Role of L-type Calcium in Modulating Pro-Arrhythmic Effects of Dofetilide in Humans

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Abstract

Dofetilide is a class III drug whose use needs to be monitored due to the possible occurrence of Torsades de Pointes (TdP). The mechanisms are unclear but research suggests that both early-afterdepolarizations (EAD) and increased dispersion of action potential duration (APD) might be involved. Importantly, drug-induced TdP is more common in women, possibly due to higher L-type calcium current (ICaL) levels. Our goal is to use numerical simulation in order to investigate pro-arrhythmic mechanisms of dofetilide in human by characterizing its effects on APD, APD dispersion and EAD formation for varying doses and ICaL levels.

1. Introduction

One of the most dangerous of potential drug side effects is the undesirable side effects of drug action on the heart. Different drugs often result in abnormalities in ionic current properties in the ventricles, which cause alterations in depolarization and/or repolarization properties. In certain cases, drug side effects can result in sudden cardiac death caused by lethal arrhythmias such as TdP [1]. In general, side effects of drugs are seen in the electrocardiograms (ECGs) which is the main tool in drug assessment trials. In particular the QT interval and the T-wave of the ECG are supposed to be the main biomarkers allowing to identify the effect of drugs on the ventricular repolarization. Dofetilide and other class III drugs are known to alter the repolarization of the ventricles, due to their block of the human ether-a-go-go related gene (hERG) ion channel. This channel is the most important contributor to the rapid delayed rectifier potassium current I_{kr}. This current controls the repolarization phase of the action potential and any alteration of this current would directly affect the QT interval and the T-wave.

In the present study, we present simulation results showing how hERG block affect the electrical activity of human ventricular tissue from the ionic level to the pseudo-ECG, using biophysically-detailed electrophysiological mathematical models. We use the monodomain model for the electrical wave propagation and the biophysically-detailed action potential model by Grandi et al. ([2]) to model the changes at the cell level. The AP model is modified to include the effect of specific doses of the anti-arrhythmic drug dofetilide on the rapid component of the delayed rectifier current as proposed by [3]. We also propose to change the L-type calcium current level in order to introduce different heart conditions and to test the role of the L-type calcium current on the generation of EADs.

2. Methods

In this section we present the models that we use in order to perform our simulation experiments. In paragraph 2.1 we present the model governing the electrical propagation through cardiac tissue and in the paragraph 2.2, we introduce the model of interaction between the hERG current and dofetilide.

2.1. Propagation model

We consider the state-of-the art monodomain model describing the propagation of the electrical wave in the heart [4]. The monodomain model is a reaction-diffusion equation coupled to an ordinary differential equations system,

$$\begin{cases} A_{\text{m}}\big(C_{\text{m}}\partial_t v_{\text{m}} + I_{\text{ion}}(v_{\text{m}}, w)\big) - \text{div}(\boldsymbol{\sigma}_{\text{m}}\boldsymbol{\nabla} v_{\text{m}}) = I_{\text{stim}}, \\ \partial_t \boldsymbol{w} + \boldsymbol{g}(v_{\text{m}}, \boldsymbol{w}) = 0, \\ v_{\text{m}}(0,.) = v_0, \text{ and } \boldsymbol{w}(0,.) = \boldsymbol{w}_0. \end{cases} \tag{1}$$

where v_{m} is the transmembrane potential. Constants A_{m} and C_{m} represent the rate of membrane surface per unit of volume and the membrane capacitance, respectively. The myocardium conductivity tensor is represented by $\boldsymbol{\sigma}_{\text{m}}$. The function I_{stim} and I_{ion} are the stimulation and the transmembrane ionic currents. The field of variables $\boldsymbol{w}$ is a vector containing different chemical concentrations and

various gate variables. Its time derivative is given by the vector of functions $\boldsymbol{g}$. Constants v_0 and $\boldsymbol{w}_0$ are the initial conditions of the monodomain problem. We compute the pseudo-ECG at a given location x and time t from the monodomain solution following this formula:

$$ECG(y,t) = \int_{\Omega_H} (-\boldsymbol{\nabla} v_m(x,t)).\boldsymbol{\nabla}_y \frac{1}{|x-y|} dx. \quad (2)$$

2.2. Drug model

Most of the recent mathematical transmembrane ionic models in cardiac electrophysiology include a detailed description of the different ion channels mechanism. Following the Hodgkin and Huxley model [5], these models include a set of ordinary differential equation describing the time evolution of the membrane voltage, different concentrations and the gate variables responsible for opening and closing different ionic channels. The time evolution of the ionic of the membrane voltage (v_m) takes this form [1, 2]

$$\frac{dv_m}{dt} = \frac{1}{C_m}\left(\sum_{j \in \text{channels}} I_j + I_{stim}\right),$$

where C_m is the membrane conductance and I_{stim} is the cell stimulus. For each $j \in$ channels, the current induced by the ionic species flowing through the channel j is given by,

$$I_j = g_j O_j (v_m - E_{ion,j}),$$

where g_j and O_j respectively stand for the maximal conductance and the open probability of the channel j, and $E_{ion,j}$ is the reversal potential for the species flowing through the channel j.

