Computer Modelling and Analysis of the Effects of Microgravity on Rat Ventricular Excitation

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Abstract. Microgravity during spaceflight may cause cardiac arrhythmias. Experimental studies mimicking microgravity condition have shown some changes in cardiac tissue properties. However, it is unclear how such changes in the cardiac tissue are pro-arrhythmic. The aim of this study was to evaluate the functional impact of microgravity on cardiac electrical excitation by a simulation approach. Experimentally observed decrease in L-type Ca\(^{2+}\) channel current (\(I_{CaL}\)), increases in Na+-K+ pump current (\(I_{NaK}\)) and the intercellular electrical coupling from rat with 4-weeks tail suspension were incorporated into computer models of rat ventricular myocytes and one—dimensional (1D) ventricular transmural strand. At the cellular level, it was shown that the changes in cellular membrane ion channels abbreviated the duration of action potentials (APDs) of cells, resulting in a reduced transmural dispersion in APD. At the 1D tissue level, these changes resulted in a mild increase in the conduction velocity of excitation waves, but a shortened QT interval in ECG with a depressed ST phase and flattened T-wave, which are consistent with experimental observations. They also caused a reduced tissue vulnerability to the genesis of unidirectional conduction block in response to a premature stimulus. Further analysis showed that among the microgravity-induced cellular changes, a reduced \(I_{CaL}\) played a more important role in producing sick functional changes. In conclusion, this study provides new insights into understanding of impaired cardiac functions in microgravity condition during spaceflight.

Introduction

The heart is the core part of cardiovascular system. Its structural abnormality and functional dysfunctions may cause fatal cardiac arrhythmias leading to sudden death. During spaceflight, flow-direction of body fluids changes with the loss of gravity resulting in a series of adverse effects in cardiac electrophysiology, which may be pro-arrhythmic. It has been reported that severe cardiac arrhythmia of an astronaut during spaceflight led to an early termination of spaceflight trip [1]. Though there is no report on fatal arrhythmias during spaceflight, impaired cardiac function could still affect the normal duty of astronauts, causing a great economic loss. Therefore, it is important to understand the mechanism(s) of arrhythmogenesis in the microgravity during spaceflight.

One of the traditional experimental methods to mimic microgravity in the space is to suspend the tail of the rat. By doing so, microgravity-induced changes of cardiac electrophysiology and the function of the heart (reflected by the electrocardiogram (ECG)) can be determined. It has been shown that microgravity causes remodellings in cellular electrophysiology and intercellular electrical coupling [2, 3]. However, it is unclear how such remodeling in cardiac tissue properties
are pro-arrhythmic. Therefore, in this study, biophysically detailed rat ventricular cell models were modified to incorporate experimental data of rat tail suspension to examine effects of microgravity on the function of the heart. Further analysis was also conducted to investigate possible predominate factors affecting ventricular excitation, which may provide theoretical basis for anti-arrhythmia target under the microgravity condition.

**Methods**

**Single Cell Model**

The Pandit et al. models [4] of action potential of rat endocardial and epicardial ventricular cells were used to investigate effects microgravity on rat ventricular excitation based on experimental data. Previous study has shown that a 4-week tail suspension reduced the $I_{Ca}$ by 50.9%, but increased $I_{NaK}$ by 106.9% as suggested by the increase in the expression of Na$^+$-K$^+$-ATPase α2 subunit in cardiomyocytes [3]. To simulate the microgravity condition, the formulas of $I_{Ca}$ and $I_{NaK}$ in the Pandit et al. model were modified accordingly as follows:

$$I'_{Ca} = (1 + k_{Ca}) \cdot I_{Ca},$$

$$I'_{NaK} = (1 + k_{NaK}) \cdot I_{NaK},$$

Where $I'_{Ca}$ and $I'_{NaK}$ are $I_{Ca}$ and $I_{NaK}$ in microgravity condition, $k_{Ca}$ and $k_{NaK}$ are scaling factors and equal to -0.509 and 1.069 respectively.

The action potential for ventricle cells was described as follows:

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

Where $V$ is transmembrane potential, $t$ is time, $C_m$ is the cell membrane capacitance, $I_{stim}$ is a supra-threshold stimuli which is used to evoke the action potential of ventricular cell. $I_{ion}$ is the total ionic current described as the following equation:

$$I_{ion} = I_{Na} + I_{Ca} + I_f + I_{K_1} + I_{NaCa} + I_{CaP}$$

In this study, a series of supra-threshold stimuli (S1=0.6nA) with a duration of 5ms were applied to the endocardial and the epicardial cells at a frequency of 5Hz. The ODE equation (3) was numerically solved by the explicit Euler method with a time step of $1 \times 10^{-7}$s.

