Modelling the Integrated Regulation Role of β-Adrenergic Signaling and CaMKII in Human Myocyte Electrophysiological Properties

Ling Dai[1], Yunliang Zang[1], Dingchang Zheng[2], Ruyi Luo[3], Ling Xia[1]

[1]Department of Biomedical Engineering, Zhejiang University, Hangzhou, China
[2]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK
[3]Hangzhou Science and Technology Information Research Institute, Hangzhou, China

Abstract

Both β-Adrenergic receptor (β-AR) signaling pathway and Ca^{2+}/Calmodulin-dependent protein kinase II (CaMKII) play important roles in regulating cardiac excitation-contraction coupling. However, the laboratory experiments cannot quantify these regulatory roles easily, computer models have been used as an alternative way. The aim of this study was to use computer models to preliminarily investigate the combined role of β-AR and CaMKII in human cardiac myocyte properties

With the hypothesis that the β-AR is mainly meditated by the targets of protein kinase A (PKA) phosphorylation, the influence of PKA was incorporated into a modified ORd's model. The formulations of L-type Ca^{2+} current, slow-activating delayed rectifier K^+ current and phospholamban were modified. The simulation results were then compared with and without the administration of isoproterenol (ISO).

Our simulation showed that, in comparison with the control, at the cycle length of 1000 ms ISO shortened APD90 by 15ms (265 ms vs 250 ms), and the amplitude of Ca^{2+} transient was increased by approximate 60%. This increase was not observed for $[Na^+]$. Our findings agreed well with published experimental observations.

In conclusion, a computer model has been developed to investigate the role of β-AR and CaMKII in human myocyte electrophysiological properties. This model can be used as a platform to further investigate their role in cardiac arrhythmias

1. Introduction

The β-Adrenergic receptor (β-AR) signaling pathway plays a key role in normal cardiac function. The stimulation of β-AR by adrenergic agonists can increase heart rate, contractile ability, relaxation rate and automaticity [1]. Ca^{2+}/Calmodulin-dependent protein kinase II (CaMKII) also plays an important role in regulating cardiac excitation-contraction coupling (ECC) [2] and is a critical factor for developing myocardia hypertrophy and heart failure [3].

Computational models have become useful tools to study signaling networks in the field of cardiovascular research. Saucerman et al. [4] integrated β-AR signaling pathway into a rat ventricular myocyte model developed from the Luo-Rudy model. Their model was used to investigate the effect of specific substrate and to design new laboratory experiments. Soltis et al. developed a model of CaMKII and protein kinase A (PKA) signaling in the rabbit ventricular [2], providing new insight into their combined effect in ECC. Their hypothesis was that the β-AR was mainly meditated by the targets of PKA phosphorylation [5]. Recently, Heijman et al introduced a detailed description of local control of β-adrenergic stimulation [6], and their model precisely represented the localized β-AR signaling and its effects on the whole ventricular myocyte. However, its computing time was too long. Until now, the majority of published computer models were based on the ventricular myocyte of different animals, and there was few for human ventricular myocyte.

The aim of this study was to develop a computer model to preliminarily investigate the combined role of β-AR and CaMKII in human cardiac myocyte properties, including the rate dependence of action potential duration (APD), $Ca^{2+}$and $[Na^+]$ transient amplitude.

2. Methods

Our model was developed from the ORd's model. The formulations of L-type Ca^{2+} current (ICaL), slow-activating delayed rectifier K^+ current (IK_s), and phospholamban (PLB) was modified to introduce the influence of PKA.

ICaL in the original ORd model is expressed as [7]:

$$I_{CaL} = \overline{I_{CaL}} \bullet d \bullet (1-\phi_{ICaL,CaMK}) \bullet (f \bullet (1-n) + f_{Ca} \bullet n \bullet j_{Ca}) + I_{CaL,CaMK} \bullet d \bullet \phi_{ICaL,CaMK} \bullet (f_{CaMK} \bullet (1-n) + f_{Ca,CaMK} \bullet n \bullet j_{Ca})$$

