Effects of Fibroblast on Cardiac Electro-Mechanics: a Cube Modeling Study

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Abstract

Previous studies of cardiac electromechanical coupling have largely focused on myocytes, while fibroblasts have not been widely concerned. This study aimed to verify possible influences of fibroblasts on cardiac electro-mechanics with a real coupled cube model. At the cellular level, the ten Tusscher mathematical model of the human ventricular myocyte and the passive fibroblast model were combined with the J. Jeremy Rice mathematical model of contraction and cooperativity mechanisms. At the tissue level, regions of myocytes and fibroblasts were considered to be elastic bodies with different elastic modulus. Numerically, the finite difference method solved the excitation equations, and the finite element method settled the equations governing tissue mechanics. The results showed that fibroblasts slow down wave propagation and increase mesh contraction. The influence of fibroblasts on cardiac excitation and contraction should be pursued in future heart modeling studies.

1. Introduction

The heart consists of myocytes, vasculature cells and connective tissue cells [1]. Fibroblasts, one of the nonmyocyte cell populations of the heart, have been recognized to contribute importantly to multiple aspects of myocardial function and pathophysiology [2].

Computational study of cardiac modeling, including electrophysiology and mechanics, has been utilized as an important alternative to experimental study, to explore cardiac dynamics in both normal and pathological situations. Cardiac coupled electromechanical models are developed from one dimension to three dimensions to reflect the close relationship between myocardium electrical and mechanical activities [3]. However, these models only describe the cardiac myocytes properties, other types of cells like vasculature and connective tissue cells are not considered. Besides, it has been reported that myocyte-fibroblast coupling modulated action potential (AP) morphology and action potential duration (APD). These studies implicate that the effects of fibroblasts on cardiac electrophysiology and mechanics should not be ignored. So far two electrophysiological models of ventricular fibroblasts: the passive model [4] and the active model [5] have been developed. However, to our best knowledge, there is no mechanical model for cardiac fibroblasts yet.

In this study, a strongly coupled myocardial-fibroblastic electromechanical cube model was proposed, which integrated the fibroblast model with the myocardial electrophysiological model and mechanical model at the cellular level, and excitation conduction and elastic mechanics at the tissue level. To realize the cellular electromechanical coupling, the calcium buffer was introduced in the ten Tusscher model. With the proposed model, the effects of fibroblasts on three dimensional (3D) cardiac excitation conduction and contraction were investigated in normal and pathological situations.

2. Meterials and methods

2.1. Model framework

The proposed strongly coupled myocardial-fibroblastic electromechanical cube model comprises two parts: the cell model, which stems from the ten Tusscher electrophysiological model [6], the Rice mechanical model [7] and a passive fibroblast model [4], as well as the tissue model, which includes cardiac excitation conduction and finite deformation, described by the Nash model [8].

For myocyte electrophysiology, the ten Tusscher model is taken in the present study [6]. The only modification is made on Ca^{2+} handling. We rewrite the equation of the concentration of Ca^{2+} by adding Ca^{2+} buffers to Ca^{2+} dynamics to achieve cellular electromechanical coupling. The equations of Ca^{2+} buffers are expressed as [9]:

$$\begin{aligned}\frac{dCmdn_{Ca}}{dt} &= \alpha_{cmdn}(Cmdn_{tot}-Cmdn_{Ca})Ca_i-\beta_{cmdn}Cmdn_{Ca}\\ \frac{dTrpn_{Ca}}{dt} &= \alpha_{Trpn}(Trpn_{tot}-Trpn_{Ca})Ca_i-\beta_{Trpn}[\frac{1+2(1-Force_{norm})}{3}]Trpn_{Ca}\end{aligned} \quad (1)$$

In this way, the equation of the cytosolic concentration of Ca^{2+} in the ten Tusscher model turns into,

$$\frac{dCa_i}{dt}=i_{leak}-i_{up}+i_{rel}-\frac{i_{CaL}+i_{bCa}+i_{pCa}-2i_{NaCa}}{2V_cF}-\frac{dCmdn_{Ca}}{dt}-\frac{dTrpn_{Ca}}{dt} \quad (2)$$

For mechanics, the Rice mechanical model of cardiac

myofilament [7, 9] is adopted and coupled with the above mentioned electrophysiological model.

