Cell-to-ECG Modeling and Clinical Trial ECG Evaluation of ECG J-to-T Peak Interval

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Abstract

Drug induced prolonged QT is associated with torsade de pointes (TdP), and therefore has been under a thorough investigation by FDA for the last 10 years. The main focus has been on the rapid delayed outward rectifier potassium current (Ikr) effects on the ECG QT interval. Lately, multi-ion channel effects like late-sodium and calcium currents have also been investigated, and the new ECG parameters like Tpeak-to-Tend (TpTe) and J-to-Tpeak (JTp) have been shown to correlate with multiple ion-channel changes.

This study used a newly modified Cell-to-ECG whole heart model to simulate multi-ion channel effects on QT, TpTe and JTp intervals. The heart model combined the modified ion-channel with added Late Sodium current (I_{naL}) and a human ventricle heart geometry. The simulation induced the blockage of Ikr, I_{naL}, separately, and combined. The clinical data was from an FDA sponsored clinical trial with 22 healthy subjects who each received a single dose of a pure hECG blocker (dofetilide) and 3 drugs that also block calcium or sodium (quinidine, ranolazine, and verapamil) as part of a 5-period, placebo-controlled cross-over trial.

The modeling results showed the I_{kr}-only-block prolongs QT by prolonging both TpTe and JTp intervals. The combination of I_{kr} and I_{naL} block caused QT and TpTe prolongation, but to a lesser extent; the JTp interval was shortened. The clinical trial data verified that for hECG blocker dominant drugs like dofetilide and quinidine, QT, TpTe and JTp were all prolonged with the increase of drug concentration; while balanced I_{kr} and I_{naL} by ranolazine had no effect on JTp. The modeling simulation predicted the trend of clinical results. I_{naL} block can shorten the JTp prolongation caused by Ikr block.

1. Introduction

The adverse cardiac effects by drugs have been a focus of the FDA and drug companies since a series of released drugs were withdrawn from the markets in the 1990s [1]. Since all the drugs withdrawn increased the risk of torsade-de-pointes (TdP) with different levels of blockage of the potassium channel encoded by the human *ether-à-go-go* related gene (hERG), which is reflected on the heart rate corrected QT interval (QTc) prolongation of ECG, the focus of cardiac safety regulation has been on the measurement of the QT interval changes during clinical trials [2,3]. However, there are at least 2 major issues with the QT interval: 1) it is a poor surrogate of TdP, since there are other factors besides duration of repolarization playing important roles, like dispersion and occurrence of early after depolarizations; 2) when multiple ion channels are affected by a drug, it is not all reflected on QT interval changes [1].

Lately there are many efforts trying to find other ECG parameters, especially T wave morphology related parameters. The purpose is to improve the sensitivity and specificity of identifying drug compounds associated with the risk of TdP and other adverse cardiac effects [4-6]. In order to evaluate the new T wave morphology ECG parameters along with the QT interval, the FDA sponsored a prospective clinical trial with several on-the-market drugs [7].

In the clinical trial, 22 healthy subjects received a single dose of a selective hERG blocker (dofetilide) and three drugs that also block calcium or sodium (quinidine, ranolazine and verapamil) as part of a five period, placebo controlled cross-over trial. The trial results revealed that T wave morphology changes are directly related to amount of hERG block, but less sensitive to multichannel block. In this clinical study, ranolazine, which blocks both hERG and late sodium currents (InaL), prolonged QTc by prolonging T peak-to-T end interval (TpTe) with no effect on the heart rate corrected J-to-T peak interval (JTp). Since ranolazine is one of the drugs which have significant QTc prolongation but do not cause TdP, the combination of JTp and QT might be useful for differentiating 'good' and 'bad' QT prolongation drugs.

The focus of this study is to simulate the combination of Ikr and InaL ion currents with a previous published computational cell model and whole heart model [8], and to evaluate JTp, TpTe, and QT changes found in the clinical study.

2. Methods

The model includes both cell model and forward model.