Since there is a lack of experimental data of PKA signaling in human ventricular myocyte, Soltis's PKA

signaling model [5] was used. It is formulated as:

$$fCaL = 1 \bullet (0.017 \bullet LCCb_PKAp / fCaLbase + 0.983)$$

Where fCaLbase = 0.0328 and the adjusted ICaL is

$$ICaL_{adj} = ICaL \bullet fCaL$$

IKs formulations were modified from the ORd model [7] as follows:

$$fIKsbase = 0.0734$$

$$fIKs = 0.2 \bullet IKs_PKAp / fIKsbase + 0.8$$

$$Xs05 = 11.60 \bullet fracIKs$$

$$Xs1ss = \frac{1.0}{1.0 + \exp(-(Vm + Xs05)/8.932)}$$

$$GKsadj = GKs \bullet fIKs$$

$$IKsadj = GKsadj \bullet \left(1 + \frac{0.6}{1 + \left(\frac{3.8 \bullet 10^{-5}}{[Ca^{2+}]_i}\right)}\right) \bullet Xs1 \bullet Xs2 \bullet (Vm - E_{Ks})$$

PLB inhibits SERCA when unphosphorylated [8]. So the ratio of its phosphorylation affects Ca^{2+} cycle in myocyte. When phosphorylated, Ca^{2+} uptake by SR Ca-ATPase increases, and this is represented by Jup in ORd model. These formulations were modified by adding one factor describing PKA phosphorylation level.

$$fPLBbase = 0.9926$$

$$fPLB = 1 \bullet (PLB_PKAn / fPLBbase) \bullet 3/4 + 1/4$$

$$fJupp = \frac{1}{1.0 + KmCaMK \bullet fPLB / CaMKa}$$

$$Jup = (1.0 - fJupp) \bullet Jupnp + fJupp \bullet Jupp - Jleak$$

3. Results

3.1. APD90 rate dependence

Figure 1 shows that, in control mode, the rate dependence of APD90 was in accordance with data from O'Hara et al [7]. With 1μm ISO applied, the APD90 at each cycle length (CL) was shortened in comparison with the control and experimental data. With fast heart rate, especially with CL<400ms, shortening effect was not notable. However, with increased CL, the shortening effect became obvious and it reached the maximum (15ms, from 265 vs 250 ms) at CL=1000 ms.

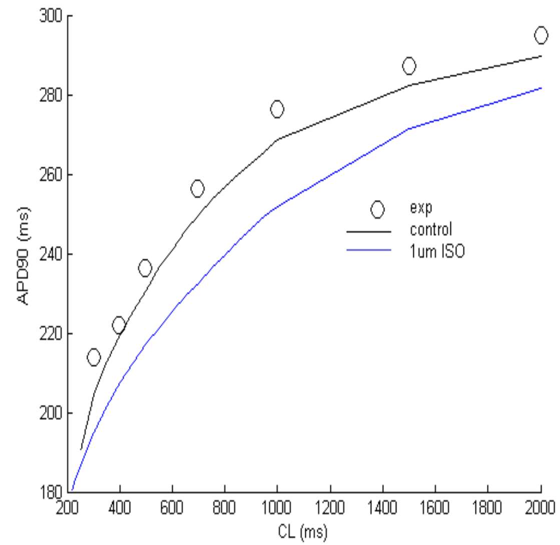

Figure 1. Simulated APD90 in control and with 1μm ISO applied. Experiment data from O'Hara [7] are provided for comparsion.

3.2. APD90 restitution

As shown in Figure 2, the stimulation results of APD90 restitution matched well with the experimental data from Franz et al [9], except at CL<350 ms. This may relate to the APD alternans reported by O'Hara et al [7].

Figure 2 also shows that, with 1μm ISO applied, APD90 restitution was shortened obviously. The shortening effect was relatively small when extra stimulus CL was below 400 ms. This suggests that when heart rate is fast, restitution is less affected

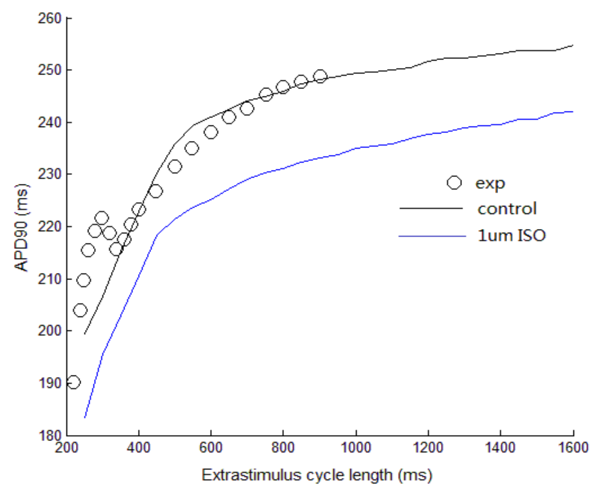

Figure 2. Simulated APD90 restitution at different cycle lengths in control and with 1μm ISO applied. Experiment data from Franz et al [9] are provided for comparison.

