

Regulation of Electrical Coupling Between Bio-pacemaker and Ventricular Myocytes on Autonomous Signal Propagation: A Simulation Study

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Abstract

Experiments showed that the expression of connexin – Cx43 was suppressed in biological pacemakers (bio-pacemaker). Decreased Cx43 inhibited electrical coupling between bio-pacemakers and adjacent cardiac cells, which can maintain the synchronous pacemaking behaviour of bio-pacemaker. At the same time, moderate Cx43 is necessary to encourage autonomous electrical signal being propagated to non-rhythmic cardiac tissue. In this study, we simulated the electrical cell coupling among pacemaker myocytes (PMs) and ventricular myocytes in a two-dimensional idealized cardiac tissue model. We explored the effect of cell coupling pattern on the initiation of spontaneous signal in and the propagation capacity of the automaticity. If remaining cell coupling unchanged, the PMs tissue could not produce automaticity. When decreasing the coupling among PMs, PMs tissue presented synchronous pacemaking activity but the electrical signal could not propagate to the adjacent ventricular tissue. Then, according to the heterogeneity of intrinsic sinoatrial node, we divided PMs into central PMs and peripheral PMs. Only cell coupling of central PMs was decreased. In this way, PMs tissue could generate automatic pacemaking activity which could drive ventricular tissue. Our study might provide new sight into the electrical propagation mode of bio-pacemaker.

1. Introduction

The sinoatrial node (SAN) can produce automatic beatings and drive the whole heart because it can provide three factors: automaticity of single cardiac myocytes (CMs), electrical gap junction, and cardiac cellular networks (1). The traditional treatment of atrioventricular node dysfunction is installing an artificial electrical pacemaker in the ventricle. However, the patient has to face with complication risks during implanting surgery (2). And pediatric patient needs to replace the device with the

change of the shape because of the fixed size of implantable pacemaker (3). Besides, the electrical pacemaker may be affected by electromagnetic interference in daily life (4). The biological pacemaker (bio-pacemaker) is hoped to substitute for electrical pacemaker and have the function of SAN when SAN failed to work. Our previous work has created a bio-pacemaker cell model based on a ventricular myocyte model (5). But if the automaticity of the single bio-pacemaker cell could produce synchronous pacing behaviour and propagate the spontaneous electrical signal to adjacent CMs still need to explore.

Biological experiments showed that the cell coupling between CMs decided the propagation between CMs. In SAN, cell coupling is little to maintain synchronization of both frequency and waveform (6). Bio-pacemaker experiments exhibited similar results. Bio-pacemaker can be transformed from ventricular myocytes (VMs) by gene therapy. Infecting transcription factor T-box 18 (*TBX18*) into VMs via adenoviral vectors made VMs show pacemaker cell morphology and spontaneous signal (7, 8). This kind of myocytes was called induced sinoatrial node (iSAN). Experiment results showed that iSAN expressed less *Cx43* gene than original VMs (7, 8). *Cx43* is a kind of connexin, usually expressing in cardiac cells (9). The decrease of *Cx43* weakened the electrical coupling between cells, which is helpful to maintain the pacemaking activity of the excitable cell. At the same time, intracellular Ca^{2+} -oscillations in iSAN was asynchronous (10). That is to say, sparse *Cx43* reduced coupling between cells and retarded the propagation of the electrical signal. Except for gene therapy, stem cells could also be induced to differentiate into pacemaker cells. For example, rat bone marrow stem cells (11) and adipose-derived stem cells (12-14) can differentiate into pacemaker cells by infecting *TBX18*. Experiment results showed that *Cx43* was also repressed in induced pacemaker (11), which was concordant with gene therapy experiments. A two-cell system showed that the spontaneous electrical signals produced by pacemaker cell could propagate to a quiescent

