A Simulation Study on the Reentrant Waves in the Pacing Ventricular Tissues

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Abstract. The aim of the study is to investigate the relationship between the reentrant waves and $I_{K1}$, and probe the effect of $I_{K1}$ on the reentrant waves. Firstly, based on the TNNP06 model, the single pacing cell is derived by depressing $I_{K1}$. And then, a 400 cells ×400 cells 2D tissue is developed by coupling the pacing cells together. Thirdly, the S1-S2 protocol is applied to inspire the reentrant waves. Next, the processes of the reentrant waves in the tissue corresponding to different $I_{K1}$ are analysed. In addition, the action potentials of the cells in special locations are recorded and discussed. With the decrease of the $I_{K1}$, the reentrant waves spin slowly and the period of reentrant waves increases. Meanwhile, the range of the action potential of the cells becomes larger when $I_{K1}$ becomes smaller. The results suggest that with the decrease of $I_{K1}$, the reentrant wave is weakened, and the systolic and diastolic functions of the tissue are enhanced at the same time.

1. Introduction

There are many disadvantages for electrical pacemakers [1-4], though they have been used for about 6 decades with refinement. As a consequence, the biological pacemakers have been a hotpot in recent years [5-8]. There are various approaches to creating biological pacemakers: (1) gene transfer, (2) cell fusion, (3) embryonic stem cells [9]. One of the approaches is to suppress the Kir2 encoded ion channel, the inward – rectifier potassium channel $I_{K1}$.

Miake et al. are the first to find that the ventricular myocyte could be transformed into pacing cells by suppressing $I_{K1}$ [10]. And then, the consistent conclusion are conclude by Kappor et al. and Hu et al. Kappor et al. discover the ectopic pacing activities in the ventricle when $I_{K1}$ was sufficiently reduced [11]. When TBX 18 was transferred to the ventricular myocytes, the $I_{K1}$ is inhibited, and these myocytes are converted into pacing cells. Moreover, the pacemaker activities are detected in the atrioventricular block ventricle by Hu et al. [12].

The effect of the suppression of $I_{K1}$ on pacing of ventricular myocytes is also validated by the model studies. The TNNP06 ventricular myocyte model is analyzed by Tong et al., and it is found that the myocyte paces automatically when $I_{K1}$ is reduced to 8% or less [13]. The analysis on the Luo-Rudy model shows that the ventricular myocytes present pacing activities when $I_{K1}$ is depressed by 81% or more [14]. The study on the reduced TNNP model also illustrates the effect of the suppression of $I_{K1}$ on the automaticity of the ventricular myocytes [15].

$I_{K1}$ plays an important role in the reentrant waves in the ventricle. It has been investigated in the non-pacing ventricle [16, 17]. However, when the ventricular tissue is automatic induced by the small
What is the effect of $I_{K1}$ on the reentrant waves? In the study, the relationship between the reentrant waves and $I_{K1}$ in the pacing tissue is investigated.

2. Methods

2.1 Model for Single Cell

In the study, we adopt the TNNP 2006 model [18] to simulate the human ventricular myocytes, which is described in Equation (1).

$$\frac{dV}{dt} = -\frac{I_{ion} + I_{stim}}{C_m}$$

in which,

$$I_{ion} = I_{Na} + I_{K1} + I_{Io} + I_{Kr} + I_{Ks} + I_{CaL} + I_{NaK} + I_{NaCa} + I_{pK} + I_{pCa} + I_{bCa} + I_{bNa}$$

In equation (1), $V$ is the action potential; $I_{ion}$ is the sum of all the transmembrane ion currents; $I_{stim}$ is the external stimulus current and is set to 0 in the study; $C_m$ is membrane capacitance per unit surface area; $I_{K1}$ is the inward-rectifier K$^+$ current; $I_{Kr}$, $I_{Ks}$ and $I_{Io}$ are the outward slow, rapid, and transient and rectifier potassium currents, respectively.

In the simulation, $G_{K1}$ is depressed to different values to obtain the robust pacing cells.

2.2 Model for 2D Tissue

A 400 cells ×400 cells 2D model is developed to simulate the ventricular tissue which is coupled by the pacing cells transformed from the endo-myocardial ventricular myocytes. And the electrical equivalent circuit of the tissue is shown in Figure 1.

The reaction-diffusion equation is adopted to describe the propagation of the excitation in the 2D tissue, which is described in Equation (2):

$$\frac{\partial V}{\partial t} = -\frac{I_{ion} + I_{stim}}{C_m} + D\Delta V$$

where, $D$, the diffusion coefficient, represents the electrical coupling among the cells. $\Delta$ is the Laplace operator. The other variables are the same to those in Equation (1).

