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SENSITIVITY OF ACTION POTENTIAL TO CHANGES OF INWARD RECTIFIER POTASSIUM CURRENT IK1 IS DIFFERENT IN RECENT MODELS OF HUMAN VENTRICULAR CARDIOMYOCYTES

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Abstract: *The inwardly rectifying potassium current I_{K1} is one of the principle ionic currents responsible for repolarization phase of mammalian action potentials (APs). To estimate the impact of individual ionic currents on AP configuration, mathematical models have been widely used. In this study, we compare the effects of alcohol-induced changes of I_{K1} on AP duration (APD) as simulated in four recently published computer models of human ventricular cells. As expected, increasing or decreasing I_{K1} conductance by 20% respectively caused a shortening or a lengthening of APD. However, the effect was largely model-dependent, ranging from 1% to about 15% change of APD. Given the conflicting available experimental data on the features of I_{K1} in human ventricular myocytes there is a need for a set of well-established end-point constraints for a reliable human ventricular myocyte model to be generated.*

Keywords: Cardiac cell, Action potential, Inward rectifier potassium current, Quantitative modelling.

1. Introduction

In our recent work, we studied the effects of ethanol on the inward rectifier potassium current (I_{K1}) in adult rat ventricular myocytes (Bébarová et al., 2013). The results showed that ethanol affects I_{K1} in dual ways; it causes an inhibition of I_{K1} at very low concentrations up to 0.8 mM (equivalent to ~0.37‰ of ethanol in the blood) and an increase at concentrations above 20 mM (equivalent to ~0.92‰ of ethanol in the blood). To simulate the functional consequences of these changes of I_{K1} on human cardiac cells we decided to use our own and three other recently published models of human ventricular myocytes (Hrabcová et al., 2013; O'Hara et al., 2011; Fink et al., 2008; Iyer et al., 2004) for comparison. Surprisingly, changes of I_{K1} led to substantially different effects on AP in these four models indicating different sensitivities of the models to I_{K1} variations.

2. Methods

To compare the sensitivity of action potential (AP) to changes of I_{K1} in recently published models selected for this study (Hrabcová et al., 2013; O'Hara et al., 2011; Fink et al., 2008; Iyer et al., 2004), we performed simulations of APs and I_{K1} at 1Hz stimulation at steady-state (after 300 s stimulation – control conditions) and after an increase and decrease of I_{K1}-channels conductivity (g_{K1}) by 20%. In each case, AP duration at 90% repolarisation (APD_{90}) and relative change of APD_{90} were evaluated.

The simulations on our model (Hrabcová et al., 2013) were performed using the computational system MATLAB 7.2 (MathWorks, Natick, MA, USA) and the solver for stiff systems ODE-15s. Simulations on the other models (O'Hara et al., 2011; Fink et al., 2008; Iyer et al., 2004) were performed using the computational environment for cellular modelling, CORv.0.9.31.1409 (Dr. Alan Garny), and the CellML codes of the models available at http://models.cellml.org/electrophysiology.

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3. Results

Fig. 1 shows the simulated APs using all four models under conditions described in methods. In all cases, as expected, the 20% decrease of g_{K1} caused a reduction of I_{K1} and, consequently, a prolongation of AP duration. Analogically, the 20% increase of g_{K1} resulted in an increase of I_{K1} and subsequent shortening of AP duration. However, as evident from the figure, the potencies of the I_{K1} changes to affect AP were substantially different in these models.

