Role of Funny Current in Biological Pacemaker Based on Human Ventricular Model

Yacong Li[1], Kuanquan Wang[1], Qince Li[1], Xiangyun Bai[1], Henggui Zhang[1,2,3,4]

[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] Space Institute of Southern China (Shenzhen), Shenzhen, China, 518117
[4] Key Laboratory of Medical Electrophysiology, Ministry of Education, Collaborative Innovation Center for Prevention and Treatment of Cardiovascular Disease/Institute of Cardiovascular Research, Southwest Medical University, Luzhou, China

Aims: Biological pacemaker (biopacemaker), generated by turning non-pacemaking cardiac myocytes into automaticity has been proposed to be a promising alternative to electrical pacemaker for treating patients with impaired native cardiac pacemaker. It has been shown that overexpressing the hyperpolarization-activated funny channel current (I_f) can induce automatic pacing activities in ventricular myocytes (VMs). However, the role of I_f expression in generating automaticity in VMs has not been fully understood. In this study, we implemented a computational approach to investigate mechanism by which overexpression of I_f helps VMs to become biopacemakers.

Methods: The TP06 model for the electrical action potential (AP) of the human VMs was modified by incorporating I_f formulation. The channel conductance I_f (G_f) was changed systematically from 0 to 1 nS/pF.

Results: When $G_f \geqslant 0.09$ nS/pF, the VMs showed spontaneous pacing activities. With an increase of G_f, the cycle length (the time interval between two consecutive APs) was gradually shortened. During the time course of spontaneous APs, changes in the intracellular ion concentrations occurred due to the secondary effect of I_f, leading to accumulation of intracellular calcium concentration ($[Ca^{2+}]_i$) as well as the intracellular sodium concentration ($[Na^+]_i$). However, a decrease in the intracellular potassium concentration ($[K^+]_i$) was observed. By clamping $[Na^+]_i$ and $[K^+]_i$ to a constant level (10.56 and 134.8 mM respectively), a fast and stable spontaneous pacemaking activity was observed.

Conclusion: Overexpressing I_f in VMs is able to produce automatic rhythms in VMs. With the increase of I_f, the pacing ability becomes stronger, implicating the important role of I_f magnitude in biopacemaker. To generate a stable and optimized pacemaker one may also need to consider the role of dynamical behaviours of $[Na^+]_i$ and $[K^+]_i$. This study provides new insights into the mechanism of creating biopacemakers using I_f overexpression.