundary-element torso model including lungs, ventricular blood pools, and an anisotropic myocardium.

Simulated normal ECG (black), 11-fold reduction of \(\Delta I_{Ks}\) (red), and 11-fold reduction with 8 mV rightward shift in voltage dependence (blue). The vertical scales are in mV, horizontal tick marks are placed at 100-ms intervals.

The T-wave model, including \(I_{Ca,L}\) heterogeneity, intraventricular blood flow, low-conductivity limbs, and a skeletal muscle layer.

References

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Diagram of the TNNP model for the human ventricular myocyte. The heart model consists of a network of 22 million such elements, allowing it to be computationally simulated. The membrane potential was recorded using a realistic cardiac anatomy, and anisotropic ventricles with transmural fiber orientation. Simulations were repeated with a loss-of-function mutation (\(\Delta I_{Ks}\)) in \(KCNQ1\), which is associated with LQT1 syndrome [1]. When co-expressed with wild-type protein, the dominant-negative effect of \(\Delta I_{Ks}\) caused a decrease in current density and a shift of 8 mV in voltage dependence [1]. From the simulated membrane potentials, the ECG was computed using a boundary-element torso model including lungs, ventricular blood pools, and an anisotropic myocardium.

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