2.1. Cell models

The cell model was based on ten Tusscher's human cell model [9]. The fast potassium channel was added from Fink-Noble model, which used a Markov process to describe the dynamics part [10]. A Late sodium current was then added based on Xia's paper [11], which takes two gates formulation:

$$I_{NaL} = G_{NaL} m_L^3 h_L (V_m - E_{Na}) \qquad (1)$$

where m_L is an activation gate and h_L is an inactivation gate. Each of these gates is governed by Hodgkin-Huxley-type equations for gating variables and characterized by a steady-state value ($m_{L,\infty}$ and $h_{L,\infty}$) and a time constant (τ_{mL} and τ_{hL}) for reaching this steady-state value, both of which are functions of trans-membrane potential (V_m).

$$\begin{aligned}
m_{L,\infty} &= \frac{\alpha_{m,L}}{\alpha_{m,L} + \beta_{m,L}} \\
\tau_{mL} &= \frac{1}{\alpha_{m,L} + \beta_{m,L}} \\
\alpha_{m,L} &= \frac{0.32(V_m + 47.13)}{1 - \exp(-0.1(V_m + 47.13))} \qquad (2) \\
\beta_{m,L} &= 0.08 \exp\left(\frac{-V_m}{11.0}\right) \\
h_{L,\infty} &= \frac{1}{1 + \exp\left(\frac{V_m + 91}{6.1}\right)} \\
\tau_{hL} &= 600ms
\end{aligned}$$

G_{NaL} is the maximum value of late sodium conductance, $G_{NaL} = 0.0065\ mS/uF$; and E_{Na} is the Nernst potential for sodium.

2.2. Forward model

The forward model was developed based on actual scanned 3-D heart ventricles, left and right. A bidomain model-based Finite-Element-Model (FEM) and Boundary-Element-Model (BEM) coupling formulation in the cardiac electric field was used [12]. The formula to solve forward model is divided into 2 parts: inside myocardium and from the heart surface to the torso. For the inside myocardium portion, FEM method is applied to consider the anisotropy of myocardium. From the heart surface to torso, BEM method is applied for higher computational efficiency.

2.3. Model simulation design

The model simulation parameters were set to match the FDA clinical trial's experiments [7]. In their patch clamp experiments, dofetilide has about 55% I_{kr} block at the population's mean maximum concentration (Cmax); Ranolazine has about 26% I_{kr} block and 21% I_{naL} block at Cmax.

The current modeling set the I_{kr} and I_{naL} conductance to 6 levels, with level 1 for base level with no block, and level 2-6 have the block percentages as shown in Table 1.

Table 1: Settings of I_{kr} potassium and I_{naL} late sodium channel's conductance

Level	**1**	**2**	**3**	**4**	**5**	**6**
hERG block (%)	0	5	10	15	20	26
I_{naL} block (%)	0	4	8	12	16	21

The model simulations were run in 3 batches: 1) only applying I_{kr} block; 2) only applying I_{naL} block; 3) applying both I_{kr} and I_{naL} blocks.

2.4. ECG measurements

The ECG measurements of JTp, TpTe, and QT were based on a software, QT Guard Plus™ of GE Healthcare, which was designed for cardiac safety clinical trial and repolarization analysis. The module includes the core algorithm of GE's 12SL™, a widely used multi-lead ECG interpretation algorithm, and a principal-component-analysis (PCA) based T wave morphology analysis. In the QT Guard Plus, JTp, TpTe, and QT are calculated based on a composite signal of vector magnitude of 12-lead signals [5].

The end of T wave algorithm is described in [13], which used the slope of T wave and the area of T wave for the criteria. The peak of T wave was not simply based on the maximum point of T wave, since it is not reliable with plateau of T wave or when notch appears. Instead, a center of T wave plateau region was selected [14].

