Effects of L-type calcium channel and human ether-a-go-go related gene blockers on the electrical activity of the human heart: a simulation study

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Received 9 October 2013; accepted after revision 11 April 2014; online publish-ahead-of-print 16 September 2014

Aims
Class III and IV drugs affect cardiac human ether-a-go-go related gene (I_{Kr}) and L-type calcium (I_{CaL}) channels, resulting in complex alterations in repolarization with both anti- and pro-arrhythmic consequences. Interpretation of their effects on cellular and electrocardiogram (ECG)-based biomarkers for risk stratification is challenging. As pharmaceutical compounds often exhibit multiple ion channel effects, our goal is to investigate the simultaneous effect of I_{CaL} and I_{Kr} block on human ventricular electrophysiology from ionic to ECG level.

Methods and results
Simulations are conducted using a human body torso bidomain model, which includes realistic representation of human membrane kinetics, anatomy, and fibre orientation. A simple block pore model is incorporated to simulate drug-induced I_{CaL} and I_{Kr} blocks, for drug dose = 0, IC_{50}, 2 × IC_{50}, 10 × IC_{50} and 30 × IC_{50}. Drug effects on human ventricular activity are quantified for different degrees and combinations of I_{CaL} and I_{Kr} blocks from the ionic to the body surface ECG level. Electrocardiogram simulations show that I_{CaL} block results in shortening of the QT interval, ST elevation, and reduced T-wave amplitude, caused by reduction in action potential duration and action potential amplitude during the plateau phase, and in repolarization times. In contrast, I_{Kr} block results in QT prolongation and reduced T-wave amplitude. When I_{CaL} and I_{Kr} blocks are combined, the degree of I_{CaL} block strongly determines QT interval whereas the effect of I_{Kr} block is more pronounced on the T-wave amplitude.

Conclusion
Our simulation study provides new insights into the combined effect of I_{CaL} and I_{Kr} blocks on human ventricular activity using a multiscale computational human torso model.

Keywords
hERG block • L-type calcium block • QT interval • ECG modelling • Computer simulation • Dispersion of repolarization

Introduction
Calcium (Ca^{2+}) is the ionic link in cardiac excitation–contraction coupling, which, in cardiac cells, starts following the upstroke of the action potential (AP) and causes the opening of the L-type voltage-dependent Ca^{2+} channels. These ion channels are expressed by the CACNA1C gene. L-type Ca^{2+} channels constitute one of the most important Ca^{2+} entry pathways into the cell and have been classified by their sensitivity to dihydropyridine-based compounds (e.g. nifedipine). Different compounds have been developed to target calcium channels and in particular L-type calcium channels. The compounds aim to modulate the cardiac ventricular L-type Ca^{2+} current (I_{CaL}). These agents have been classified to three main classes: phenylalkylamines (e.g. verapamil), benzothiazepines (e.g. diltiazem), and dihydropyridines (e.g. nifedipine).1 Calcium channel blockers have wide clinical applicability and they are used to decrease blood pressure in patients with hypertension. Calcium channel blockers are also frequently used to alter heart...
rate, to prevent cerebral vasospasm, and to reduce chest pain caused by angina pectoris. However, it has been shown that they could increase the mortality rate in elderly patients, and have been known to have multiple side effects. They have also been associated with a risk of cancer. Abnormalities in \( I_{\text{CaL}} \) in particular, have also been linked to ventricular arrhythmias, impaired excitation–contraction coupling leading to heart failure, as well as atrial fibrillation. These abnormalities could be related to cardiac diseases or to drug-induced side effects. In both cases, they result in ionic currents abnormalities, which cause alterations in both ventricular depolarization and repolarization properties.

Of particular concern are changes in ventricular repolarization caused by combined \( I_{\text{CaL}} \) and rapidly activating potassium current \( I_{\text{Kr}} \) alterations, which can manifest themselves as changes in the QT interval and T-wave of the electrocardiogram (ECG), and have been linked to increased risk of arrhythmic death. QT prolongation is considered an indicator of increased risk of torsades de pointes and can lead to the abandonment of the compound development. However, some QT prolonging drugs present no arrhythmic episodes and some others are known to be useful antiarrhythmic drugs for most patients. Interpretation of drug-induced effects on the ECG is however challenging due to the variability of cardiac substrates and also to the frequent multichannel action of most compounds. Therefore, a better understanding of drug-induced changes in the ECG and how they relate to ionic mechanisms and arrhythmic risk is needed.

