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Study of repolarization heterogeneity and electrocardiographic morphology with a modeling approach

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Abstract

Background: Increase of heart repolarization heterogeneity has been linked to severe or even life-threatening arrhythmia like torsades de pointes and other forms of ventricular tachycardia. Although electrocardiography (ECG) still remains as the most convenient and cost-effective method of monitoring electrical activity of the heart, the link between ECG morphology and repolarization heterogeneity is not clear. Previous attempts of using QT interval dispersion from multiple leads to assess the heterogeneity changes were not successful either.

Method: The aim of this study is to use a cell-to-ECG model to study ECG morphology changes while varying transmural heterogeneity. The heterogeneity is simulated by increasing the difference of M cell Ikr block factors from either endocardial or epicardial cells. The model-simulated ECGs were processed and measured. The ECG parameters studied include QT interval dispersion of standard 12-lead ECG, QT peak dispersion, and T-peak to T-end interval (TpTe). An ECG vector magnitude signal based on 12-lead ECG was formed to estimate the global QT interval (vs lead-by-lead QT interval used for calculating QT dispersion) and also the global TpTe (TpTe_VM).

Results: The results based on the model simulation show that the TpTe_VM is highly correlated with transmural dispersion of repolarization (TDR), with a correlation coefficient of 0.97. The correlation coefficients of QT interval dispersion and QT peak dispersion with TDR are 0.44 and 0.80, respectively.

Conclusion: In conclusion, the cell-to-ECG model provides a unique way to study electrophysiology and to link physiologic factors to ECG morphology changes. The simulation results suggest that global TpTe can be a strong indicator of TDR.

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Keywords: QT prolongation; Transmural dispersion; Cell model; Forward model

Introduction

More and more studies have shown that the QT interval prolongation induced by drugs is only one of several surrogates to torsades de pointes (TdP), and the other surrogates include early afterdepolarizations (EADs) and increase of dispersion of ventricular repolarization (DVR).[1-3] Compared with the other 2 factors, that is, EAD and DVR, QT is a weaker link to TdP because some studies showed that QT interval prolongation is not highly correlated with the incidence of drug-induced TdP, but EAD and increase of DVR are.[2]

However, the QT interval remains to be the only electrocardiographic (ECG) marker required for the thorough QT study for new drug test on cardiac safety, mainly because it can be visualized and edited by overreaders, although measuring the QT interval accurately and consistently remains to be a challenge. Early afterdepolarization can be indirectly assessed if it triggers premature ventricular beat; but otherwise, it is difficult to measure from the surface ECG. Over the years, some studies have suggested that T-peak to T-end interval (TpTe) might be related to transmural dispersion of repolarization (TDR). However, TpTe has not been accepted as a valid test mainly because of 2 reasons: (1) lack of solid scientific proof to link TDR to TpTe of ECG and (2) large variability of T-peak positions from lead to lead, making it very inconsistent.

Many experiments have been conducted by using single cell–based assay, in vitro heart preparation, and animal model during preclinical studies of drug development. Those studies have shown that EADs and increase of TDR are stronger indicators for TdP than prolongation of action potential

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duration (APD) only. The studies based on wedge preparation conducted by several research laboratories have also shown that TpTe measure based on the pseudo-ECG from a single slice of the heart ventricular tissue is correlated with the TDR change.[4] However, there is a need to link TDR to torso ECG in the whole-ventricle level. Such experiment will be very difficult to carry out either in vivo or in vitro, especially any measurement of midmyocardium cells (M cells).

The aim of this article is to study the relationship of TDR with ECG by a modeling approach. A cell-to-ECG forward model is created to study different repolarization heterogeneity/dispersions and their corresponding ECG parameters. The cell-to-ECG model consists of a cell model and a forward model that converts cell's APs to a torso potential ECG. Several excellent cell models have been published over the years.[5-8] We adopted the model created by ten Tusscher's group[7-9] because it is based on human heart cells and also includes both Ikr and Iks ion channels, which can be used to simulate drug-induced AP prolongation and thus QT prolongation.