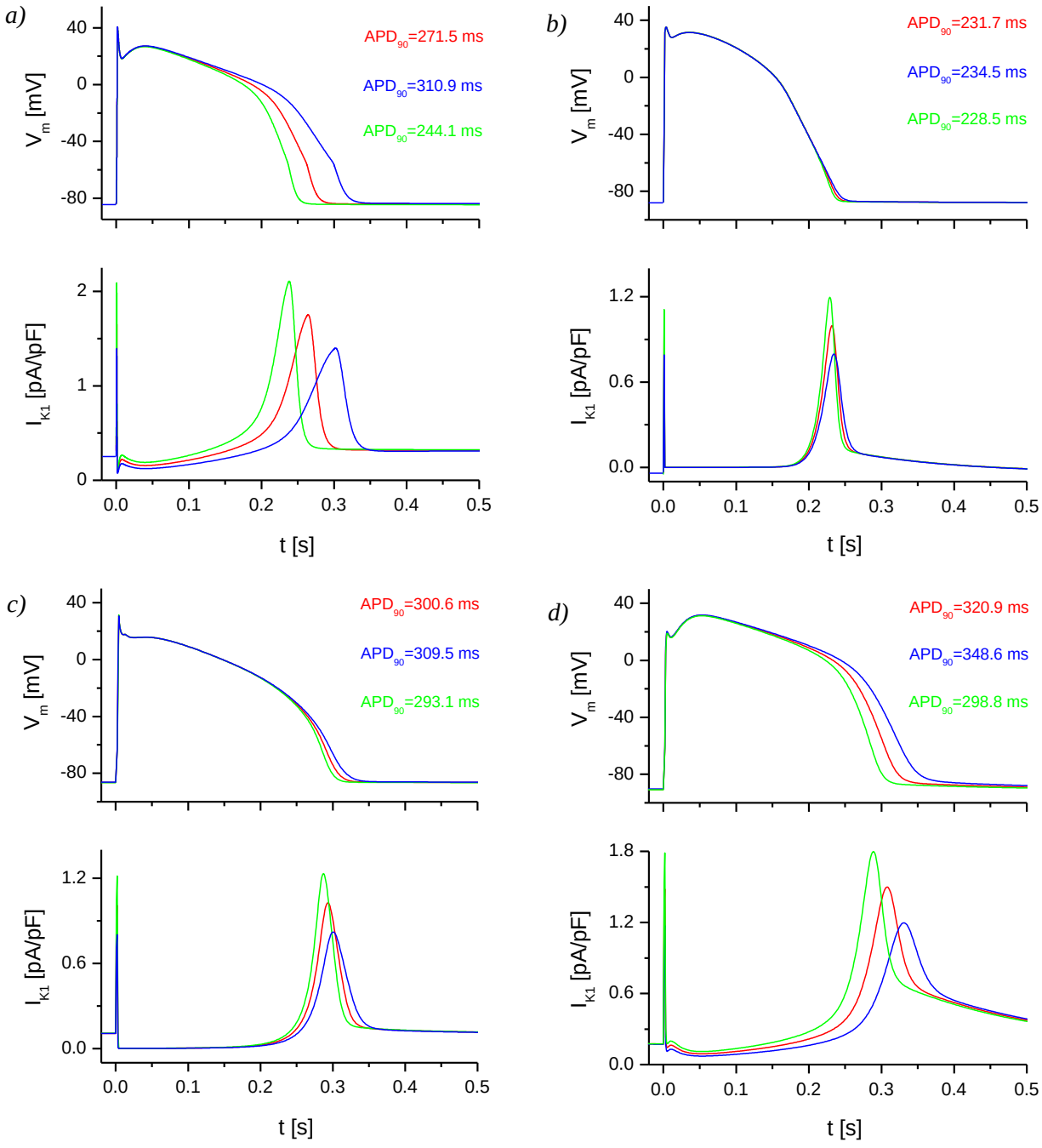

Fig. 1: Simulations of APs and I_{K1} in 1Hz steady-state (control conditions - red lines) and after decrease or increase of g_{K1} by 20% (blue and green lines respectively) using the models of human ventricular cardiomyocytes recently published by: a) Hrabcová et al. (2013) ;b) O'Hara et al. (2011); c) Fink et al. (2008); and d) Iyer et al. (2004). APD_{90} stands for the duration of action potential at 90% of repolarisation.

Fig. 2 shows that the highest sensitivity of AP to changes of I_{K1} was found in the model of Hrabcová et al. (2013) where the 20% decrease of g_{K1} caused a relative increase of APD_{90} by 14.5% and the 20% increase of g_{K1} caused a relative decrease of APD_{90} by 10.1%. On the contrary, the lowest sensitivity of AP to

changes of I_{K1} was exhibited by the model of O'Hara et al. (2011) where the same changes of g_{K1} resulted in only 1.2% increase and 1.4% decrease of APD_{90}, respectively.