The human action potential model by Grandi [2] was modified to include detailed representation of the drug action on the myocardial cell as in [1, 3, 6]. The idea is to block the ion channel on which the drug is acting. The level of the block depends on the concentration of the drug and the IC_{50} value corresponding to the targeted ionic channel. Following [1, 3, 7, 8], for a given drug dose $[D]$ and the IC_{50} value of the drug with respect to the channel j the formulation of drug action on the channel conductance is given by

$$g_j([D]) = g_j \left(\frac{1}{1 + \left(\frac{[D]}{IC_{50}}\right)^n}\right). \quad (3)$$

The exponent n is called the Hill coefficient and is used in order to provide a good fitting of the drug response curve. It is usually different from a drug to another [9], but in this work n will be equal to one. In this paper our interest will concern the potassium membrane ionic channels, since dofetilide and most of the class III drugs are known

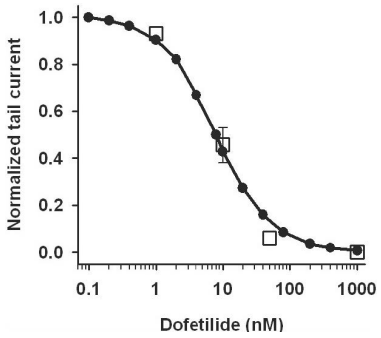

Figure 1. Dose response curve: normalized value of the current *vs* dofetilide dose.

to be hERG blockers. The ionic model is changed to alter the rapid delayed rectifier potassium channel conductance g_{kr} according to equation (3). The IC_{50} of dofetilide is equal to 8.7nMol. It is experimentally extracted from the dose response curve (see Figure 2.2). The model was also modified in order to include different cell types (epi, endo and M-cells) by calibrating the transient outward current (Ito) following [2].

3. Results

A 1D tissue model representing the transmural heterogeneity of the heart was stimulated at 1Hz in the endocardium. The electrophysiological activity was simulated for dofetilide doses [D]=0-120 nM and for ICaL from fCaL=1.0-1.4 of control. All the simulations in this study were performed using Chaste software [6, 10]. Fixing the L-type calcium current at control level and increasing the drug dose of dofetilide from 0 nMol to 120 nMol results in APD increase up to 20% (see Figure 3 (left)). The APD dispersion is increased by 20-30 ms (see Figure 3 (right)). Also maintaining the drug dose at 0 nMol and increasing

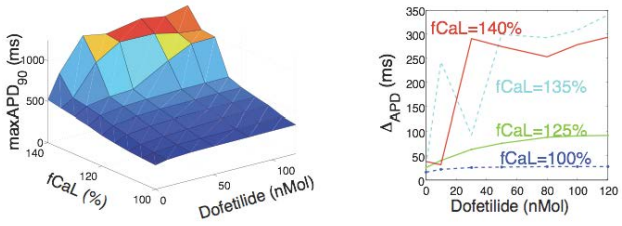

Figure 2. Effect of Dofetilide doses and L-type calcium levels on the maximum APD value (lfet) and the APD dispersion (right).

the L-type calcium current level from 100% to 140%, increases the APD dispersion and the maximum APD, but no EADs appears. By increasing both drug dose and L-type calcium current level, we remark EADs appearance for certain values of both parameters. We can see for ex-

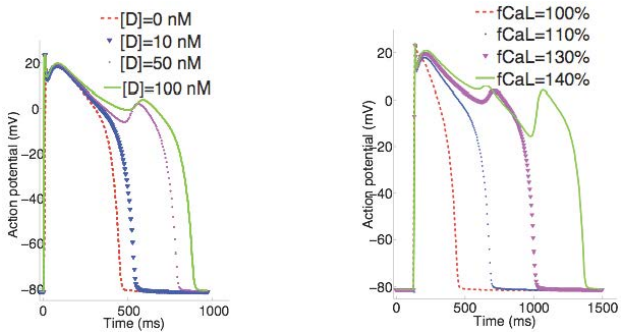

Figure 3. Effect of dofetilide dose on the generation of the EADs, L-type calcium current level 130% (left). Effect L-type calcium current on the action potential and the genesis of EADs, for dofetilide dose [D]=100 nMol (right).

