Simulation Study of Electrotonic Coupling between Human Atrial Myocytes and Mechanosensitive Fibroblasts

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Abstract

This study aimed to investigate the effect on adjacent myocyte of fibroblasts (Fbs) with the incorporation of mechano-gated currents induced by mechanical compression (I_{ci}) of cardiac Fbs.

The human atrial myocyte (hAM) was modeled by the Courtemanche-Ramirez-Nattel model. With two different experimentally observed Fbs compression (2 μm and 3 μm), I_{ci} was numerically simulated as I_{cil} and I_{cih}. They were then incorporated into two types of electrophysiological models of human atrial Fbs: passive and active models, respectively.

In both passive and active models, I_{ci} depolarized the membrane potential of cardiac Fbs. When coupled with passive Fbs, the action potential of myocyte duration at 90% (APD_{90}) was increased in comparison with uncoupled hAM. With the incorporation of I_{ci} into passive Fbs, APD_{90} of myocyte was further increased. When coupled with active Fbs, similar increases were obtained with the incorporation of both $I_{ci.}$ Furthermore, the resting potential and the maximum value of the action potential of hAM were also increased for both models and with both I_{ci}.

The preliminary simulation study confirmed that mechanosentitive currents in fibroblasts play an important role in mechano-electrical coupling.

1. Introduction

Fibroblasts (Fbs) constitute the most numerous non-myocyte cell populations in the heart [1]. However, little is known about ion currents in human cardiac Fbs. So far, several types of potassium ionic channels, as well as sodium and chloride voltage-gated channels, proton channels and non-voltage gated non-selective cation transient receptor potential channels have been found in cardiac Fbs [2]. Cardiac Fbs are electrically non-excitable cells [3]. They do not respond to an electrical stimulus, but they are efficient mechano-electrical transducers under both physiological and pathophysiological conditions [4]. Fbs can respond to mechanical stimuli imposed by the contractile activity of the surrounding myocardium or by external stretch and compression [5-6], with changes in their membrane potential [7].

Experimental studies have suggested that cardiac Fbs interacts electrically with myocytes through gap junctions [3, 8-9]. Since the mechanical stress appears to be one of the main factors responsible for membrane potential of cardiac Fbs, the resting membrane potential and action potential (AP) characteristics in myocytes will depend on the activity of mechanosensitive ions in neighboring Fbs in addition to the activity of their own. However, little is known about how membrane potential and currents change in Fbs for mechanical stimuli, and how they are transmitted to adjacent myocytes [10].

There are two different electrophysiological models of Fbs: the passive model and the active model [11]. However, to our best knowledge, neither introduced mechanosensitive currents in Fbs. This study aimed to (1) simulate the compression induced current (I_{ci}) in Fbs based on the experimental results of mechanosensitive ion currents; (2) investigate the effect of I_{ci} on Fbs; (3) investigate the effect of the myocyte-Fb-I_{ci} coupling on action potential (AP) morphology and action potential duration (APD) of human atrial myocyte (hAMs) at the cellular level.

2. Materials and methods

2.1. I_{ci} in Fbs

Although I_{ci} in acutely isolated cardiac Fbs has been characterized, it has not yet been modeled. The experimental data of [6] from isolated rat atrial Fbs was fitted to a curve, as shown in Figure. This curve has the same form as I_{kp} in [12], resulting in the following

equation:

$$I_{ci} = \frac{K_{ci}(V_{Fb} - V_{ci})}{(1 + \exp\frac{(21.52 - V_{Fb})}{67.98})} \quad (1)$$

where K_{ci} is the conductance, V_{Fb} is the membrane potential of Fb, V_{ci} is the reverse potential. V_{ci} is close to 0 mV which is introduced by Na^+, K^+, Cs^+ [5-6]. In our study, V_{ci} is equal 0 mV. To fit the experimental data, K_{ci} was assumed to be 0.256 mS/μF (when Fbs compression is 2 μm) and 1.0533 mS/μF (when Fbs compression is 3 μm) respectively.