**1D Transmural Strand Model of Rat Ventricle**

A multicellular model of 1D transmural strand of ventricular tissue was developed using the following formula:

$$\frac{\partial V}{\partial t} = -I_{ion} + \nabla \cdot (D \nabla V)$$

Where $D$ is the diffusion coefficient and is set to $1.13 \times 10^{-2}$ mm$^2$s$^{-1}$ as used in a previous study [5]. It has been shown that 4-weeks tail suspension mildly up-regulated the expression of connexin 43 by 11% [3]. Therefore, diffusion coefficient of 1D transmural strand model in the microgravity condition was increased by 11% as experimental observation [3].

The 1D model of the ventricular strand has a length of 3 mm, including 2 mm endocardial strand connected with 1 mm epicardial strand. Our simulation used a spatial resolution of 0.1 mm which is approximate to the length of a ventricle cell. Therefore, the 3mm ventricle strand can be seen as 20 nodes of endocardial sections and 10 nodes of epicardial sections. Vulnerability of 1D ventricle
strand was measured using a standard S1-S2 stimuli protocol. A supra-threshold stimuli (S1) was applied to the first 0.3 mm endocardial segment, and then an additional test stimulus (S2, with the same strength and duration as S1) was applied to the segment with a length of 0.6 mm, 1.0 mm away from the beginning of endocardium.

The pseudo-ECG is calculated as the integral of space gradient of membrane potential from a preset virtual electrode in the extracellular space as shown in previous studies [6,7], which was described as follows:

$$\Phi = \int \frac{D\mathbf{V} \cdot \mathbf{r}}{r^3} dV$$

(6)

Where $\Phi$ is the potential at the virtual electrode position, $\mathbf{r}$ is the vector from virtual electrode to a point in the tissue. In this study, the virtual electrode was placed at the middle right side of the tissue, 1mm away from the endocardial cells.

**Results**

**Computer Modeling Microgravity Effects on Action Potential Characteristics in Ventricular Myocytes**

Simulations were conducted to evaluate the functional impact of microgravity-induced remodeling on membrane ion channels (i.e., decreased $I_{CaL}$ and increased $I_{NaK}$) on ventricular action potentials of endocardial and epicardial cells. Figure 1 illustrates simulated action potential recordings from epicardial and endocardial ventricular myocytes under control and 4-weeks microgravity conditions. Microgravity shortened the APD in both epicardial and endocardial myocytes under control and 4-weeks microgravity conditions (Figure 1A and 1B). Epicardial myocytes has a more significant reduction in APD$_{50}$ than in APD$_{90}$ as shown in Figure 1C and 1D. APD$_{50}$ was reduced by 49.6% and 43.4%, whilst APD$_{90}$ was reduced by 34.9% and 36.5% respectively. A heterogeneous APD reduction was observed between endocardial and epicardial cells, resulting in a reduced transmural dispersion of APD$_{90}$ by 7.1ms (Figure 1 E).

![Figure 1](image_url)

**Figure 1.** Simulated action potential of endocardial and epicardial ventricle cells in control and 4-weeks microgravity conditions.
Effects of Individual Remodelled Ion Channel on Action Potential

A reduction of $I_{CaL}$ and an augment of $I_{NaK}$ have been observed experimentally in 4-weeks microgravity condition, resulting in the reduction of APD. However, the relative contribution of each remodelled ion channel current in regulating APD during microgravity is unknown. Therefore, the effect of each remodelled channel on APD was simulated separately (Figure 2). Simulation results show that decreased $I_{CaL}$ played a predominant role in reducing both APD$_{50}$ and APD$_{90}$ in microgravity condition (Figure 2A and 2B). The transmural gradient of APD$_{90}$ from endocardial to epicardial cells reduced more significantly by decreasing $I_{CaL}$ than by increasing $I_{NaK}$. The reduction of APD$_{90}$ is greater when both remodelled ion channel currents were considered (Figure 2C).

Simulated Excitation Propagation across the 1D Ventricular Strand in Microgravity Condition

Simulated action potential propagation in the 1D ventricle strand is shown in Figure 3A. Action potential was evoked from the endocardial cells, propagating to the direction of epicardium. It is shown that microgravity accelerated repolarization of action potential in the 1D tissue (Figure 3A). Meanwhile, the conduction velocity of action potential propagation across the tissue (Figure 3B) was non-noticeably increased, which was attributable to the up-regulated expression of connexin 43 under microgravity condition. In addition, as the spatial dispersion of APD is strongly correlated with the QRS and T waves in ECG, a pseudo ECG was also simulated in different conditions. Simulation results (Figure 3C) shows that microgravity resulted in a reduction of QT interval as well as a depression of ST phase and the amplitude of the T-wave, which are consistent with experimental observation [3]. In simulations, it was shown that the QT interval was reduced from 89.6ms in control condition to 53.1ms under the microgravity condition.
Figure 3. Excitation propagation across the 1D ventricle strand in control and microgravity conditions.

