Gender and Age Based Differences in Risk of Proarrhythmia by Dofetilide: A Computational Model Study

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Abstract

The aim of this study was to investigate the risk of proarrhythmia by dofetilide in gender and age based differences using action potential duration and triangulation of action potential. Left ventricular epicardial, midmyocardial and endocardial action potentials were simulated using a modified Luo Rudy model. Sex, age and regional differences in current densities and voltage dependent parameters for I_{CaL}, IK_r, IK_s, and I_{to} were incorporated into the model by modifying the equations representing them. A model of dofetilide was developed and included into a ventricular cell model.

This study has demonstrated that gender and age based differences in ionic currents and drug induced action of dofetilide might explain in part the higher susceptibility of EADs and prevalence of TdP in adult females and the higher risk of cardiac events in males than females during childhood.

1. Introduction

Male/female differences in cardiac electrophysiology have long been noted, but only in recent years has there been an increased awareness and appreciation of the influence of a patient's sex on presentation of various cardiac arrhythmias [1]. A number of gender differences exist in the human electrocardiogram (ECG): women have higher resting heart rates than do men, but a longer rate-corrected QT (QTc) interval. However, young boys and girls have similar QTc, in men abbreviates and then gradually increases until the age of 50 when QTc approaches that of women [2]. These sex and age dependent changes in ventricular repolarization are also present in congenital long QT syndrome (LQTS) patients. Many drugs associated with acquired LQTS have a greater risk of inducing torsades de pointes (TdP) arrhythmia in women than in men [3].

The QT interval of the surface ECG represents the average of the sum of the duration of the ventricular action potentials (AP), which is governed mainly by the repolarization process. In turn, repolarization of the action potential is determined by a balance between inward depolarizing and outward repolarizing currents. Hence, a reduction in net repolarizing currents results in prolongation of both the action potential and the QT interval. Drugs that prolong the duration of the action potential (APD) might do so by reducing repolarizing K currents and/or increasing depolarizing Na or Ca currents.

Prolongation of the QT interval (the time elapsed between ventricular depolarization and repolarization) on the surface electrocardiogram (ECG) is caused by an increase in the duration of the action potential (APD) of ventricular myocytes, which is brought about most frequently by a decrease in the net repolarizing current. Prolongation of the ventricular APD as a result of inhibition of the rapid component of the delayed rectifier K^+ current (IKr) is the primary mechanism underlying the therapeutic effect of Class III anti-arrhythmic agents. However, prolongation of APD and QT interval can also be arrhythmogenic and lead to malignant ventricular tachyarrhythmia such as TdP. Prolongation of the QT interval is not a pharmacological property that is unique to anti-arrhythmic agents. Unfortunately, prolongation of the QT interval is a common effect, albeit secondary to the intended effect, of numerous non-anti-arrhythmic agents, cardiovascular drugs and non-cardiovascular drugs that belong to various therapeutic classes [4].

Normally, action potential duration is primarily the sum of the plateau and fast repolarization phase of the action potential. Thus, action potential duration can be prolonged by delaying (prolongation of plateau) or slowing of fast repolarization (prolongation of the fast repolarization phase). The latter was described as triangulation of the action potential. Triangulation results from a reduction in outward repolarizing currents and/or an increase of depolarizing inward currents during fast repolarization (in monophasic action potential recordings,

dispersion of repolarization may also contribute to triangulation). It is important to stress that triangulation can occur with prolongation, no change, or even shortening of the action potential duration [5]. As inward currents approach outward currents, repolarization stalls; when inward currents exceed outward currents, then depolarization can yield early afterdepolarizations (EAD).

The aim of this study was to investigate the risk of proarrhythmia by dofetilide in gender and age based differences using action potential duration and triangulation of action potential.

2. Methods

Left ventricular endocardial, midmyocardial and epicardial action potentials were simulated using the Luo–Rudy (LRd) model of the mammalian ventricular action potential [6]. The model incorporates the transient outward potassium current, (Ito) [7]. Sex, age and regional differences in current densities and voltage dependent parameters for I_{CaL}, were incorporated into the model by modifying the equations representing this current [8]. We modified ion current densities based on experimental data obtained from adult male, adult female, young male and young female hearts of various species. The rapid component of the delayed rectifier potassium current (IKr) in females is 0.83 times that of males [9]. The slow component of the delayed rectifier potassium current (IKs) in young is 0.8 times that of adult in endocardial tissue [10], [11]. The transient outward potassium current (Ito) in females is 0.75 times that of males [12].