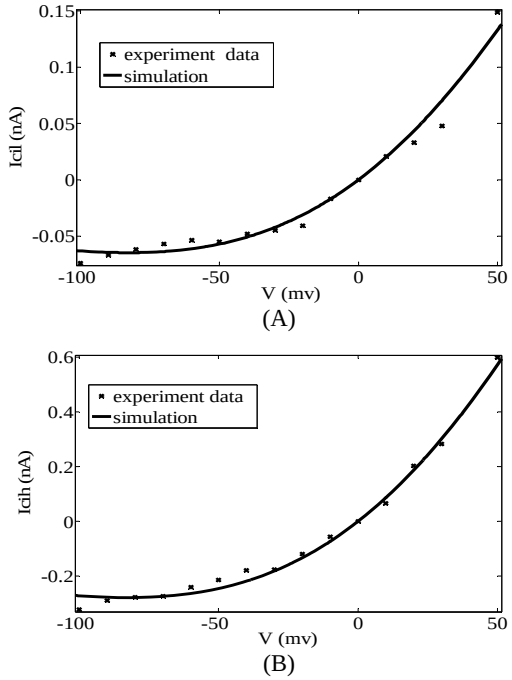


Figure 1 Current-voltage relationship of experimentally measured I_{ci} and fitted curve. (A) Fbs compression is 2 μm (I_{cil}). (B) Fbs compression is 3 μm (I_{cih})

2.2. Electrophysiological models of hAMs and atrial Fbs

In this study, the Courtemanche-Ramirez-Nattel (CRN) [13] model was used to represent the hAM AP dynamics since this model could computationally efficient and correctly replicate APD restitution of the adult hAM.

Because the role of active conductances in the Fb membrane during Fb-myocyte coupling is still unclear [14], both passive and active electrophysiological models of Fbs were used in this study to simulate atrial Fbs AP dynamics.

For the passive model:

$$I_{Fb} = G_{Fb}(V_{Fb} - E_{Fb}) \quad (2)$$

where I_{Fb} is the current of Fb, V_{Fb} is the membrane potential of Fb, G_{Fb} is the membrane conductance and E_{Fb} is the reversal potential. According to the experimental data, G_{Fb} ranges from 0.1 to 4 nS [3], and E_{Fb} ranges from -50 to 0 mV [4, 15-17]. In this study, we used G_{Fb} = 0.5 nS, E_{Fb} = -20 mV.

The active Fb model is the same as [14], which is based on the general formulation of [11]. The resting membrane potential of the atrial Fb can have a significant influence on the electrophysiological behavior of the coupled myocyte, -47.75 mv was chosen in this study.

2.3. Myocyte-Fb-I_{ci} coupling

According to [11], the equations of the myocyte-Fb coupling model are defined by:

$$\frac{dV_{m,myo}}{dt} = -\frac{1}{C_{m,myo}}\left[I_{myo}(V_{myo},t) + I_{stim} + \sum_{i=1}^{n} G_{gap}(V_{myo} - V_{Fb})\right]$$
$$\frac{dV_{Fb}}{dt} = -\frac{1}{C_{Fb}}\left[I_{Fb}(V_{Fb},t) + I_{ci} - I_{gap}\right] \quad (3)$$

where $V_{m,myo}$ and V_{Fb} are the membrane potential of the hAM and Fb respectively, $C_{m,myo}$ and C_{Fb} are the membrane capacitance of the hAM and Fb respectively, I_{myo} and I_{Fb} are the net membrane current of the hAM and Fb respectively. I_{stim} is the stimulus current applied to the hAM membrane, and I_{gap} is the current that flows through the gap junction between the hAM and each Fb. G_{gap} represents the gap-junctional conductance, and n represents the coupling Fbs number. It has been reported that G_{gap} ranges from 0.3 to 8nS in cultured cell [15] and C_{Fb} from 6.3 to 75 pF [11, 18]. In this study, C_{Fb}= 6.3 pF and G_{gap}= 1.0 nS were used.

3. Results

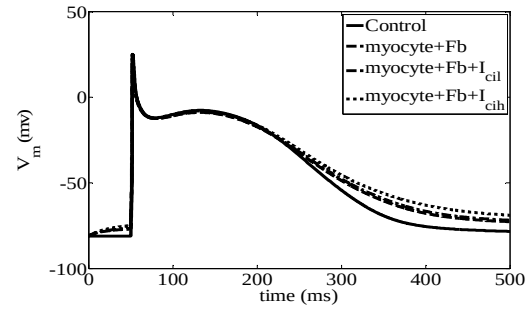
3.1. Action potential of myocyte

Figure 2 illustrates the APs of myocyte when employing both passive and active Fb models. The results under four different schemes are given: uncoupled with hAM as a control; coupled with Fb only; coupled with Fb with the incorporation of I_{cil} and I_{cih}.