Recent reviews have highlighted how computational modelling and simulation can help in the investigation of arrhythmias and antiarrhythmic therapy. Recent studies have specifically shown the usefulness of whole-ventricular computer simulations to investigate drug effects on the electrical activity of the heart. In this study, we aim at using a multiscale computational human torso model to investigate and quantify the combined effect of \( I_{\text{CaL}} \) and \( I_{\text{Kr}} \) block on human ventricular activity from the ionic to the ECG level.

### What’s new?

- A mathematical model of the human cardiac ventricles embedded in a torso is used to simulate the effect of multiple ion channel block on the electrical activity of the heart from ion channel to electrocardiogram.
- L-type calcium block results in QT interval shortening, ST elevation, and T-wave amplitude reduction, caused by decrease in action potential duration and action potential amplitude and in dispersion of repolarization.
- When L-type calcium current \( (I_{\text{CaL}}) \) and rapidly activating potassium current \( (I_{\text{Kr}}) \) blocks are simultaneously applied, QT interval is more sensitive to the degree of \( I_{\text{CaL}} \) block whereas T-wave amplitude is mostly determined by \( I_{\text{Kr}} \) block.

### Methods

#### Human multiscale torso–heart model

A human model of the cardiac ventricles embedded in a torso is used and illustrated in Figure 1A and B. The human ventricular model includes realistic representation of human ventricular kinetics, anatomy, and fibre orientation as previously described in Zemzemi et al. Briefly, the anatomical model is based on data presented in Chapelle et al. and the computational mesh contains 2,401,151 vertices and 14,336,528 tetrahedral elements. The Ten Tusscher and Panfilov human AP model is used to represent human membrane kinetics throughout the myocardium, including epicardial, endocardial, and mid-myocardial ionic properties based on transmural location. Therefore, transmural heterogeneity in the human AP was introduced in our human ventricular model, in agreement with previous studies such as Okada et al.

The human ventricular model is coupled to the diffusion equation in the torso to take into account the propagation of the electrical wave from heart to torso to compute the ECGs on the body surface. To mimic Purkinje network activation, the endocardium surface is then progressively activated from apex to base to produce a simulated activation sequence illustrated in Figure 1A, in line with the experimental results by Durrer et al.

#### Drug/ion channel interaction model

The human AP model was modified to enable simulation of drug action on \( I_{\text{CaL}} \) and \( I_{\text{Kr}} \) using the simple pore block model. The degree of channel block is a function of drug concentration and the drug half maximal inhibitory concentration (\( IC_{50} \)) value for the targeted ionic channel. Thus, for a given drug dose \( [D] \) and \( IC_{50} \) value with respect to the channel \( j \) the formulation of drug action on the ionic current conductance \( g_j \) is given by:

\[
g_j([D]) = g_j \left( \frac{1}{1 + \left( \frac{[D]}{IC_{50}} \right)^n} \right)
\]

with Hill coefficient \( n = 1 \).
node located at the base of the left ventricle. Previous studies have linked changes in T-wave amplitude with the Wilson ventricular gradient, which is the gradient of the transmembrane potential in the ventricles. As in references, we therefore quantified the Wilson ventricular gradient by computing the spatial dispersion of ventricular repolarization. To do so, the spatial dispersion of transmembrane potential throughout the human ventricles is calculated at each time step during the simulations, as the voltage difference between the maximal and minimal values of the transmembrane potential throughout the ventricles at each time step. Its maximum value over time during the repolarization phase is quantified and referred to in the paper as the maximum (spatial) dispersion of transmembrane potential, for each simulation.

Results

The human whole-ventricular model embedded in the torso (Figure 1A and B) was used to simulate the effect of \( I_{CaL} \) and \( I_{Kr} \) blocks on ventricular electrophysiology and the ECG. Figure 1C shows the simulated effect of \( I_{CaL} \) block on a representative ventricular AP at a point located at the base of the ventricles.