3.3. $[Ca2+]_i$ Peak

In EC coupling, $[Ca^{2+}]_i$ elevation causes more Ca^{2+} binding to myofilament protein troponin C, which activates contraction [8]. As shown in Figure 3, with increased pacing frequency, $[Ca^{2+}]_i$ peak value was elevated, indicating enhanced contraction. With 1µm ISO applied, this enhancement was greater than control. Their difference was greater with increasing pacing frequency, suggesting ISO stimulated EC coupling more significantly.

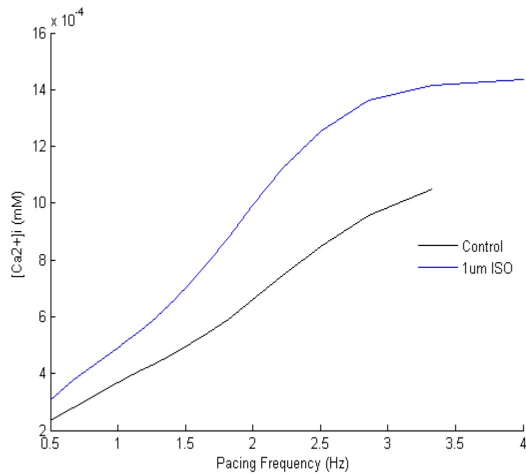

Figure 3. $[Ca2+]_i$ peak value increased with pacing frequency in control and with 1µm ISO applied.

3.4. $[Na+]_i$ Peak

NCX system in cardiac myocytes is the dominant element in Ca^{2+} extrusion, and small perturbations in $[Na+]_i$ may change EC coupling greatly [8].

Figure 4 shows $[Na+]_i$ with pacing frequency from 0.25 to 4 Hz, which was normalized to that from 0.25 Hz. The experiment data from Pieske et al. [10] is also provided. With fast heart rate, $[Na+]_i$ increased sharply, suggesting that Ca^{2+} extrusion by NCX enhances heavily which balances the elevation of $[Ca2+]_i$.

Stimulation results of $[Na+]_i$ peak value in different modes is given in Figure 5. The difference between control and 1µm ISO could be neglected when pacing frequency was in normal range between 1 and 2.5Hz. This suggests that applying 1µm ISO has not affected the physiological $[Na+]_i$ level.

3.5. Simulated action potential

Figure 6 shows the action potential in control and with 1µm ISO applied at 1 Hz pacing frequency. With ISO, the action potential duration time was shortened and the dome at early phase was more obvious.

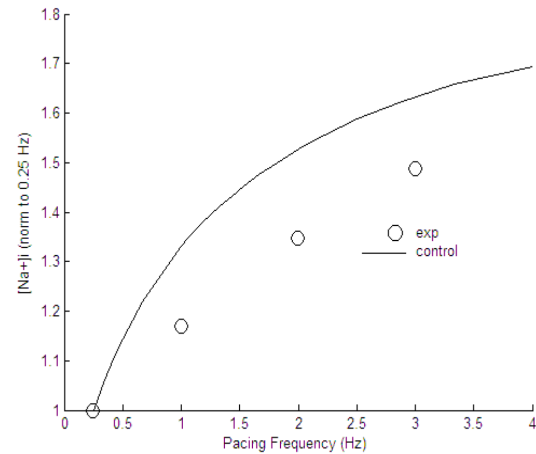

Figure 4. Normalised $[Na+]_i$ to 0.25Hz at different pacing frequencies.