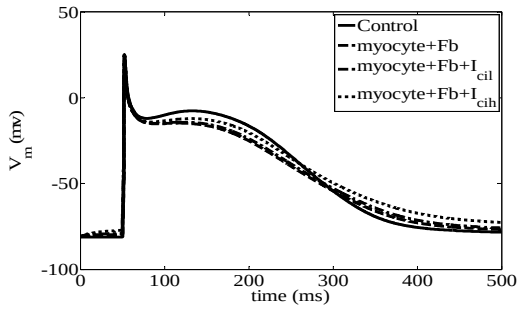
With the passive Fb model, tt can be seen from Figure 2(A) that, with the coupling of Fb, the repolarization in was prolonged when compared with control. Their corresponding AP durations at 50% repolarization

(APD_{50}) in the control and other three schemes were 184 ms, 185 ms, 186 ms, and 189 ms respectively. For APD_{90}, more obvious increase was observed (304 ms for control, 382 ms for coupling with Fb only, 403 ms for coupling with Fb+ I_{cil}). With I_{cih}, the membrane potential was -61.6 mv at 500 ms, and it did not return to -70.6 mV required for APD_{90}. The resting potential (V_{rest}) of hAM remained at -81.2 mv for the control before the fast depolarization, while I_{ci} depolarizated V_{rest} slightly. In addition, the the maximum value of the AP (V_{max}) increased slightly from 24.6 mV (control) to 25.8 mV (with I_{cih}). Moreover, the maximum upstroke velocity decreased slightly from 218 mV/ms to 206 mV/ms, 204 mV/ms and 203 mV/ms.

With the active Fb model, the APD_{90} in the control and other three schemes was 304 ms, 326 ms, 340 ms and 390 ms, respectively. However, the APD_{50} decreased from 184 ms to 156ms, 164 ms and 175 ms. For the resting potential, similar phenomenon were observed with the passive Fb model.



(A)

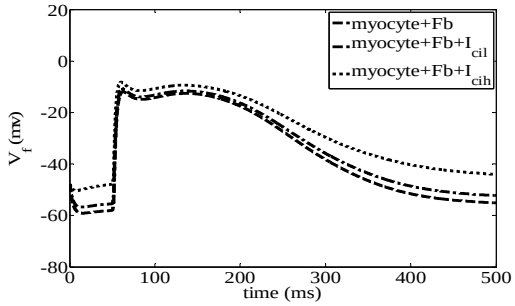


(B)

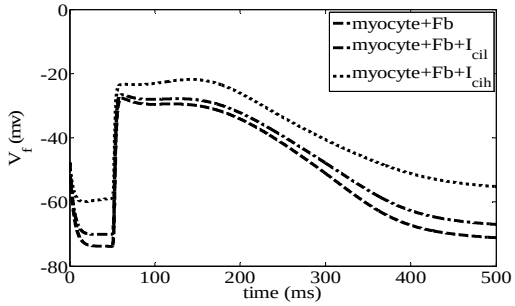
Figure 2. .Action potential of myocyte after coupling with passive Fb (A) and active Fb (B).

3.2. Action potential of Fbs

Figure 3 (A) shows the APs of the passive Fbs when it was coupled with myocyte under different conditions. It can be seen that with the increase of I_{ci}, V_{max} increased slightly, with their corresponding values of -11.9 mV, -10.8 mV and -8.2 mV. The membrane potential at 500 ms was also increased from -55.1 mV to -52.2 mV then to -44.0 mV. Figure 3 (B) shows the APs of the active Fbs. As can be seen that I_{ci} depolarized Fb more obviously. When Fb adopted active electrical model, it displays much more electronic changes after coupling.



(A)



(B)

Figure 3. Action potential of Fb after coupling with myocyte using passive (A) and active (B) models.

4. Discussion and conclusions

In this study, I_{ci} in Fbs has been simulated, and the effects of Fbs and I_{ci} on the APs of hAMs and Fbs have been investigated at the cellular level. In both passive and active Fbs models, for the AP of hAMs, our simulation showed that the resting potential was depolarized slightly when compared with the uncoupled situation. With the incorporation of increased I_{ci}, the phenomenon is more obvious. In addition, coupling I_{ci} prolonged APD_{90} of hAMs. For the AP of Fbs, our results were consistent with the experimental data [5-6].

However, there are some limitations in this study. Firstly, we just simulated I_{ci} of the whole cell. Other I_{ci} components, including the non-selective cation current through G_{ns}, K^+ current, and current I_p,generated by electrogenic Na-pumping [5], have not been taken into consideration. However, to integrate these current components such as stretch actived currents into atrial myocytes models, more experimental data is required. Secondly, the Ca^{2+}-activated K^+ currents of human

cardiac Fbs [19] have not been incorporated into the Fb model. Thirdly, the I_{ci} in rat atrial Fbs was used due to the lack of I_{ci} data in hAMs. Nevertheless, this preliminary simulation study confirmed that mechanosentitive currents in Fbs play an important role in mechano-electrical coupling.

Acknowledgements

This project is supported by the 973 National Basic Research & Development Program (2007CB512100) and the National Natural Science Foundation of China (81171421, 61101046).

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