**Figure 1** (A) A cross-section of the human ventricles showing the activation times map transmurally and on the endocardium. (B) Distribution of the body surface potential (right) for the IC50 \( I_{CaL} \) block dose in a snapshot taken during the repolarization phase. (C) Simulated effect of different doses (control, 1 \( \times \) IC50, 2 \( \times \) IC50, 10 \( \times \) IC50, 30 \( \times \) IC50) of \( I_{CaL} \) blocker on a representative ventricular AP at a point located at the base of the ventricles. X-axis time (ms), Y-axis potential (mV). (D–H) Simulated effect of combined \( I_{CaL} \) and \( I_{Kr} \) blockers on the second lead of the ECG. Drug dose is 0 \( \times \) IC50, 1 \( \times \) IC50, 2 \( \times \) IC50, 10 \( \times \) IC50, and 30 \( \times \) IC50 for \( I_{Kr} \) blocker in Panels D–H, respectively, and in each panel a different dose of \( I_{CaL} \) block is shown with a different colour as shown in the legend. X-axis shows time in ms, Y-axis potential in mV.
increase in APD and shortening of APD\(_{90}\). Indeed APD\(_{90}\) shortens from 290 ms in control to 242, 219, 150, and 126 ms for I\(_{\text{CaL}}\) block dose of 0.39 mV) for IC\(_{50}\) and 2\(\times\)IC\(_{50}\), respectively. The effect of IC\(_{50}\) block was shown in our previous work,\(^1\) and as expected, it leads to a progressive prolongation of the APD\(_{90}\) from 290 ms in control conditions to 312 ms for IC\(_{50}\), 30\(\times\)IC\(_{50}\), and to 320, 334, and 337 ms) for 2\(\times\)IC\(_{50}\), 10\(\times\)IC\(_{50}\), and 30\(\times\)IC\(_{50}\), respectively. This corresponds to APD\(_{90}\) prolongation by 7.5, 10, 15, and 16% for IC\(_{50}\), 2\(\times\)IC\(_{50}\), 10\(\times\)IC\(_{50}\), and 30\(\times\)IC\(_{50}\), respectively. This corresponds to APD\(_{90}\) prolongation by 7.5, 10, 15, and 16% for IC\(_{50}\), 2\(\times\)IC\(_{50}\), 10\(\times\)IC\(_{50}\), and 30\(\times\)IC\(_{50}\), respectively. 

Drugs often exhibit multichannel action and therefore their effects on the heart are difficult to interpret. This is especially the case, when the ion channels affected by the drug have counteracting effects on cardiac behaviour such as I\(_{\text{CaL}}\) and I\(_{\text{Kr}}\), inward and outward currents, respectively, and both important during the plateau and repolarization phases of the human ventricular AP. Therefore, simulations using the human torso model were conducted to investigate the effect of combined I\(_{\text{CaL}}\) and I\(_{\text{Kr}}\) blocks on the ECG for 25 different dose combinations. Figure 1D–H displays ECG traces obtained for five I\(_{\text{CaL}}\), block doses, for no I\(_{\text{Kr}}\) block (e.g. control, Figure 1D), and IC\(_{50}\), 2\(\times\)IC\(_{50}\), 10\(\times\)IC\(_{50}\), 30\(\times\)IC\(_{50}\) doses of I\(_{\text{Kr}}\) blocker (Figure 1E–H, respectively).

For all I\(_{\text{Kr}}\) blocker doses, the most notable effects of increasing I\(_{\text{CaL}}\) block in the ECG are a progressive shortening of the QT interval and simultaneous elevation of the ST segment with increasing dose. Indeed, the QT interval decreases from 315 ms in control to 265 ms (by 15%) for I\(_{\text{CaL}}\) block dose of IC\(_{50}\), to 240 ms (by 23%) for 2\(\times\)IC\(_{50}\), to 176 ms (by 44%) for 10\(\times\)IC\(_{50}\), and to 157 ms (by 57%) for I\(_{\text{CaL}}\) block dose of 30\(\times\)IC\(_{50}\). The ECG changes caused by I\(_{\text{CaL}}\) block in Figure 1D–H, and specifically the QT shortening, are explained by the AP changes shown in Figure 1C, and in particular the decrease in both APD and plateau levels caused by the reduced I\(_{\text{CaL}}\) as blocker dose is increased. Our simulations result also show that when I\(_{\text{Kr}}\) block is added to I\(_{\text{CaL}}\) block, QT shortening still occurs but becomes milder due to the APD\(_{90}\) prolongation by IC\(_{50}\) than for 10\(\times\)IC\(_{50}\). This corresponds to increasing IC\(_{50}\) block dose results in de-

