Modeling the Chronotropic Effect of Isoprenaline on Bio-pacemaker: A Simulation Study

Yacong Li[1], Kuanquan Wang[1], Qince Li[1,3], Henggui Zhang[2,3]

[1] School of Computer Science and Technology, Harbin Institute of Technology, Harbin, China
[2] School of Physics and Astronomy, the University of Manchester, Manchester, UK
[3] Peng Cheng Laboratory, Shenzhen, China

Abstract

Comparing with traditional electrical pacemaker, one of the superiorities of biological pacemaker (bio-pacemaker) was that it can facilitate chronotropic responses of autonomic nervous regulation. Autonomic nervous regulates intrinsic sinoatrial node (SAN) by two neurotransmitters: isoprenaline and acetylcholine. Here we simulate the chronotropic effect of isoprenaline (ISO) on the pacemaking ability of bio-pacemaker because how the bio-pacemaker response to autonomic nervous regulation is still not clear. In this study, we built an ISO-influenced pacemaker model based on a ventricular pacemaker model. ISO targeted four ionic currents in bio-pacemaker model: I_{Kr}, I_{Ks}, I_f and I_{CaL}, whose effects was referenced from that in SAN. Simulation results showed that an increase in I_{Kr} and I_{Ks} caused by ISO made maximum diastolic potential more negative, which motivated the activation level of I_{Na}, thus accelerated pacemaking rate. ISO can accelerate the action of I_f, so that promote pacemaking activity. But the increased I_{CaL} have a negative effect on pacemaking cycle length, which is contrary to common sense. We clarified the effect of each current on pacemaking ability in sub-cellular level.

1. Introduction

The intrinsic sinoatrial node cell can response to emotion by autonomic nervous regulation which is difficult to replicate in artificial electrical pacemaker (1, 2). Autonomic nervous regulation implements its function by sympathetic nervous system and vagus nervous system. Experiment in HCN-induced biological pacemaker (bio-pacemaker) showed that the bio-pacemaker can be modulated by nervous system (3, 4) which indicated that bio-pacemaker may have advantage comparing with electrical pacemaker in clinical use. As a result, the mechanism of autonomic nervous regulation in bio-pacemaker is needed to be clarified.

The intrinsic sinoatrial node cell is modulated by β-adrenergic stimulation via isoprenaline (ISO), a b-adrenoceptor agonist, which is a part of autonomic nervous regulation in human heart. According to this theoretical basis, the biological pacemaker cell should also be influenced by ISO in subcellular level. In this study, we simulated the effect of ISO on bio-pacemaker based on its effect on SAN. Previous study indicated that ISO may have influence on SAN by the kinetics of five ionic channel currents: rapid delayed rectifier potassium current (I_{Kr}), slow delayed rectifier potassium current (I_{Ks}), L-type calcium current (I_{CaL}), hyperpolarization activated current (I_f) and inward sustained current (I_{st}) (5). We modified four of these currents (I_{Kr}, I_{Ks}, I_{CaL}, I_f) that included in bio-pacemaker cells developed from ventricular myocytes model (6) and analyzed their action on pacemaking behaviours under different ISO dose. This study may provide insight into how bio-pacemaker works in clinic use.

2. Methods

The electrophysiological behavior of a single pacemaker cell could be described by the following ordinary differential equation:

$$\frac{dV_m}{dt} = -\frac{I_{ion}}{C_m} \tag{1}$$

I_{ion} of pacemaker cell could be described by

$$\begin{aligned} I_{ion} &= I_{Na} + I_{K1} + I_{to} + I_{Kr} + I_{Ks} + I_{CaL} \\ &+ I_{NaK} + I_{NaCa} + I_{pCa} + I_{pK} + I_{bCa} + I_{bNa} + I_f \end{aligned} \tag{2}$$

ISO can increase I_{CaL}, I_{Kr} and I_{Ks}, and shift the activation of I_{Kr} to more negative potentials and increases the rate of its deactivation. ISO also change the kinetics of I_f by shifting the activation curve of I_f. The formulations of ISO dose-dependent model can be found in Ref. (5).