3. Results

The first part of the simulation was to apply I_{kr} block only based on the setting on the table 1, where I_{naL} block is not applied. Figure 1-a shows the resulted vector magnitude (VM) lead for 6 levels of I_{kr} channel block, ranging from 0 to 26%, with each tracing corresponding to one block case. The bottom curve is the base case with 0 block, and the top curve has 26% block. Individual ECG lead, like V3, shows more obvious T wave notch when more significant I_{kr} blocks were applied. Both V3 and VM

leads show significant T wave morphology changes with more flatness on top of T wave, and T wave notches. The QT interval is increased from 386 to 414 msec, JTp is increased from 222 to 238 msec, and TpTe is increased from 72 to 84 msec, as shown in Figure 1-b.

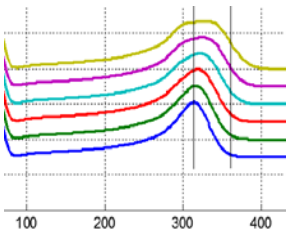

Figure 1-a. The resulted vector magnitude ECG of 6 settings of hERG channel block, ranging from 0 to 26%, which each tracing corresponding to one block case. The bottom curve is the base case with 0 block, and the top curve has 26% block.

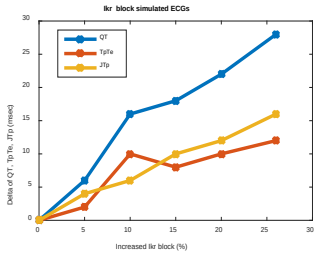

Figure 1-b, ECG parameters QT, TpTe, JTp changes with only increased I_{kr} blocks. All 3 intervals are prolonged.

The second batch of simulations applied I_{naL} block only with the setting as shown in table 1, where I_{kr} block was not applied. Figure 2 shows the plot of VM lead for 6 levels of I_{naL} block, ranging from 0 to 21%, with each tracing corresponding to one block case. The bottom curve is the base case with 0 block, and the top curve has 21% block. We can see that the T wave morphology changes are not as obvious as in hERG block cases above, and that both the JTp and QT intervals are gradually reduced with the increase of InaL block.

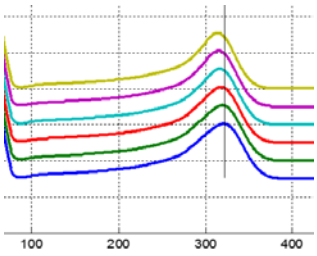

Figure 2. The resulted vector magnitude ECG of 6 settings of InaL channel block, ranging from 0 to 21%, with each tracing corresponding to one block case. The bottom curve is the base case with 0 block, and the top curve has 21% block.

The third batch of simulations applied both I_{kr} and I_{naL} blocks as in Table 1. Figure 3-a shows the VM lead for 6 simulated cases with the bottom one having no block and top one having 26% block of I_{kr} and 21% block of I_{naL}. It shows prolonged QT interval and T wave plateau increase.

The T wave notch is more obvious from lead v3. The QT interval was increased from 386 msec to 404 msec, TpTe was increased from 72 to 96 msec, while JTp was slightly decreased from 222 to 216 msec as in Figure 3-b.

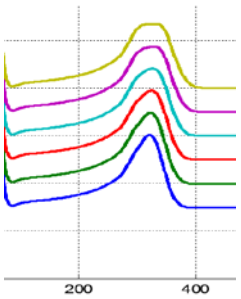

Figure 3-a. The resulted vector magnitude ECG of 6 settings of both hERG and I_{naL} channels block, ranging 0 to 26% for I_{kr} and from 0 to 21% for I_{naL}, with each tracing corresponding to one block case. The bottom curve is the base case with 0 block, and the top curve has 26% block for I_{kr} and 21% block for I_{naL} respectively.

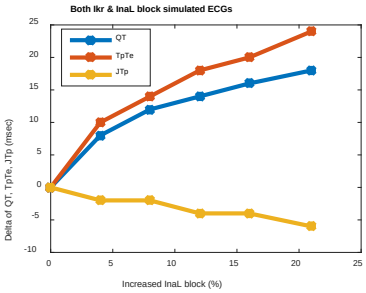

Figure 3-b, ECG parameters QT, TpTe, JTp changes with both increased I_{kr} and I_{naL} blocks. The QT and TpTe are prolonged, but JTp is flat or slightly shortened.