For the electrophysiological models of fibroblast, two types can simulate the characteristics of fibroblasts, the passive model [4] and the active model [5]. Here we use the passive model, that is,

$$I_f = G_f (V_f - E_f) \tag{3}$$

where I_f is the current of fibroblast, V_f is the membrane potential of fibroblast, G_f is the membrane conductance and E_f is the reversal potential. According to experiments, G_f ranges from 0.1 to 4 nS [10], and E_f ranges from -60 to 0 mV [11]. In this study, we use G_f =0.5nS, E_f =-50mV.

At the tissue level, fibroblasts and myocytes are assembled into a 3D cube. The tissue electrophysiological fibroblast-myocyte is expressed as [12]:

$$C\frac{dV}{dt} = -I_{ion} + \sum_{k=1}^{n} G_{gap}^{k}(V^k - V) \tag{4}$$

where C is C_m or C_f, I_{ion} is I_m or I_f, n is the number of coupled neighbors (either myocytes or fibroblasts), and G^k_{gap} is the gap junction conductance between a cell (either a myocyte or a fibroblast) and its k^{th} neighbor (either a myocyte or a fibroblast). Based on experiments, it was recorded that C_f ranges from 6.3 to 75pF [5], G_{gap} ranges from 0.3 to 8nS in cultured cells [13]. Here we use C_f =50pF and Ggap = 100nS (for the myocyte-myocyte coupling), Ggap = 0.6nS (for the myocyte-fibroblast coupling), Ggap = 0.03nS (for the fibroblast-fibroblast coupling).

For tissue mechanics, the mechanical model proposed by Nash and Panfilov [8] is adapted to model myocytes mechanics. Considering the possible poor flexibility of the fibroblast regions, local strains were very small, so the elastic mechanics was used to calculate the displacement of fibroblast with a large fibroblast elastic modulus. In this way, relative displacements of the fibroblasts inside area are very small, while deformations of the boundary of fibroblast areas are obvious, relatively. The main equations of regions of fibroblasts mechanics are

$$[K^e]\{d^e\} - \{f^e\} = 0$$

$$[K^e] = \int_{V_0} B^{\mathrm{T}} D B \mathrm{d}V_0$$

$$E = \sum_{i=1}^{n} \psi_i E(x_i, y_i)$$

$$\mu = \sum_{i=1}^{n} \psi_i \mu(x_i, y_i)$$

$$B_i = \begin{bmatrix} \frac{\partial \psi_i}{\partial x} & 0 & 0 \\ 0 & \frac{\partial \psi_i}{\partial y} & 0 \\ 0 & 0 & \frac{\partial \psi_i}{\partial z} \\ \frac{\partial \psi_i}{\partial y} & \frac{\partial \psi_i}{\partial x} & 0 \\ 0 & \frac{\partial \psi_i}{\partial z} & \frac{\partial \psi_i}{\partial y} \\ \frac{\partial \psi_i}{\partial z} & 0 & \frac{\partial \psi_i}{\partial x} \end{bmatrix}, \quad i = 1, 2, \ldots, n \tag{5}$$

$$D = \frac{E(1-\mu)}{(1+\mu)(1-2\mu)} \begin{bmatrix} 1 & \frac{\mu}{1-\mu} & \frac{\mu}{1-\mu} & 0 & & 0\ 0 \\ \frac{\mu}{1-\mu} & 1 & \frac{\mu}{1-\mu} & 0 & & 0\ 0 \\ \frac{\mu}{1-\mu} & \frac{\mu}{1-\mu} & 1 & 0 & & 0\ 0 \\ 0 & 0 & 0 & \frac{1-2\mu}{2(1-\mu)} & & 0\ 0 \\ & & & & \frac{1-2\mu}{2(1-\mu)} & 0 \\ 0\ 0 & & 0\ 0 & & 0 & \frac{1-2\mu}{2(1-\mu)} \\ 0\ 0 & & 0\ 0 & & & \end{bmatrix}$$