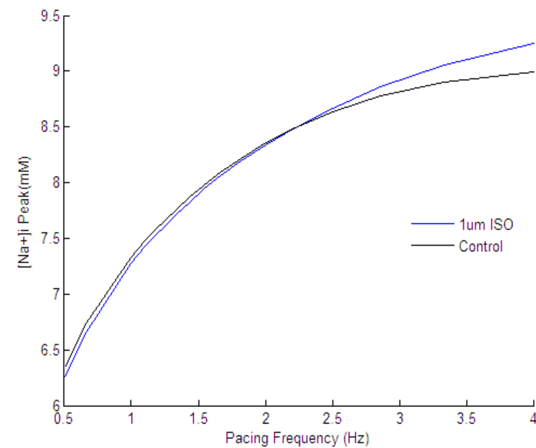

Figure 5. $[Na+]_i$ peak increases with pacing frequency in control and with 1µm ISO applied.

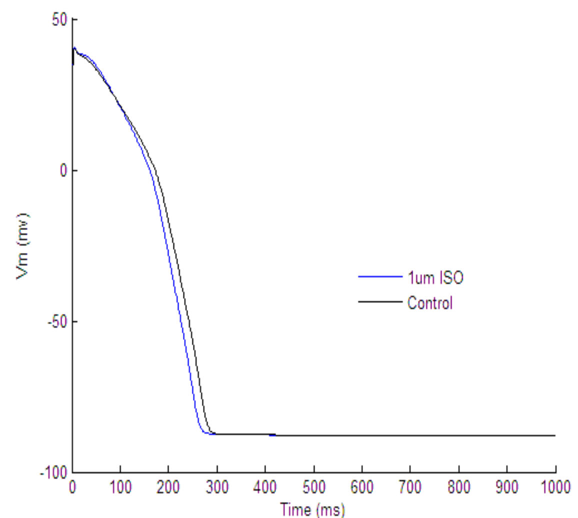

Figure 6. APs in control and 1µm ISO applied states when pacing frequency is 1Hz.

4. Discussion

In this study, a human ventricular myocyte model has been developed to investigate the response of β-adrenergic. In control, our simulation results agreed well with the experiment data. Although there was few existing data from human ventricular myocyte when 1μm ISO was applied, our simulation results were comparable with the myocyte model from other mammals [4, 6].

It has been reported that β-adrenergic stimulation would adjust I_{CaL}, I_{Ks}, PLB and SR Ca^{2+} uptake, ryanodine receptor and SR Ca^{2+} release, troponin I (TnI), Na^+ current , Na^+-K^+ pump current , ultrarapid plateau K^+ current, transient outward K^+ current and inward rectifier K^+ current [6],. We only adjusted $I_{CaL,}$ I_{Ks} and PLB, because they played the dominant roles in changing physiological behavious of myocycte. This simplification reduced the computation requirements and made this model suitable for macroscopic simulation. For the same benefit, the localized distribution of substrates of PKA was also neglected

I_{Ks} is the main current shortening APD. In our simulation, when the phosporylation of I_{Ks} was eliminated, the shortening effect was dismissed, and with enhanced I_{CaL} the APD was even prolonged. PLB's phosporylation enhanced the uptake of Ca^{2+} by SR in diastole. This would increase Calcium induced Calcium release (CICR) in systole and increase contraction force. The phosphorylation of I_{CaL} increases its open probability and conductivity. This augments RyR's open probability, so the CICR and Ca^{2+} transit is enhanced. $[Na^+]_i$ balances the $[Ca^{2+}]_i$ through NCX. So when pacing frequency increases, $[Na^+]_i$ increases and more Ca^{2+} is pumped out. This prevents over burden of Ca^{2+} when stimulated by β-adrenergic.

One limitation of this study was that the dynamic model of β-adrenergic signaling pathway was adapted from the rabbit, and there may be some differences between species. Future research needs to be followed up with dynamic parameters of this pathway in human ventricular myocyte. This could open a new experiment filed. We believe that our model could be refined with more human experiment data. Additionally, we focused mainly on the effect of PKA phosporylation and the effect of CaMKII was simplified. Nevertheless, our model provides an important tool to investigate β-adrenergic signaling pathway in human ventricular myocyte, and can be a platform to further investigate their roles in cardiac arrhythmias.

References

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Address for correspondence.

Prof Ling Xia
Department of Biomedical Engineering
Zhejiang University
China
xialing@zju.edu.cn