Dofetilide is a class III antiarrhythmic drug for treatment of patients with persistent atrial fibrillation and flutter. It is a specific blocker of IKr/hERG. Dofetilide blocks IKr in all myocardial tissues with high potency. Block is voltage dependent and most prominent at depolarized potentials. A model of dofetilide was developed (see Figure 1) and included into a ventricular cell model in order to simulate the action potential and analyze the blockade of IKr by dofetilide. The interaction of dofetilide in accordance with experimental studies has drug-receptor interaction in open and in inactivated states [13]. The dofetilide concentrations used were 10, 30 and 100 nM (IC_{50}= 7.5 nM).

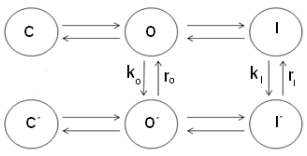

Figure 1. State diagram with dofetilide interaction. c=closed, o=open and I=inactivated.

The concept of triangulation has been developed as an additional in vitro biomarker for proarrhythmia. It quantitatively measures the slowing of repolarization in monophasic action potentials. The triangulation of action potential was calculated as the difference between APD_{90} (APD at 90% of repolarization) and APD_{30} (APD at 30% of repolarization). The endocardial, midmyocardial and epicardial cells were paced with different basic cycle length (300, 500, 1000, 2000 and 5000 ms).

3. Results

We used adult male, adult female, young male and young female models of endocardial, midmyocardial and epicardial cells to assess age and sex disparities in prolongation of APD and susceptibility to early afterdepolarizations (EADs).

Simulations revealed significant APD differences in sex and age. Figure 2 shows epicardial action potentials with BCL=1000 ms in control, 10 nM, 30 nM and 100 nM of dofetilide. In control, the APs were significantly longer in adult female than adult male, whereas there were not discernible differences in the shape and time course of young male and young female action potentials.

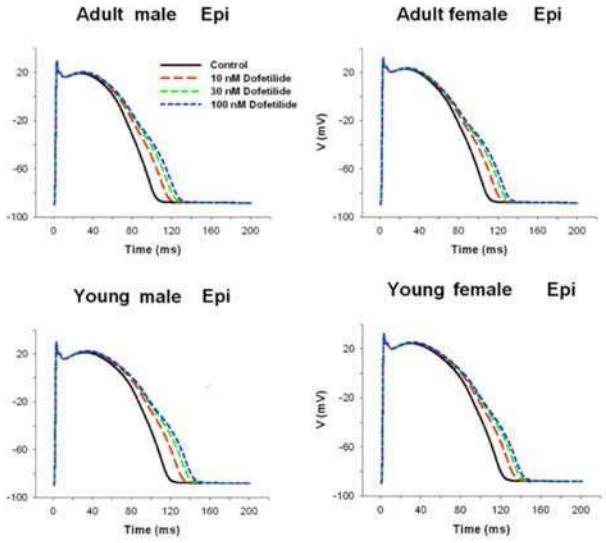

Figure 2. Epicardial action potentials with BCL=1000 ms in control, 10 nM, 30 nM and 100 nM of dofetilide.

Adult female AP had more prolongation of APD than adult male AP with 10 nM, 30 nM and 100 nM of dofetilide, but in young male and young female, sex differences were reversed such that young male AP had more prolongation of APD than young female AP. Epicardial APs had prolongation of APD with not EADs with all concentrations of dofetilide in all models.

Midmyocardial action potentials with BCL=1000 ms in control, 10 nM, 30 nM and 100 nM of dofetilide are illustrated in figure 3. Simulations of adult female had incidence of EADs with 10 nM, 30nM and 100 nM of dofetilide, but simulations of adult male had prolongation of APD with no EADs. With 10 nM of dofetilide, young male and young female had prolongation of APD but with 30 nM and 100 nM of dofetilide both had incidence of EADs.

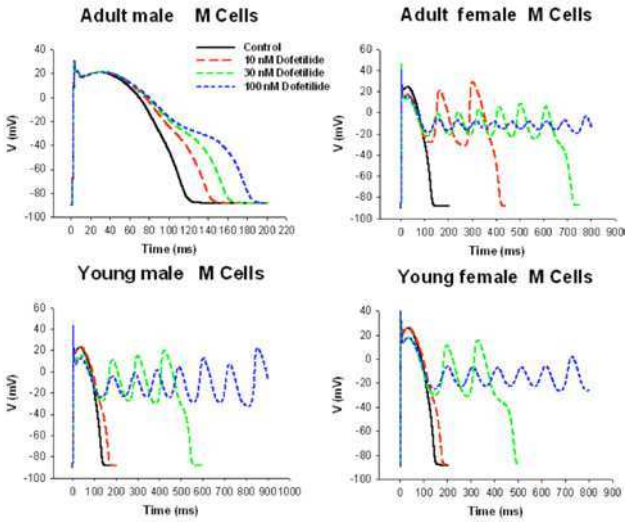

Figure 3. Midmyocardial action potentials with BCL=1000 ms in control, 10 nM, 30 nM and 100 nM of dofetilide.