$$\{f^e\} = \int [\psi_n]^{\mathrm{T}} \{p\} \mathrm{d}s$$

where $[K^e]$ is the element stiffness matrix, $\{d^e\}$ is the vector of nodal variables, $\{f^e\}$ are the external nodal traction forces, B_i is the global strain-displacement matrix, D is the constitutive matrix, E and μ are the elastic modulus (Young's modulus) and Poisson's ratio respectively. According to the relevant research [14], E=5kPa and μ=0.49 are chosen. From Eq.(5), the deformation of fibroblasts can be calculated.

2.2. Computational procedure

The basic process of models calculation is as follows: All derivatives in electrophysiological equations of myocytes and fibroblasts are calculated by finite difference approximations. Following each time integration step, all parameters of these cells are updated, T_a are interpolated at finite element Gauss points. Stresses of these active Gauss points are served as inputs to govern the tissue mechanics model. The nonlinear least square iteration is used to solve the stress equilibrium equations. Deformation tensors are then updated to govern equations of the electrical conduction. For fibroblast regions, after the evaluation of stiffness matrix and consistent load vector, the nodal displacement matrix of fibroblasts are finally calculated.

In this study, we considered isotropic conduction. The 3D model parameters are the following: finite difference approximations are computed using a time integration step of Δt=0.01ms and a apace integration step of Δx= Δ y=0.2mm. The mechanics mesh is defined containing 5×5×5 finite elements. Each mechanical element includes 11×11×11 electrical grid points. Thus, the whole area has 41×41×41 grid points and the distance between every two elements is 2.2mm. The time integration step of mechanics is 2ms.

3. Results

3.1. Electromechanical coupling at cellular level

Figure 1 shows the AP, Ca_i and T_a curves of myocyte generated by the proposed coupled model. The maximum Ca_i in the coupled model was lower than that in the ten Tusscher model. This was due to the modification of the

cytosolic concentration of Ca^{2+}(see Eqs.(1)-(2)). T_a has the maximum force of 0.0205N/mm^2 (20.5kPa), which is consistent to the general range (10 ~ 75kPa) depending on the sarcomere length [15].

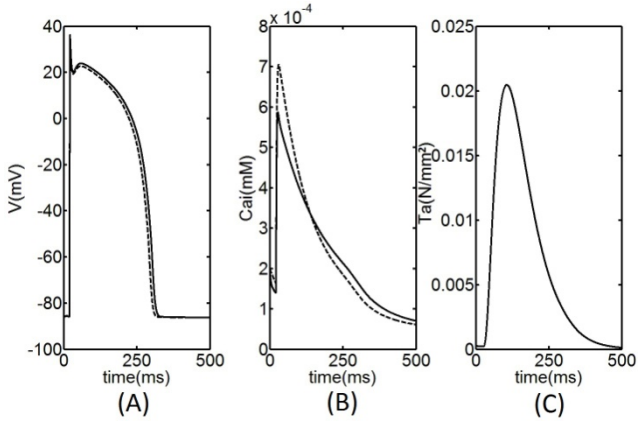

Figure 1. Simulated results under 1-Hz pacing generated of the proposed myocyte electromechanical coupling model and the original ten Tusscher model: (A) steady-state AP, (B) Ca_i and (C) T_a. Solid lines represent the proposed model and dashed lines are the ten Tusscher model.