Discussion

In this work, we have shown the ability of computer simulations to provide insights into the effect of multiaction ion channel blockers on the electrical activity of the human heart and its reflection on...
Figure 2  (A) Effect of different combinations of $I_{Kr}$ and $I_{CaL}$ blocks doses ($0 \times IC_{50}, 1 \times IC_{50}, 2 \times IC_{50}$) on the second lead of the ECG. X-axis time (ms). Y-axis potential (mV). (B) Effect of different combinations of $I_{Kr}$ ($0 \times IC_{50}, 1 \times IC_{50}, 2 \times IC_{50}$) from left to right and $I_{CaL}$ ($0 \times IC_{50}, 1 \times IC_{50}, 2 \times IC_{50}$) from top to bottom on the APD$_{90}$ distribution. Colour bar in millisecond.
the body surface ECG. This is possible through the use of a multiscale human torso–heart anatomical model with biophysically detailed representation of human ventricular membrane dynamics, fibre orientation, and electrophysiological heterogeneity. Our study extends our previous work showing the effect of potassium and sodium channel block on the ECG.\textsuperscript{15,16} Here, we focus on investigating the manifestation of the simultaneous block of the inward $I_{\text{CaL}}$ and the outward $I_{\text{Kr}}$ on human whole-ventricular activity, which has opposite effects on cardiac repolarization and therefore presents a challenge in the interpretation of the ECGs.

![Figure 3](https://example.com/figure3.png)

**Figure 3** Effect of combining doses of L-type calcium and hERG blockers (control, 1 × IC\textsubscript{50}, 2 × IC\textsubscript{50}, 10 × IC\textsubscript{50}, 30 × IC\textsubscript{50}) on the QT interval (units are mV, ms, and ms, respectively) (A), on the APD\textsubscript{90} (B), and on the maximum dispersion of the transmembrane potential during the repolarization phase (C). The APD\textsubscript{90} is computed from a point located at the base of the left ventricle.
Our results show that $I_{\text{CaL}}$ block results in shortening of the QT interval, reduction of T-wave amplitude, elevation of the ST segment, and slight widening of the QRS complex. The changes in the ECG are explained by the shortening of APD, reduction of AP amplitude during the plateau phase, decrease of maximum dispersion of the transmembrane potential, and a slight reduction in conduction velocity.

Clinical data on the effect of calcium blockers on the ECG have mostly focused on their effect on the atria and the atrioventricular node, rather than in the human ventricles and the ECG, and often in combination with other drugs. Our simulation results are however in agreement with experimental studies reporting APD and QT shortening caused by verapamil in feline wedge preparations. Furthermore, the QT interval shortening and the ST segment elevation in human have also been linked to L-type calcium channel function. Thus, Antzelevitch et al. reported that gene mutations mainly in CACNA1C and CACNB2 result in loss of $I_{\text{CaL}}$ function and cause a QT shortening and ST elevation, as reported in our simulations. It has also been reported in Proano et al. that overdoses of calcium blockers come with abnormalities in T-wave and ST segment. These abnormalities could be seen in our simulation in Figure 1D and E for high doses of L-type calcium block (e.g. 10 $\times$ IC50 and 30 $\times$ IC50).

Our theoretical investigation aims at providing new insights, which could be valuable for ECG interpretation. The combined action of $I_{\text{CaL}}$ and $I_{Kr}$ blocks investigated in our study is particularly interesting as the two currents have opposite effects on cardiac repolarization and therefore lead to complex and counteracting changes in ECG biomarkers with difficult interpretation. Our results show that the main effect of $I_{\text{CaL}}$ block on the ECG is QT shortening and slight ST elevation, whereas $I_{Kr}$ block results in QT prolongation and T-wave peak reduction. The simultaneous application of $I_{Kr}$ and $I_{CaL}$ blocks in doses from IC50 to 30 $\times$ IC50 block results in overall decrease in APD and QT interval, which means that for a similar IC50/dose relationship, the effect of $I_{CaL}$ block on the APD and QT interval is more pronounced than $I_{Kr}$ block in our human model.