ample in Figure 3 (left) that EADs appear for drug dose higher than [D]=50 nMol when the L-type calcium level 130% is (right). When fixing [D]=100 nMol, EADs do not appear for L-type levels lower than 110% whereas they appear for values higher than 130% (Figure 3 (right)). We

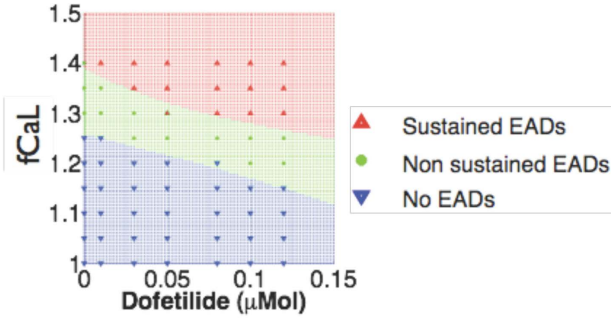

Figure 4. Classification of the EADs appearance with respect to dofetilide dose and fCaL

also found that the amplitude and duration of dofetilide-induced EADs depend on both [D] and fCaL (Figure 3). EADs prolonged APD of up to 1200ms, and increased APD dispersion of up to 300ms due to transmural differences in EADs duration (Figure 3). EADs appear for certain values of [D] and fCaL but they are not sustained in all the cases, vanishing after a certain time. In Figure 3, we provide a classification of three zones: sustained EADs, non-sustained EADs and no EADs occurrence. As explained in the introduction the ECG interval is very important in the identification of the effect of drugs on the electrical activity of the heart. We compute the pseudo-ECG following the formula in equation 2 in order to identify the effect of the drug on the ECG. We remark in Figure 5 that the QT interval is affected both by dofetilide and the L-type calcium current levels. It is highly lengthened when EADs appear. By plotting the intra-cellular cal-

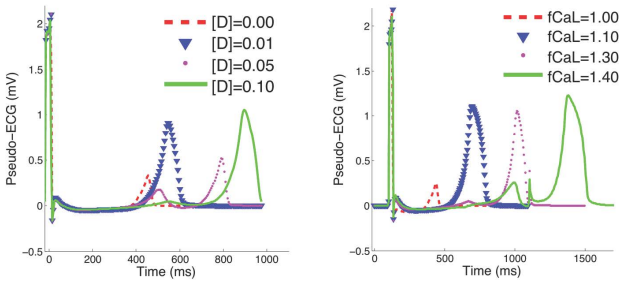

Figure 5. Effect of dofetilide doses on the pseudo-ECG for fICa=130% (left). Effect of L-type calcium current level on the pseudo-ECG for [D]=100 nMol (right).

cium concentration (Figure 6), we see that the appearance of EADs is synchronized with an increase of the intracellular calcium concentration. In the case where two EADs appear ([D]=100 nMol and fICa=140%) we also get two deflections in the intracellular calcium concentration exactly synchronized with the EADs occurrence. This means that EADs could be responsible of calcium release which may affect the mechanical activity of the heart.

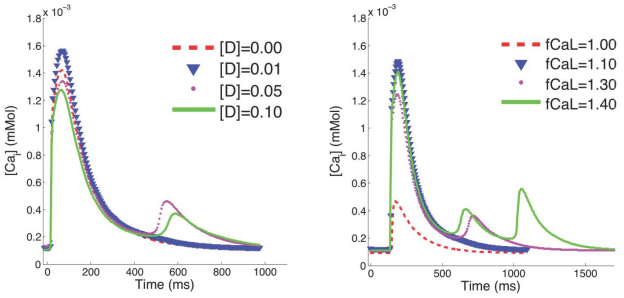

Figure 6. Effect of dofetilide doses on the intra-cellular calcium concentration for fICa=130% (left). Effect of L-type calcium current level on the intra-cellular calcium concentration for [D]=100 nMol (right)

4. Conclusion

The main result of this study is that ICaL is a key modulator of dofetilide-induced EADs in human ventricular tissue. Importantly, EADs result in significant increase in APD dispersion, which might provide the substrate for reentry and TdP. EADs appearance in the pseudo-ECG is synchronized with an intra-cellular calcium release. This calcium release may have an important effect on the mechanical behavior of the heart. This study will be continued using a full heart torso problem simulation like in [6] in order to understand in details how EADs may lead to re-entry. Forthcoming work will also investigate the effect of the calcium release on the heart motion.

Acknowledgements

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