On the 2D level, the equation (2) could be discretized as the partial differential equation (3):

$$\frac{\partial V_{i,j}}{\partial t} = -\frac{I_{ion} + I_{stim}}{C_m} + D(V_{i+1,j} + V_{i-1,j} + V_{i,j+1} + V_{i,j-1} - 4V_{i,j})$$
where, $V_{ij}$ is corresponding to that in Figure 1. $-\frac{I_{\text{ion}} + I_{\text{stim}}}{C_m}$ is the reaction, which is changed by the cell $(i, j)$ itself. And $D(V_{i+1,j} + V_{i-1,j} + V_{i,j+1} + V_{i,j-1} - 4V_{i,j})$ is the diffusion, which describes the effect of the cells surrounding the cell $(i, j)$. Both the former and the latter together contribute to the change of the action potential of the cell $(i, j)$.

3. Results and Discussions

In the section, we will investigate the reentrant waves in the tissues composed of pacing cells with different pacing strength. The propagation of the waves is displayed, and the periods of the waves are calculated to evaluate effect of $I_{K_1}$ on the reentrant waves.

When $G_{K_1}=0.2\text{nS/\mu F}$, the tissue is able to pace robustly without stimulus. Then we adopt the S1-S2 protocol to investigate the reentrant waves in the tissue. At the beginning, S1 is applied on the 5 columns of cells on the left of the tissue for 1ms to inspire the plane wave. And at 375ms, S2 is applied on the upper left quarter of the tissue for 5ms to inspire the reentrant waves. The reentrant waves emerge and keep spinning. The process is displayed in Figure 2.

![Fig 2](image.png)

Fig 2. The generation of the reentrant wave when $G_{K_1}=0.2\text{nS/\mu F}$. (a)-(d) Four status of the propagation of the reentrant wave.

In the 2D tissue, without external stimulus, the tissue depolarizes and repolarizes automatically. The more the $I_{K_1}$ is depressed, the smaller the pacing period is. However, when the S1-S2 protocol is adopted, the automatic excitation is depressed totally by the reentrant wave.

To probe the effect of the reentrant wave on the 2D tissue, the action potentials of the cell on $(200, 200)$ which is the center and the cell on $(100, 300)$ through which the wave front passes are record. The potentials are illustrated in Figure 3.

The salient feature of the action potentials is that the frequency of the tissue is much higher than that in normal ventricular tissue. What is more, the ranges of the action potentials are smaller than that of the normal (about -86mV~45mV). In particular, the action potential of the central cell varies from -68mV to 15mV, which infers the insufficient depolarization and the insufficient repolarization, resulting in the weakened systolic and diastolic functions of the tissue.
To further probe the effect of the pacing strength on the reentrant waves, we set $G_{K1}=0.05\text{nS/pF}$. The tissue paces more robustly. And then, the same S1-S2 protocol is applied and the reentrant waves are generated successfully. The snapshots of the waves are illustrated in Figure 4. The times of (a)-(d) in Figure 4 are the same as those of (a)-(d) in Figure 2, respectively.

Fig 3. The action potentials of two cells in the tissue when reentrant wave is rotating; the solid curve is the action potential for cell (200, 200), and the dash one is for cell (100, 300)

Compared with the corresponding snapshots in Figure 2, the wave fronts are later at all times, which imply that the period of the reentrant wave is longer.

To further investigate the effect of the reentrant waves on the tissue, we record the action potentials of the cells on (200, 200) and (100, 300). The details of the action potentials are illustrated in Figure 5.

Fig 4. The generation of reentrant wave when $G_{K1}=0.05\text{nS/pF}$. (a)-(d) Four snapshots of the propagation of the reentrant wave.
The average period in Figure 5 is 14.7ms longer than that in Figure 3, which means that the reentrant wave becomes slow. What is more, the action potential range of the central cell is between -74mV and 17mV, which infers that the systolic and diastolic functions of the tissue become stronger with the decrease of $I_{K1}$.

Fig 5. The action potentials of two cells in the tissue when reentrant wave is rotating; the solid curve is the action potential for cell (200,200), and the dash one is for cell (100,300)

4. Conclusion
In the study, the effect of $I_{K1}$ on the reentrant waves is investigated. Our simulation results suggest that with the decrease of $I_{K1}$, the reentrant waves are weakened, and the period of the waves becomes much longer, and the ranges of the cells in the tissue increase, resulting in the stronger systolic and diastolic functions of the tissue. In addition, though the pacing of the tissue increases with the decrease of $I_{K1}$, it is completely depressed when the reentrant waves are inspired in the tissue.

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