Importantly, our simulations show that $I_{Kr}$ block effects are more important in determining the T-wave amplitude than $I_{CaL}$ block. Moreover for high doses of $I_{Kr}$ block, our study shows that there is a critical dose of $I_{CaL}$ block, in this case 10 $\times$ IC50, in the regulation of T-wave peak: lower $I_{CaL}$ blocker doses reduce the T-wave amplitude and higher doses, increases the T-wave amplitude. Our results suggest that the maximum spatial dispersion in transmembrane potential during the repolarization phase plays an important role in this modulation, as suggested by results shown in (Figure 3C).

A strong correlation is seen between changes in APD and QT interval caused by both $I_{Kr}$ and $I_{CaL}$ blocks and also by their combination. This is mainly due to the fact that both $I_{Kr}$ and $I_{CaL}$ blockers affect the repolarization phase, and have negligible effects during the depolarization of the AP, as shown in our simulations. Therefore, $I_{Kr}$ and $I_{CaL}$ blockers also have negligible effects on conduction velocity, activation patterns under sinus rhythm and therefore the QRS complex is not affected (Figures 7 and 2). The QT interval is therefore mostly affected by changes in APD. In the presence of sodium blockers however, as considered in our previous study, increasing drug dose results in changes in activation sequence and a prolongation of the QRS and QT interval durations, without any significant effects on the APD. Therefore, the QT interval prolongation caused in the presence of sodium block is not solely correlated with APD. The human torso–heart model presented in our study could be used to simulate additional drug effects, and our results could be of value to guide the evaluation and interpretation of ECG data obtained following application of Class III and Class IV blockers exhibiting multichannel action. Future work could also extend our work to include inter-subject variability in anatomy and electrophysiology and by extending the simple pore block drug model to include inter-subject variability in anatomy and electrophysiology.

Conclusion

In this study, we present a simulation study of the effect of ion channel block on the electrical activity of the heart from drug/ion channel interactions to the ECG. The human bidomain model of the heart embodied in a torso allows for ECG simulations to be conducted with realistic representation of human anatomy and electrophysiological function, and could be used for further investigations including specific drug effects or disease conditions. We show how $I_{CaL}$ block reduces the APD and the AP amplitude during the plateau phase, which, in the ECG, results in ST elevation, QT interval shortening, and slight T-wave amplitude reduction. As drugs often exhibit multiple channel effects, we evaluated the simultaneous effect of $I_{CaL}$ and $I_{Kr}$ on human cardiac activity. As expected, $I_{CaL}$ and $I_{Kr}$ blocks have opposite effects on the QT interval of the ECG: $I_{CaL}$ reduces the QT interval whereas $I_{Kr}$ prolongs it. However, QT interval is more sensitive to $I_{CaL}$ block, and therefore combined block results in QT shortening. On the contrary, T-wave amplitude is mostly determined by $I_{Kr}$ block dose, even though both $I_{CaL}$ and $I_{Kr}$ decrease T-wave peak. Our simulations show that modulation of the T-wave peak in most cases reflects changes in the maximum spatial dispersion of transmembrane potential. Finally, our study illustrates how the multiscale nature of our human torso/heart model allows for the assessment of the consequences of drug-induced ionic changes on the AP at the cell level, on the APD distribution throughout the ventricles, activation and repolarization maps at the organ level, and on the ECG at the body surface level. Both the human model and the insights provided by the simulation study could contribute to a better characterization of drug-induced effects on the heart for pre-clinical drug testing and also to unravel the ionic basis of new biomarkers of predicting drugs cardiotoxicity.
Acknowledgements

The authors thank Drs Philippe Moireau, Miguel Fernandez, and Elsie Phe from INRIA Paris-Rocquencourt for their work on the anatomical models and meshes. We are also grateful to Professors Dominique Chapelle and Jean-Frederic Gerbeau heads of MACS and REO teams, respectively, in INRIA Paris-Rocquencourt for providing us with the meshes.

Conflict of interest: none declared.

Funding

This study was supported financially by the European Commission preDICT grant (DG-INFSo—224381), a UK Medical Research Council Career Development Award (to B.R.) and a UK Wellcome Trust Senior Fellowship in Basic Biomedical Sciences (to B.R.). Funding to pay the Open Access publication charges for this article was provided by the UK Wellcome Trust Senior Fellowship in Basic Biomedical sciences.

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