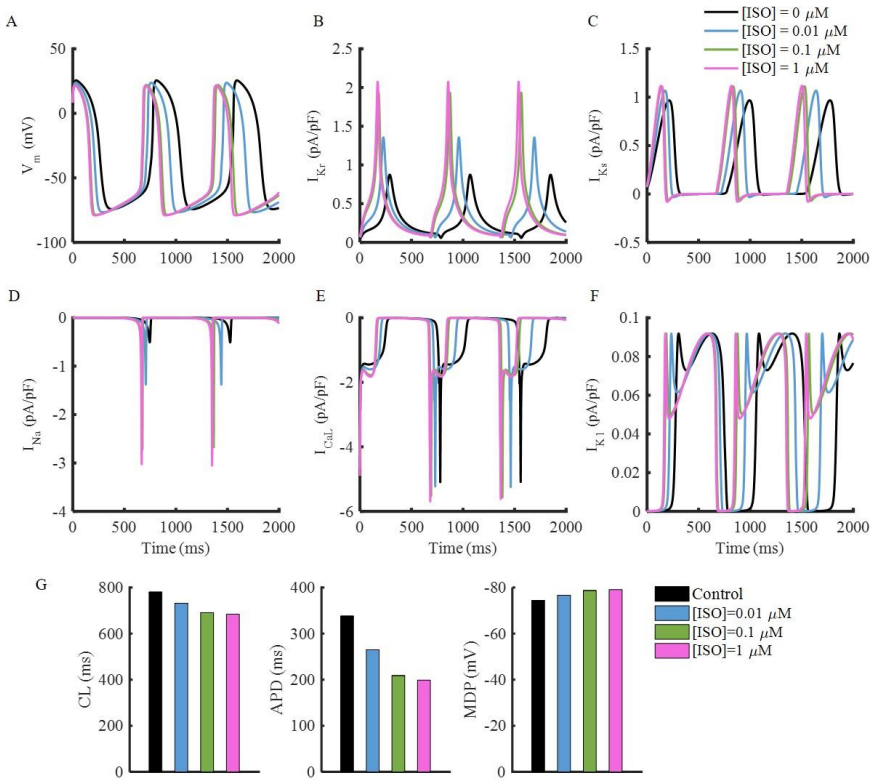

Figure. 1 (A-F) The membrane potential (V_m), I_{Kr}, I_{Ks}, I_{Na}, I_{CaL} and I_{K1} with the change of I_{Kr} and I_{Ks} under different ISO dose. (G) The cycle length (CL), action potential duration (APD) and max diastolic potent (MDP) of (A).

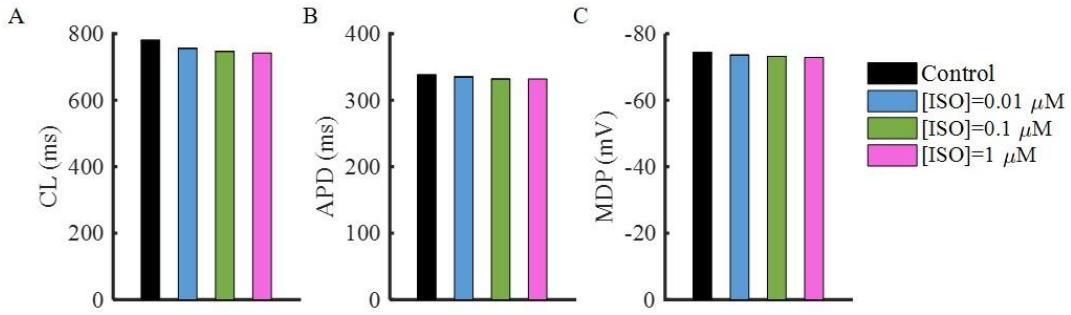

Figure. 2 The cycle length (CL), action potential duration (APD) and max diastolic potent (MDP) with the change of I_f under different ISO dose.

3. Results

3.1. Effect of ISO-induced currents change on pacemaking behaviour

We simulated the effect of ISO on different currents respectively to illustrate their effect on pacemaking activity. The peak of I_{Kr} and I_{Ks} increased, thus the max diastolic potent (MDP) became more negative, which promoted the activation degree of I_{Na}, and improved pacemaking ability (Fig. 1). The change of I_f kinetics increased I_f density and accelerated pacemaking cycle length directly (Fig. 2). However, the increase of I_{CaL} suppressed pacemaking behaviour because high $_{ICaL}$ density during repolarizing state prolonged action potential duration (APD). Also, I_{CaL} caused the accumulation of $[Ca^{2+}]_i$, thus increased I_{NaCa} and I_{NaK}, finally prolonged diastolic interval. These reasons finally caused a prolonged CL with the increase of ISO dose (Fig. 3).

