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 amplitude in patients with the long-QT type 1 syndrome. Another current must be responsible for T-wave concordance.

Introduction

The electric potential fields generated by depolarization and repolarization wavefronts 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 necessary 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

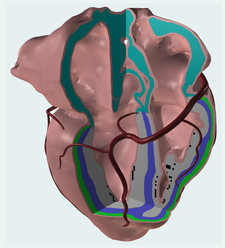
Following the discovery that I_{Ks} contributes importantly to the longer APD of M-cells [5], Gima and Rudy constructed a model in which I_{Ks} causes a concordant T wave [3]. This requires a difference between endocardial and epicardial I_{Ks} density that is not supported by experiments. Nevertheless, 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 TNNP 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 rotation.



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 TNNP model [8], with an additional transmural gradient and left/right ventricular difference [2,10] in I_{Ks}, as in the following table.

	LV epi	LV M	LV+RV endo	**RV M**	**RV epi**
G_{to} (nS/pF)	0.294	0.294	0.073	**0.504**	**0.882**
G_{Ks} (nS/pF)	**0.490**	0.062	0.245	**0.112**	**0.735**
G_{Kr} (nS/pF)	0.096	0.096	0.096	0.096	0.096
APD90 (ms)	278	330	281	309	251

Units are nS = nanoSiemens, pF = picoFarad, ms = millisecond. Bold values indicate deviations from the original TNNP model.

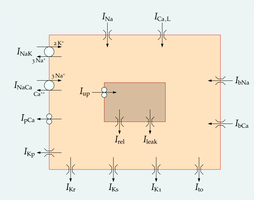


Diagram of the TNNP model for the human ventricular myocyte. The heart model consists of a network of 22 million such elements, allowing it to realistically simulate propagated depolarization and repolarization, accounting for intracellular coupling.

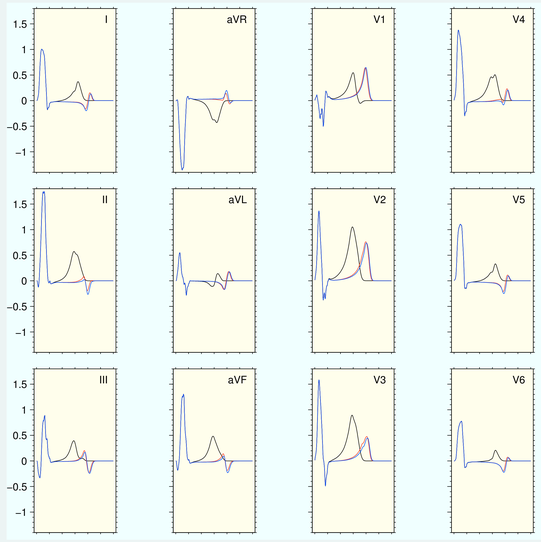
Simulations were repeated with a loss-of-function mutation (L251P) in KCNQ1, which is associated with an LQT1 syndrome [1]. When co-expressed with wild-type protein, the dominant-negative effect of L251P caused an 11-fold reduction of current density and a shift of 8 mV in voltage dependence [1].

From the simulated membrane potentials, the ECG was computed using a boundary-element torso model including lungs, ventricular blood masses, and a skeletal muscle layer.

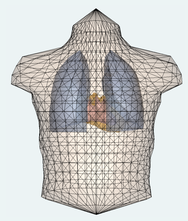
Results

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_{Ks} 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 amplitude.



Simulated normal ECG (black), 11-fold reduction of 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 torso model, including high-conductivity intracavitary blood, low-conductivity lungs, and a skeletal muscle layer (not shown).

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_{Ks} (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_{Ks}, 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_{Ks} opposes T-wave concordance, rather than causing it; and
- other currents, such as I_{Kr} and $I_{Ca,L}$, must play a role in the generation of the T wave.

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