Myofibroblasts Alter Tension and Strain of Cardiac Fiber:
A Computational Study

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Abstract

In heart pathological conditions, fibroblasts proliferate and differentiate into myofibroblasts (Mfbs). This study aimed to investigate the role of Mfbs on the mechanical contraction of cardiac fiber. Mathematical modeling was done using a combination of (1) the Maleckar et al. model of the human atrial myocyte, (2) the MacCannell et al. active model of the human cardiac Mfb, (3) our formulation of \( I_{Na,myofb} \) based upon experimental findings from Chatelier et al., and (4) the Hill three-element rheological scheme of a single segment of cardiac fiber. For Mfb-myocyte coupling, different ratios of myocytes to Mfbs and gap-junctional conductances were set based on available physiological data. Both isometric contraction and isotonic contraction were considered to illustrate the effect of Mfbs on cardiac fiber's tension and strain. The results showed that (1) Mfbs decreased APD\textsubscript{90} and increased \( V_{rest} \), depolarization, (2) Mfbs regulated myocyte peak force and (3) Mfbs reduced the fiber peak force in isometric contraction and the fiber peak strain in isotonic contraction. The identified effects demonstrated that Mfbs play an important role of modulating cardiac mechanical behavior. It should be considered in future pathological cardiac mathematical modeling, such as atrial fibrillation and cardiac fibrosis.

1. Introduction

As one type of connective tissues, cardiac fibroblasts account for approximately 75% of all cardiac cells but only contribute 5-10% of the total mammalian heart volume due to their small size [1]. During pathophysiological challenges, such as cardiac fibrosis, myofibroblast (Mfb) cell population emerges as the subpopulation of fibroblasts that are responsible for tissue remodeling [2]. Fibrosis, characterized by fibroblast proliferation and collagen production, is strongly correlated with atrial and ventricular tachyarrhythmias and sudden cardiac death [3].

Recently, clinical data and simulation studies have verified that Mfbs have several currents like cardiac myocytes. One of them is the current through voltage-gated sodium channels in Mfbs \( (I_{Na,myofb}) \) [4]. Computational models of atrial fibrosis have been used to investigate how fibroblasts modulate cardiac myocyte electrophysiology and mechanics. They showed that coupling of Mfbs to atrial myocytes resulted in shorter duration of the action potential (APD), slower conduction, and spiral wave breakups [5, 6]. Meanwhile, they found that fibroblast alignment parallel to a strain cue provided negative feedback to radical changes in local fiber orientations [7, 8]. These studies have discussed cardiac myocyte function in a lot of ways, yet they have not considered \( I_{Na,myofb} \) in Mfb-myocyte (Mfb-M) coupling, which could influence Mfb properties and contribute to electromechanical coupling in cardiac pathologies.

In previous study, we have found that the Nav 1.5 \( \alpha \) subunit, which generates \( I_{Na,myofb} \), regenerated action potentials (APs) in myocytes and Mfbs [9]. In this study, we aimed to investigate the role of Mfbs on the mechanical contraction of cardiac fiber. \( I_{Na,myofb} \) was considered in the process. Simulation results of 1D human atrial fiber mechanical dynamics with different number of coupled Mfbs and gap-junctional conductances \( (G_{gap}) \) were compared.

2. Materials and Methods

Mathematical modeling was done using a combination of (1) the Maleckar et al. model of the human atrial myocyte, (2) the MacCannell et al. active model of the human cardiac myofibroblast, (3) our formulation of \( I_{Na,myofb} \) based upon experimental findings from Chatelier et al., and (4) the Hill three-element rheological scheme of a single segment of cardiac fiber. An overview of the simulations was given as follows.

2.1. Mfb-M coupling

According to [10], the differential equations for the membrane potential of cardiac Mfb and myocyte are given by
\[ \frac{dV_{\text{Mfb},i}}{dt} = -\frac{1}{C_{\text{m,Mfb}}}(I_{\text{Mfb},i}(V_{\text{Mfb},i}, t) \\
+ G_{\text{gap}}(V_{\text{Mfb},i} - V_{\text{M}})) \] (1)

\[ \frac{dV_M}{dt} = -\frac{1}{C_{\text{m,M}}}(I_M(V_M, t) + \sum_{i=1}^{n} G_{\text{gap}}(V_M - V_{\text{Mfb},i})) \] (2)

where \( V_{\text{Mfb},i} \) and \( V_M \) represent the transmembrane potential of the \( i \)th coupled Mfb and the human atrial myocyte, respectively; \( C_{\text{m,Mfb}} \) and \( C_{\text{m,M}} \) represent the membrane capacitance of the Mfb and the myocyte, respectively; \( I_{\text{Mfb},i} \) and \( I_M \) represent the transmembrane current of the \( i \)th coupled Mfb and the human atrial myocyte, respectively; \( G_{\text{gap}} \) represents the gap-junctional conductance; and \( n \) is the total number of coupled Mfb.

### 2.2. Model of the human atrial myocyte

The mathematical model from Maleckar et al. is implemented in this study [11], which is based on experimental data and has correctly replicated APD restitution of the adult human atrial myocyte.