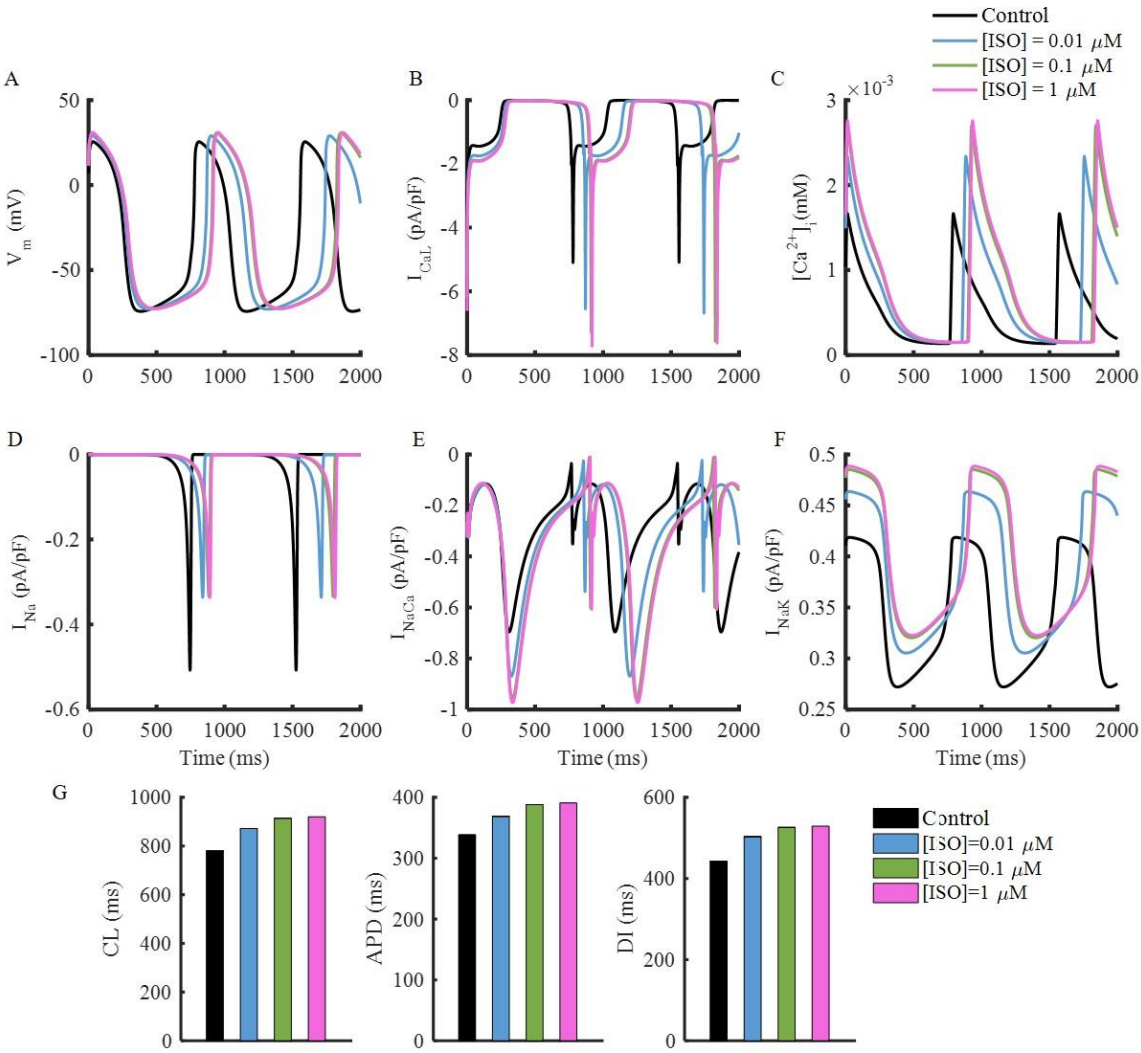

Figure.3 (A-F) The membrane potential (V_m), I_{CaL}, $[Ca^{2+}]_i$, I_{Na} I_{NaCa}, and I_{NaK} with the change of I_{CaL} under different ISO dose. (G) The cycle length (CL), action potential duration (APD) and diastolic interval (DI) of (A).

3.2. Effect of ISO dose on pacemaking behaviour

The integrated effect of ISO on pacemaking behaviour was shown in Fig. 4. The CL of pacemaker became greater with the increase of ISO although the APD shortened. The gap between CL under different ISO dose was weak due to the counteraction between the positive and negative effect of I_K, I_f and I_{CaL}.

4. Conclusion

In this study, we built an ISO-influence pacemaker model and evaluated the effect of different currents affected by ISO on pacemaking behaviour. Different from SAN, the ISO seemed to slow down the pacemaking CL in bio- pacemaker. This was mainly because the different morphology of I_{CaL} curve. In SAN, I_{CaL} had less effect on action potential during repolarizing stage, so increasing I_{CaL} can promote pacemaking activity. But in pacemaker model, the increase of I_{CaL} acted on repolarization, thus prolonged CL. This may be a potential risk when applying bio-pacemaker clinically, which should be verified in biological experiment.