Computer Modelling Temporal Vulnerability of 1D tissue to Unidirectional Conduction block Under Microgravity Condition

Further simulations were then carried out to identify whether or not microgravity could increase the susceptibility of ventricular tissue to arrhythmogenesis. With the constructed 1D ventricle strand model, a test stimulus was applied (S2, see methods) to the refractory tail of previous excitation wave to quantitatively calculate the temporal vulnerability of the 1D tissue to unidirectional conduction block under control and microgravity conditions.

Figure 4A-4C shows the space-time plot of the excitation wave propagation in response to an additional stimulus in the control and microgravity conditions. With the time interval between S1 and S2 stimuli (Δt) equal to 86.5ms and 56.2ms in control and microgravity conditions, bi-directional excitation conduction failed to occur as the untimely applied test stimulus did not give the tissue enough time to recover (Figure 4A). When the test stimuli applied within the vulnerable window, a unidirectional block was generated as shown in Figure 4B. It is noteworthy that the unidirectional block is in the direction retrograde to the propagation direction of excitation waves [8]. This could be attributed to the fact that endocardial cell has comparatively long APD than epicardial cell and takes more time to recover excitation. With increasing S1-S2 interval, the test stimuli was applied sufficiently late allowing tissue in both of the endocardial and epicardial regions enough time to recover, resulting in the generation of bi-directional conduction of excitation (Figure 4C). The width of the vulnerable time window is estimated to be 1.3ms in microgravity condition,
Figure 4. Simulated temporal vulnerability of the tissue to unidirectional conduction block in response to a premature stimulus in control and microgravity condition.

Which is smaller than that of 1.9ms in the control condition as shown in Figure 4D. As unidirectional conduction block is an essential factor to induce re-entry in 2D tissue, a decreased vulnerable time window implied a reduced risk of the occurrence of re-entrant excitation in microgravity condition. However, a reduction of APD, and therefore, the shortened wavelength of excitation helps to facilitate the maintenance of reentry as observed in previous studies [9].

**Discussion and Conclusion**

Several cases of cardiac arrhythmias have been documented during spaceflight, including a non-sustained ventricular arrhythmia from a crewmember during spaceflight [10]. These reports lead to the growing concern over spaceflight-induced arrhythmias or even sudden cardiac death during a long-time space trip. However, the underlying mechanism of arrhythmias induced during spaceflight is still unclear. The aim of this study is to identify the predominant factors affecting action potential wave propagation in microgravity condition and reveal whether microgravity induced electrophysiological remodeling could promote the genesis of arrhythmias in ventricle tissue.
In this study, we performed a series of computer simulations based on biophysical detailed models of endocardial and epicardial ventricle cells as well as 1D ventricle strand. We evaluated the functional impact of microgravity on APD, transmural dispersion of ventricular APD, the propagation of excitation in 1D tissue and vulnerability of the tissue to unidirectional conduction block. The main findings include that: (i) microgravity-induced decrease in \( I_{\text{CaL}} \) and increase in \( I_{NaK} \) abbreviated APD\(_{90} \) in endocardial and epicardial cells, resulting in a decreased transmural APD dispersion; (ii) The decrease of ICaL under microgravity condition played a main role in reducing APD\(_{90} \) (especially in epicardial ventricle cells) and transmural APD dispersion; (iii) the up-regulated expression of connexin 43 produced a slight increase in the conduction velocity across the 1D tissue; (iv) microgravity reduced tissue’s vulnerability to the genesis of unidirectional conduction block in response to a premature stimulus, which was attributable to a decreased dispersion of ventricular effective repolarization.

This study also has some limitations, including the limitations of the mathematical models of endocardial and epicardial cells that have been discussed in previous study [4]. In this study, the microgravity effect on excitation wave propagation in 1D tissue was simulated, but the substrate property of re-entry in 2D or 3D tissue need to be further studied. As microgravity induced cardiac electrophysiological changes may further affect muscle mechanical contractions, using an electromechanical feedback rat ventricle computer model [11] may be a more ideal platform to study microgravity effect on the heart when more detailed experimental data of microgravity become available. There is no fundamental alteration of the critical results shown in this study though there are some limitations.

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References