The model 4 of isometric force generation in cardiac myofilaments proposed by Rice et al. is applied to model the Ca²⁺-force relation in the present study [12].

### 2.3. Model of human atrial Mfbs

The active electrophysiological model of atrial Mfb described by Maleckar et al. is used in the present study [11]. In addition, \( I_{\text{Na,Mfb}} \) is added in the Mfb model. According to our previous work [9], equations of \( I_{\text{Na,Mfb}} \) is given by

\[ I_{\text{Na,Mfb}} = \bar{g}_{\text{Na,Mfb}} m_{\text{Mfb}}^{0.12} (V_{\text{Mfb}} - E_{\text{Na,Mfb}}) \] (3)

\[ E_{\text{Na,Mfb}} = \frac{RT}{F} \log \frac{[\text{Na}^+]_{\text{Mfb}}}{[\text{Na}^+]_{\text{in,Mfb}}} \] (4)

where \( \bar{g}_{\text{Na,Mfb}} \) is the maximum conductance of \( I_{\text{Na,Mfb}} \); \( E_{\text{Na,Mfb}} \) is the Nernst potential for Na⁺ ions; \([\text{Na}^+]_{\text{Mfb}}\) and \([\text{Na}^+]_{\text{in,Mfb}}\) are the Mfb extracellular and intracellular Na⁺ concentration, respectively; \( m_{\text{Mfb}} \) and \( f_{\text{Mfb}} \) are the activation and inactivation parameters, respectively.

### 2.4. Mechanical behavior of a cardiac fiber with inserted Mfbs

The mechanical behavior of a single segment in our model is based on the classical three-element rheological scheme [13]. It consists of a contractile element (CE), a series elastic element (SE) and a parallel elastic element (PE). Cardiac fiber is modeled as a string of segments coupled in series. Each segment is regarded as a myocyte/Mfbs complex. Mfbs are coupled to each myocyte by longitudinal connection, which distributed along the long axis of segments. The electrical component is governed by the parabolic partial differential monodomain equation. The mechanical component is described as follows [14].

\[ F^i_{\text{segment}} = F^i_{\text{fiber}} \] (5)

\[ J^i_{\text{fiber}} = \frac{L}{L_0} = \frac{\sum n_e I^i_{\text{PE}}}{\sum n_e I^i_{\text{PE}_0}} \] (6)

where \( F_{\text{segment}} \) is the total force generated by the segment. \( F_{\text{fiber}} \) is the force generated by the fiber, \( J_{\text{fiber}} \) is the stretch ratio of the fiber, \( L \) denotes the actual fiber length, \( L_0 \) is the reference length, \( I^i_{\text{PE}} \) and \( I^i_{\text{PE}_0} \) represent the reference length and the actual length of the PE of segment \( i \).

### 2.5. Simulation protocol and numerical methods

We performed the impulse propagation along a 5-cm-long homogeneous fiber with isometric contraction and isotonic contraction to illustrate the effects of Mfbs on cardiac fiber mechanical properties. Mfb-M ratio was 1, 2 and 3, respectively. \( G_{\text{gap}} \) was 0.5, 3 and 8 nS, respectively.

To ensure the coupled system reached steady-state, stimulation was repeated for 20 cycles. Results from the last cycle in each simulation were used. All state variables of the coupled model were updated by means of the forward Euler method. The time step was set to be 10 μs to ensure numerical accuracy and stability.

### 3. Results

#### 3.1. Effects of Mfb on myocyte AP and force

![Figure 1. Effects of Mfb on myocyte AP and force.](image-url)
(dashed), $G_{gap} = 3$ nS (dotted), $G_{gap} = 8$ nS (dashdot), and myocyte was coupled with 2 Mfb.

Figure 1 showed AP and force in myocytes with different number of coupled Mfb and $G_{gap}$. On electrophysiology, increased Mfb and $G_{gap}$ resulted in gradually decreased APD at 50% repolarization ($APD_{50}$), and increased the resting myocyte membrane potential ($V_{rest}$) depolarization (Figure 1a and 1b). Comparing to the control (no Mfb), $APD_{50}$ was decreased by 32% (1 Mfb), 48% (2 Mfb) and 50% (3 Mfb), and by 25% (0.5 nS), 48% (3 nS) and 49% (8 nS), respectively. $V_{rest}$ was increased by 13.8% (1 Mfb), 29.3% (2 Mfb) and 44.8% (3 Mfb), and by 20.1% (0.5 nS), 24.3% (3 nS) and 28% (8 nS), respectively. On mechanics, peak force increased with increased Mfb, while decreased with increased $G_{gap}$ (Figure 1c and 1d). It was increased by 2.7% (1 Mfb), 14.3% (2 Mfb) and 30.5% (3 Mfb), and decreased by 6.7% (0.5 nS), 11.4% (3 nS) and 13% (8 nS), respectively.