In the forward model part, there have been also quite a few research activities over the years.[10-13] These models can be divided into 2 categories according to whether the cellular-level model is involved in the high-level model as a discrete set of cells or as a continuum. The model we propose here belongs to the second case but with some major modifications. The first modification is the determination of cellular action profiles for the cell sets instead of using a parameterized action profile (defined by APD, peak amplitude, etc). The second characteristic is the application of a bidomain model based on the finite element method (FEM)–boundary element method (BEM) coupling formulation in the cardiac electric field.[11] The anisotropic properties of the cardiac muscle in the ECG forward problem are considered by FEM. In the surrounding isotropic volume conductors, the BEM is adopted. The BEM is known as a method to be applied for the numerical calculation of surface potential. Coupling is enabled by requesting continuity of the electric potential and the normal of the current density across the boundary of the heart.

Electrocardiographic parameters examined in this study include several popular ones like QT interval, QT dispersion, and QT peak dispersion (QTpD).[14,15] We also include the parameters derived from the combination of multiple leads like vector magnitude (VM) and principal component analysis (PCA). The purpose of using VM and PCA signals is for more robust measurements of ECGs.

Methods

The proposed cell-to-ECG model consists of 4 major portions as shown in Fig. 1, which include cell model, propagation algorithm, FEM-BEM method, and calculating body surface potential map (BSPM). The cell model portion calculates up to 12 ion channel currents and also generates transmural and longitudinal heterogeneities. The FEM-BEM method was used to handle forward model calculation and also tissue geometry (heart, lung, torso, etc) and conductivity. The propagation algorithm controls propagation speed on different myocardium, Purkinje fibers, and fiber orientation for anisotropic propagation. The BSPM is computed based on the derived conversion matrix from previous 3 portions.

Cell model

The cell model is based on the latest human cell model.[8,9] There are 12 ion channels built into this model, where fast and slow potassium channels Ikr, Iks, Ik1, and Ito are most relevant to this study. In this latest model, a Markov process is used to describe the dynamics of Ikr. More specifically, the Ikr status is defined by 5 states as:

$$C_1 \underset{\beta_1}{\overset{\alpha_1}{\Leftrightarrow}} C_2 \underset{\beta_2}{\overset{\alpha_2}{\Leftrightarrow}} C_3 \underset{\beta_3}{\overset{\alpha_3}{\Leftrightarrow}} O \underset{\beta_4}{\overset{\alpha_4}{\Leftrightarrow}} I,$$

where C denotes the closed state; O, the open state; and I, the inactivated state. Each state is controlled

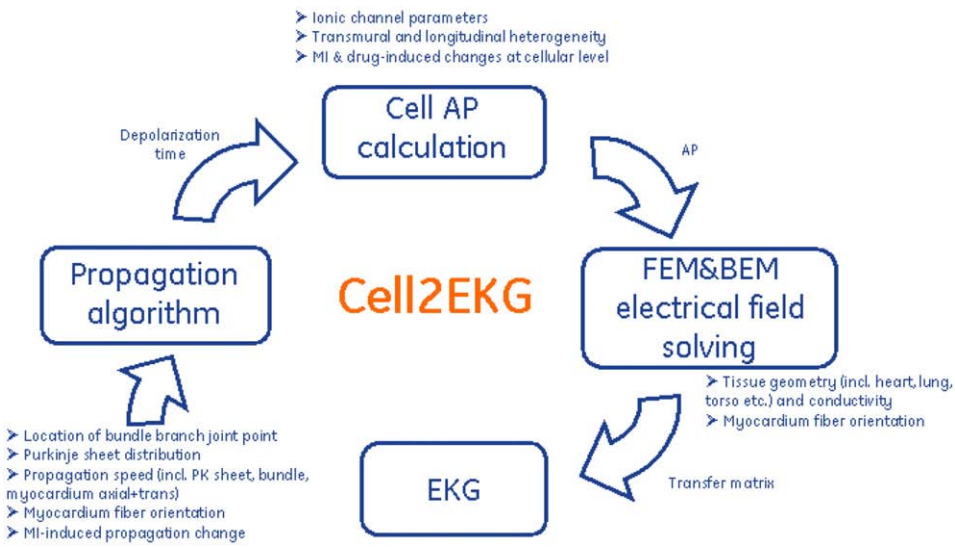

Fig. 1. A flowchart of the cell-to-ECG model.

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