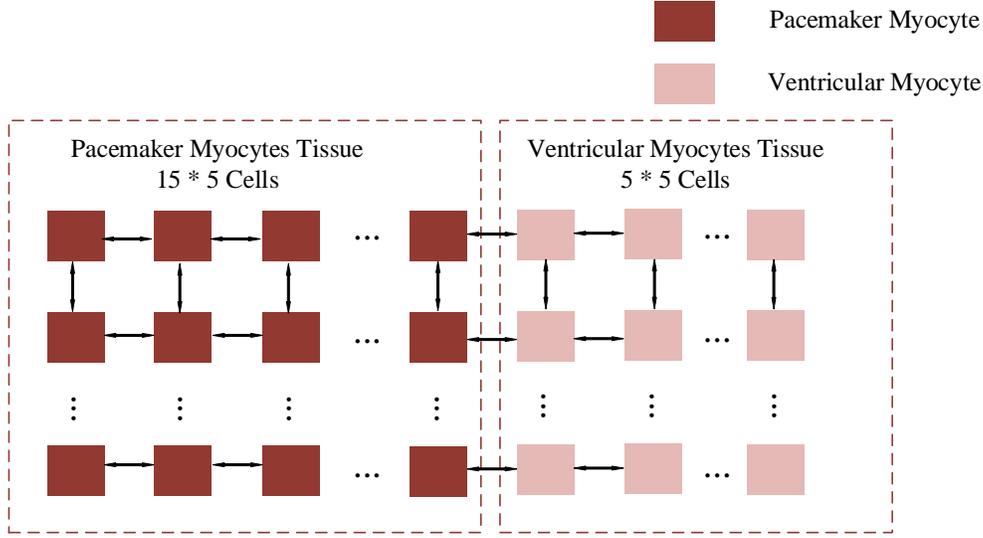


Figure. 1 The spatial distribution of a two-dimensional idealized pacemaker model. The size of ventricular myocytes tissue is 15 * 5 cells connecting with 5 * 5 pacemaker myocytes.

VM cell (15), which verified the ability of bio-pacemaker cells in propagation.

In this study, we constructed a two-dimensional (2D) idealized cardiac tissue model to simulate the effect of electrical coupling between bio-pacemaker cells and VMs on the synchronous pacemaking activity and propagation of the spontaneous electrical signal. We refactored the cell coupling by manipulating diffusion coefficient between CMs. Three different coupling patterns were engineered to illustrate how electrical coupling influenced pacemaking activity.

2. Methods

We designed an idealized electrophysiology cardiac tissue model where pacemaker myocytes (PMs) linked VMs. The model was used to simulate the propagation of spontaneous signal from PMs to VMs. The spatial construction of the idealized cardiac tissue was designed as Fig.1.

The electrophysiological behaviour of the CMs membrane could be described as follows

$$\frac{dV}{dt} = -\frac{I_{ion}}{C_m} + \nabla \cdot D \nabla V \quad (1)$$

where V is membrane potential, t is time, I_{ion} is the sum of all transmembrane ionic currents, and C_m is cell capacitance, D is diffusion coefficient between cells. We simulated the different coupling pattern by manipulating D of CMs.

The I_{ion} of VMs is defined as follows (16):

$$I_{ion} = I_{Na} + I_{K1} + I_{to} + I_{Kr} + I_{Ks} + I_{CaL} + I_{NaCa}$$

$$+ I_{NaK} + I_{pCa} + I_{pK} + I_{bCa} + I_{bNa} \quad (2)$$

According to our previous work (5), I_{ion} of PMs could be described by

$$I_{ion} = I_{Na} + c * I_{K1} + I_{to} + I_{Kr} + I_{Ks} + I_{CaL} + I_{NaCa} + I_{NaK} + I_{pCa} + I_{pK} + I_{bCa} + I_{bNa} + I_f \quad (3)$$

Where c is scale factor that simulates the suppression of I_{K1} current. The formulation of I_f is listed in Ref. (17) and the formulations of other ionic currents could be referenced in (16).

3. Results

3.1. Initiation of synchronous pacemaking activity

When keeping D of whole tissue at the original value, the PMs could not produce any spontaneous impulse. On the one hand, the influence of non-rhythmic VMs inhibited the membrane potential of PMs from rising to activation potential of I_{Na} . On the other hand, the interaction between PM cells restrained their membrane potential mutually. These two factors were responsible for the failure of synchronous pacemaking activity.

According to gene therapy experiments (7, 8), we decreased the cell coupling among PM cells to 1%. Results showed that the single PM cell produced automatic pacemaking activity, and PM tissue expressed synchronous pacemaking activity. Due to the effect of nonautonomous VMs, the PMs depolarized gradually from