Figure 4 shows endocardial action potentials (APs) at BCL=1000 ms with control, 10 nM, 30 nM and 100 nM of dofetilide. In control, the APs were significantly longer in adult female than adult male, whereas young male and young female action potentials were similar.

Adult female AP had more prolongation of APD than adult male AP with 10 nM and 30 nM of dofetilide, but in young male and young female, sex differences were reversed such that young male AP had more prolongation of APD than young female AP.

With 100 nM of dofetilide resulted in the firing of EADs in adult female but not in adult male model, whereas young male had more prolongation of APD than young female model, with not EADs.

There were significant differences in triangulation of action potentials (TRIAN) related to sex and age in simulations at different stimulation BCLs (300, 500, 1000, 2000 and 5000 ms) with control, 10 nM, 30 nM and 100 nM of dofetilide. This is illustrated in figure 5, which shows triangulation versus BCL in four models of epicardial cells.

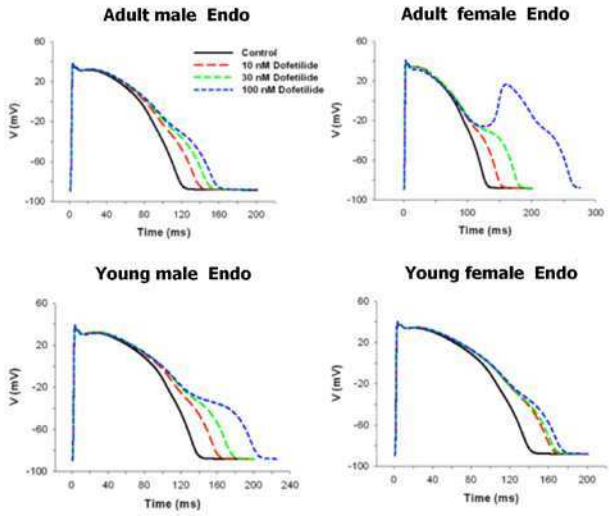

Figure 4. Endocardial action potentials with BCL=1000 ms in control, 10 nM, 30 nM and 100 nM of dofetilide.

TRIAN was longer at high stimulus BCL and decreased at lower BCLs in all models. In control, the TRIAN-BCL relationship was steeper in adult female than adult male. Whilst, this relationship was quite similar between young male and young female. All models present reverse use dependence.

In control and with all concentrations of dofetilide TRIAN of adult female was considerably higher than adult male.

Our results shown that adult female model had incidence in EADs, but not in the adult male model. This higher susceptibility to EADs is in agreement with the higher prevalence of Torsades de Pointes ventricular tachycardia in (inherited and acquired) LQTS in adult females and this action is reversed in young male and young female [14].

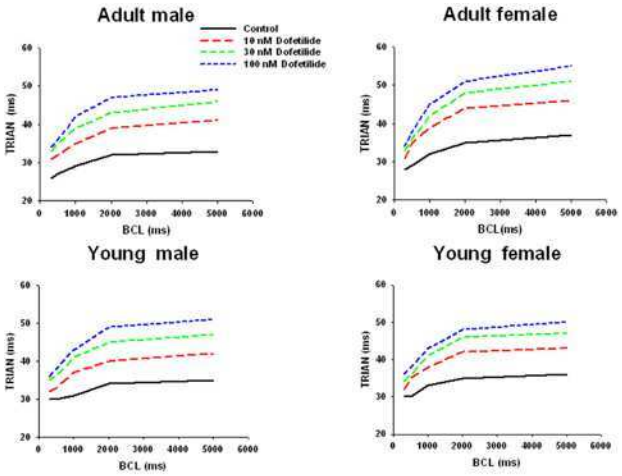

Figure 5. Triangulation-BCL relationship of epicardial action potentials.

4. Discussion and conclusions

In all cell types (epicardial, midmyocardial and endocardial) the APDs were longer in adult female than adult male, whereas in young male and young female the APDs were similar under control conditions. At all stimulation frequencies, APD of all cells types was longer in adult female than adult male under control and drug induced conditions. Also, adult female cells had longer action potentials and a higher susceptibility to early afterdepolarizations (EAD) than adult male cells under drug induced conditions. On the other hand, young male cells had longer action potentials and higher susceptibility to EADs than young female cells under drug induced conditions.

In conclusion, this study has demonstrated that gender and age based differences in ionic currents and drug induced action of dofetilide might explain in part the higher susceptibility of EADs and prevalence of TdP in adult females and the higher risk of cardiac events in males than females during childhood.

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