Acknowledgements

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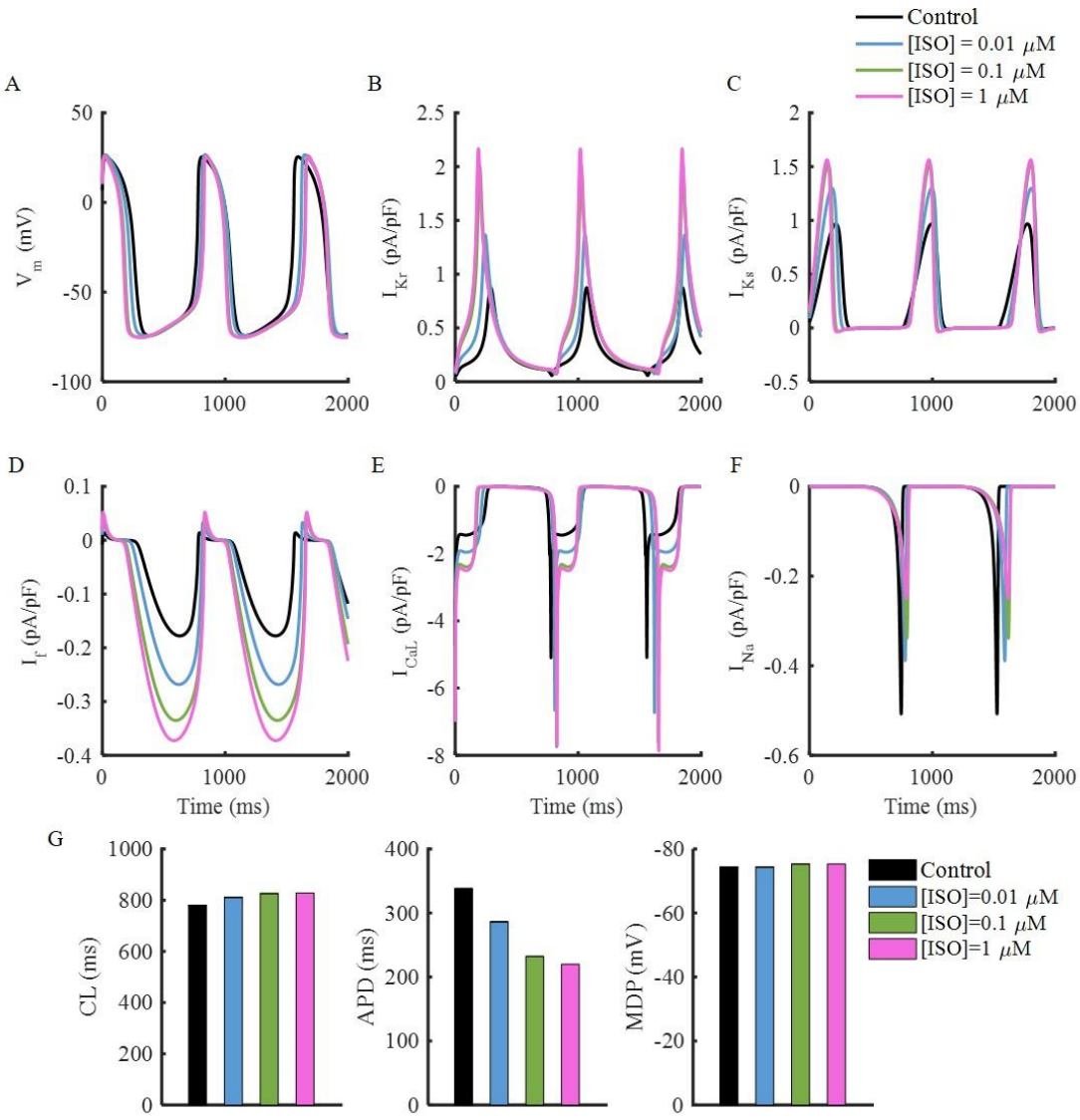

Figure.4 (A-F) The membrane potential (V_m), I_{Kr}, I_{Ks}, I_{CaL}, I_f, and I_{Na} with the change of all currents affected by ISO under different ISO dose. (G) The cycle length (CL), action potential duration (APD) and max diastolic potent (MDP)

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Address for correspondence.

Yacong Li
Room 805, Zonghe Building, Harbin Institute of Technology
Harbin, China, 150001
li_yacong@163.com