Figure 4 shows the ECG parameters measurement based on FDA's clinical trial data, measured by QT Guard Plus™ (GE Healthcare) software. It is the response-exposure plots of QTc, JTp, and TpTe of 3 drugs (two predominant hERG blockers: dofetilide and quinidine; and a balanced Ikr and InaL blocker: ranolazine) from FDA clinical trial. It shows that all drugs with hERG block have prolonged QTc, TpTe and JTp with exposure increase, with only exception of ranolazine which had no effect on JTp due to InaL block.

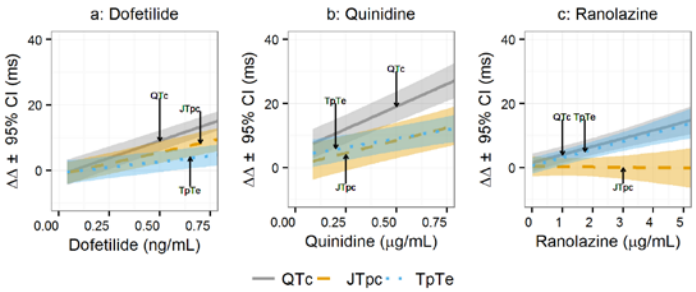

Figure 4. The response-exposure plots of QTc, JTpc, and TpTe of 3 drugs in FDA clinical trial, measured by QT Guard Plus ™ (GE Healthcare). It shows that all drugs with hERG block have prolonged QTc, TpTe and JTp with exposure increase, with only exception of ranolazine which had no effect on JTp due to I_{naL} block.

4. Discussions

The results of our cell-to-ECG model simulations show the effects of I_{kr} block and I_{naL} block on ECG morphology in general, and the specific effects on the QT, TpTe, and JTp intervals. In order to compare with the FDA clinical trial data, this study was focused on the ion channel block setting from ranolazine's patch clamp experiment with a 26% of I_{kr} block and 21% of I_{naL} block at Cmax. By applying the same block effect for I_{kr} and I_{naL} in our model, the simulation showed similar trends as the clinical trial data, i.e. the prolongation of the QT and TpTe interval, and slight decrease of JTp interval on simulated surface ECG. This is an interesting verification for the clinical trial ECG measurements, and a good match of clinical and physiological modeling results.

Another factor for the modeling simulation is to set the transmural dispersion of the ventricle, from endocardium to epicardium layers. In our model, the dispersion could be set with different ion channel conductance from layer to layer as we did in the previous studies [8][15]. However, we ignored the transmural dispersion in this study for simplicity purposes. More experiments of dispersions can be conducted in later studies.

It looks like JTp can be a useful addition to the QT interval for assessing the cardiac effect of drugs. However, detection of T peak is not a trivial task as indicated in the method section. Therefore, adding another 'controversial' ECG parameter detection to an already complicated detection of the end of T wave is not ideal from a signal processing point of view, and may not be ideal from a clinical practice point of view either. Our approach of detecting the T peak is the same as our method of detecting the T end, making it as robust and global as possible. That is why we tried to avoid any lead-by-lead approach, and instead, used a global composite lead, like the VM. When T wave morphology gets complicated as a plateau or notch appears, our method takes the center of the T wave plateau region, which is more robust than simply picking the maximum point of T wave. This T peak measurement has been verified by our modeling simulation to better reflect transmural dispersion than the maximum point of T wave [8].

For the future research of modeling multi-ion channel effects on ECG, we would like to try different ion channel models and with different dispersion experiments.

Acknowledgements

The author would like to acknowledge Dr. Jose Vicente of FDA for his contributions of ECG data analysis and providing the information of drug compounds' patch clamp experiments.

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