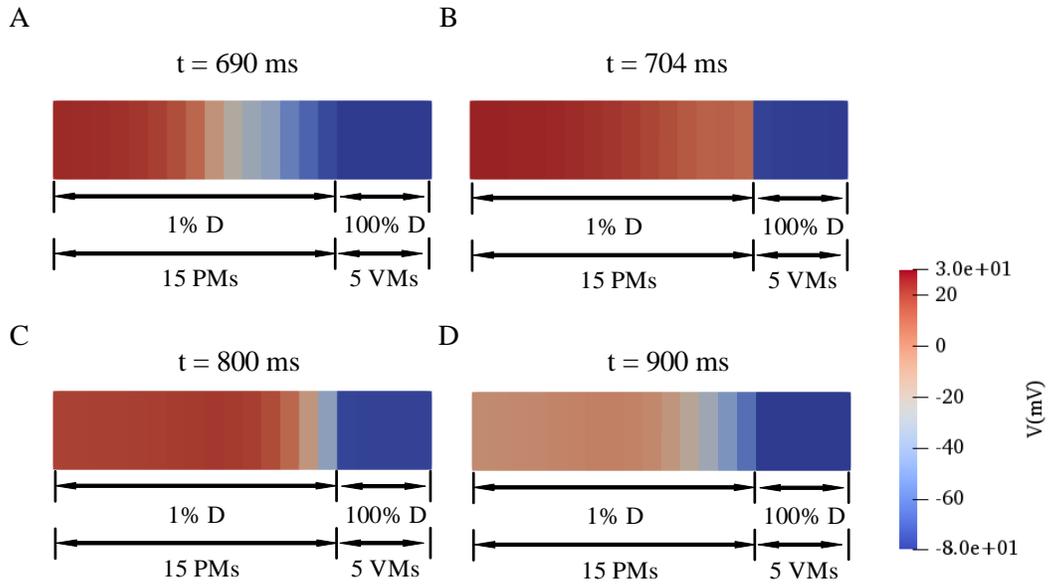


Figure. 2 The snapshots of conduction of spontaneous action potentials in idealized cardiac tissue when cell coupling of all PMs decreased to 1%. A-D reflects the voltage of each single cardiac cell when the simulation time is 690, 704, 800, 900 ms respectively.

left to right (Fig. 2A and 2B) and repolarized gradually from right to left (Fig. 2C and 2D). However, the spontaneous potential of PMs could not drive the VMs because of their weak coupling.

3.2. Propagation of automaticity

SAN has heterogeneity that may relate to different electrotonic coupling (18). The cell coupling of peripheral SAN cells is greater than the central SAN. We mimic the heterogeneity of SAN by modifying D according to the distance of PMs from VMs. The PMs was divided into central PMs (the first 10 PM cells) and peripheral PMs (the 5 PM cells close to VMs). As seen in Fig. 3, the D of central PMs were reduced to 1% where the D of peripheral PMs kept 100%. On this condition, the spontaneous synchronous pacemaking activity was initiated at first (Fig. 3A and 3B) and the automaticity propagated to VMs (Fig. 3C and 3D).

4. Conclusion

In this study, we build a 2D cardiac tissue model and modified the cell coupling among CMs. The different coupling patterns were simulated and results showed that a low but enough level of electrical coupling among PM cells was required to provoke spontaneous pacemaking activity in PM tissue and propagate the automaticity to adjacent VMs. Our work verified that the pacemaker had a

best pacemaking ability when being combined with cardiac tissue in the manner of how SAN combined with atrial tissue.

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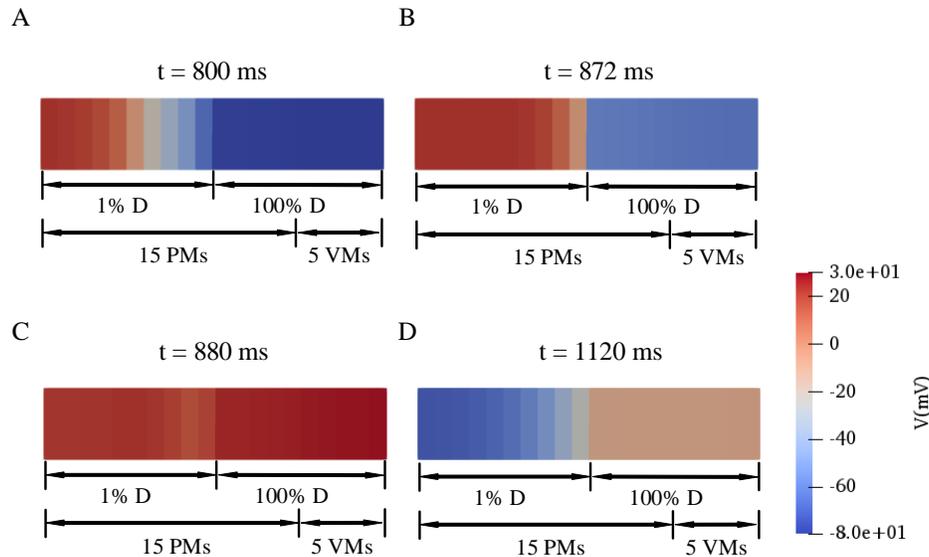


Figure. 3 The snapshots of conduction of spontaneous action potentials in idealized cardiac tissue when cell coupling of first 10 PMs decreased to 1%. A-D reflects the voltage of each single cardiac cell when the simulation time is 800, 872, 880, 1120 ms respectively.

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