3.2. Effects of Mfb on tension and strain of cardiac fiber

![Figure 2](image)

Figure 2. Effects of Mfb on $F_{fiber}$ (isometric contraction) and $\lambda_{fiber}$ (isometric contraction) of cardiac fiber. In (a) and (c), pure myocyte (solid), myocyte with 1 Mfb (dashed), myocyte with 2 Mfb (dotted), myocyte with 3 Mfb (dashdot), $G_{gap} = 3$ nS. In (b) and (d), pure myocyte (solid), $G_{gap} = 0.5$ nS (dashed), $G_{gap} = 3$ nS (dotted), $G_{gap} = 8$ nS (dashdot), and myocyte was coupled with 2 Mfb.

In Figure 2, traces of cardiac fiber tension and stretch ratio were presented for simulations of isometric contraction with sarcomere length of 1.78 µm and isometric contraction with applied force of 10 mN/mm².

In isometric contraction (Figure 2a and 2b), peak $F_{fiber}$ both decreased when the number of Mfb and $G_{gap}$ increased. Comparing to the control (no Mfb), it was decreased by 2.9% (1 Mfb), 5.5% (2 Mfb) and 7.9% (3 Mfb), and by 0.8% (0.5 nS), 5.5% (3 nS) and 11.8% (8 nS), respectively.

In isotonic contraction (Figure 2c and 2d), the minimum of $\lambda_{fiber}$ also both decreased when the number of Mfb and $G_{gap}$ increased. It was decreased by 1.2% (1 Mfb), 2.1% (2 Mfb) and 2.9% (3 Mfb), and by 0.5% (0.5 nS), 2.1% (3 nS) and 4.3% (8 nS), respectively.

4. Discussion

This study investigated the roles of Mfb in myocyte AP and in 1D cardiac fiber mechanical behavior. Numerical simulations of the coupled Mfb-M system were performed by employing a combination of models of the human atrial myocyte and Mfb (including $I_{Na,Mfb}$), models of Ca²⁺-force relation and myocyte mechanical segment. Specifically, effects of Mfb with different number of coupled Mfb and $G_{gap}$ on atrial fiber properties were investigated. Coupling Mfb could result in: (1) decreased $APD_{50}$ and increased $V_{rest}$ depolarization, (2) increased the peak force with increased Mfb, and decreased the peak force with increased $G_{gap}$, and (3) decreased the peak value of $F_{fiber}$ in isometric contraction and the minimum of $\lambda_{fiber}$ in isotonic contraction.

Our simulations showed a depolarizing effect of coupled Mfb on $V_{rest}$ of atrial myocytes. Figure 1 showed a maximum depolarization of 14 mV for a myocyte with 3 Mfb. Previous experimental studies have shown the depolarization of neonatal rat ventricular cardiomyocyte strands when Mfb interacted with myocytes. Modeling studies have also shown that fibroblasts depolarized coupled myocytes. MacCannell et al verified that $V_{rest}$ of the coupled myocyte was depolarized slightly (~2.7 mV) for up to 10 fibroblasts per myocyte, and was insensitive to $G_{gap}$ [10]. However, Maleckar et al reported that a $G_{gap}$ of 8 nS and two active 1 fibroblast resulted in a $V_{rest}$ elevation of 8.3 mV [15].

Coupling human atrial myocytes with Mfb also resulted in diverse effect on AP morphology during repolarization. It has been found that fibroblasts functioned as strong current sources at rest and as both sources and sinks during the AP when they employed a myocyte-fibroblast coupling model with a high $G_{gap}$ [15]. In that study, the prolongation of repolarization was emerged early in the AP, and plateau was prolonged or shortened depending on both the fibroblast $V_{rest}$ and number of coupled fibroblasts. Ventricular myocyte AP was compared when fibroblasts with a membrane capacitance of 6 pF or 60 pF were coupled to a myocyte. It showed that APD was shortened much more when large fibroblasts were coupled. In our simulations, increasing the number of Mfb and $G_{gap}$ decreased $APD_{50}$.

For mechanics, previous studies have verified that...
mechanical cues activated cardiac Mfbs [16]. Mfbs were regarded as a critical determinant of cardiac mechanics. Computational modeling was used to demonstrate the acute mechanical effects on cardiac fibroblast structure and organization [17]. It was verified that an axial strain environment could guide fibroblast proliferation, orientation and migration [18]. Several groups have demonstrated that cellular organization was tightly linked to the mechanical feedback loop between cells and matrix [7]. This studies were about the stretch-induced responses of quiescent cardiac Mfbs. However, the inverse process, the Mfbs-induced responses of cardiac mechanics, has not yet been widely understood. Our results showed that coupling Mfbs changed cardiac fiber mechanical properties. Coupling Mfbs both decreased tension and strain of cardiac fiber.

5. Summary

This study demonstrated the effects of Mfbs on cardiac fiber mechanical properties. Our results showed that Mfbs regulated the peak and valley values of fiber mechanical parameters in both isometric contraction and isotonic contraction. The effects proved that Mfbs should be considered in future pathological cardiac mechanical mathematical modeling, such as atrial fibrillation and cardiac fibrosis.

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References


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