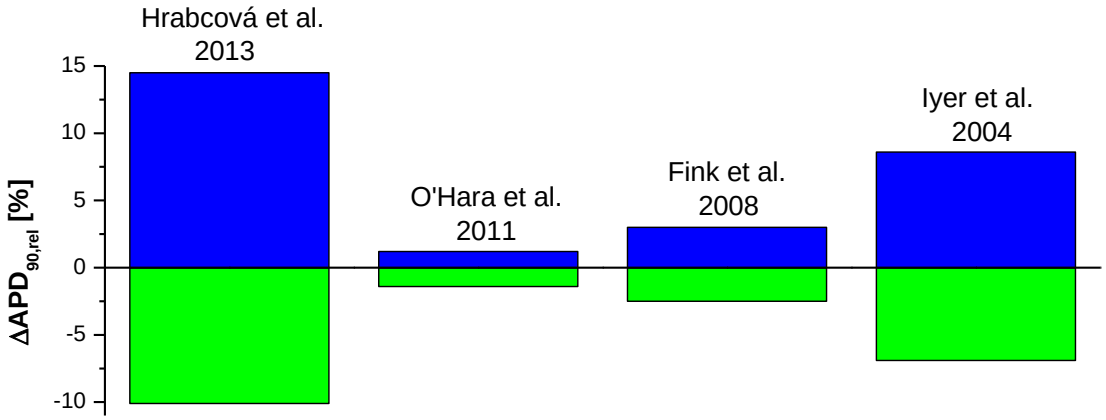

Fig. 2: Comparison of relative increase and decrease of APD_{90} (blue and green columns respectively) evoked respectively by a decrease or increase of g_{K1} by 20% from control values in the models of human ventricular cardiomyocytes recently published by Hrabcová et al. (2013), O'Hara et al. (2011), Fink et al. (2008) and Iyer et al. (2004).

4. Discussion and Conclusions

The prominent differences between sensitivities of APD to changes of I_{K1} in the explored models reflect the inconsistencies in mathematical description of I_{K1} properties due to the lack of experimental data from human ventricular cardiomyocytes gathered up to date. The highest sensitivity was observed in the model of Hrabcová et al. (2013) with formulation of I_{K1} based on the description in Iyer et al. (2004) while the lowest sensitivity was found in the model of O'Hara et al. (2011).

During the last decade, other comparative studies have been published in an effort to define the contribution of individual components of potassium current to repolarization of the AP. For example, Fink et al. (2006) have compared ten Tusscher et al. (2004) and Iyer et al. (2004) models and have concluded that the effects of a fixed percentage reduction of I_{K1} give rise to significantly different prolongation of AP in these two models. However, they noted that it was not possible to determine unequivocally which of these models would be more reliable for simulation of AP repolarization because reliable data on I_{K1} in human ventricle were not available in the whole range of physiological voltages. In 2008, Fink et al. reformulated I_{K1} to better reproduce the data obtained from human ventricular myocytes in their new model. Later on, Grandi et al. (2010) proposed an improved computational model of the human epicardial and endocardial myocytes, based on some of the best features of previous models combined with newer data. I_{K1} blockade increases APD rather modestly in these two later models consistently with other published experimental data (Rudy et al., 2008).

Nevertheless, the experimental results related to the properties of I_{K1} in human ventricular myocytes are not yet complete, and the sample size of available data sets is too small so far. Because of ethical reasons, it is practically impossible to study sufficient numbers of normal human cardiac cells to fully characterize their electrophysiological properties. On occasion, experimental animal models can help to fill important gaps in the missing data. They should be, however, used with caution. For example, I_{K1} changes appear to affect the APD considerably more in guinea pig (Miake et al., 2003) and dog (Jost et al., 2013) than in human cardiomyocytes.

In conclusion, the formulation of I_{K1} in the models of Fink et al. (2008) and Grandi et al. (2010) seem to be currently best adjusted to available measured experimental data from human cardiomyocytes and will likely provide the most reliable view on the effect of ethanol induced block of I_{K1} on action potential in human ventricular cells.

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