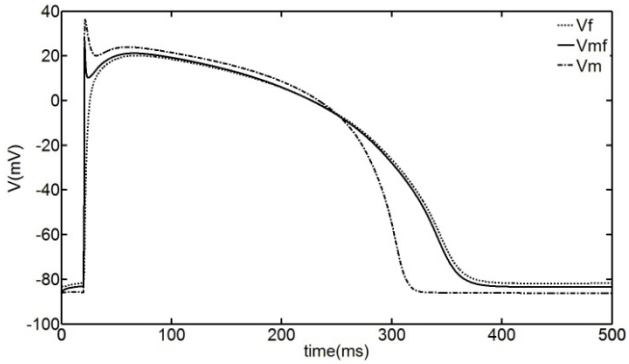

Figure 2. Active potential of myocyte (V_m) and fibroblast (V_f) after coupling.

Figure 2 shows the effect of coupling three passive fibroblasts to a ventricular myocyte with a G_{gap}=20nS. In contrast to Figure 1, coupling passive fibroblasts to the simulated myocyte lengthened the ventricular APD (90% repolarization) from 289ms to 335ms, and the peak of the AP is decreased from 36.3mV to 26.5mV.

3.2. Point stimulus in 3D cubic cardiac tissue

Figure 3 shows the effects of central point stimulus on 3D human cubic cardiac tissue. The top line has no fibroblast and the other two lines have fibroblasts, existed as 1×1×1 or 2×2×1 at the lower right, respectively. Stimulate period is 700ms.

From Figure 3, we can see that the propagation of excitation wave on the bottom line is slower than that on the top line. This may be attributable to the poor elasticity of fibroblasts and smaller gap junctional conductance between a fibroblast and a myocyte (or fibroblast) as compared to that between two myocytes that further caused slower conduction. It was obvious that an increased area of fibroblasts was associated with an increased continuous mesh deformation, especially after 720ms. This may be explained by the dependence of the potential on the size of tissue regions with fibroblasts. This means fibroblasts reduce conduction velocity and aggravate contraction.

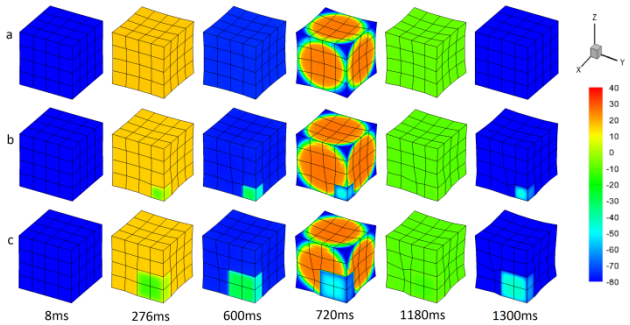

Figure 3. Electromechanical coupling in human cubic cardiac tissue. (a) myocyte cells only; (b) myocytes with fibroblasts in one mechanics element at the lower right; (c) myocytes with fibroblasts in 2×2×1 mechanics elements at the lower right.

4. Discussion

In this study, we present a 3D cubic electromechanical model composed of cardiac myocytes and fibroblasts to investigate effects of fibroblasts on cardiac excitation and contraction. The present study adds fibroblasts to the 3D cubic electromechanical model to reflect more realistic mechanisms of heart and explore possible influences of fibroblasts on cardiac electrophysiology and mechanics.

The results show that, at the cellular level, myocyte-fibroblast coupling prolongs APD; at the tissue level, inclusion of fibroblasts slows down excitation wave propagation, resulting in increased mesh contraction. In this study, material electrophysiological and mechanical models of cardiac muscles are used rather than simplified formula and properties of fibroblasts have been considered to improve the authenticity of simulation.

Except above results, this study also has some limiting assumptions. Firstly, conduction in myocytes and fibroblasts in this model is set to be isotropic. Secondly, only fibroblast is considered as the mechanism of electromechanical coupling. The other two, stretch activated ionic channels and second messengers/Ca^{2+} handling in cardiomyocytes are not considered. Finally, the mechanisms of fibroblast mechanics should be further studied. Researches on fibroblast mechanics are

mainly based on experiments [16]. In this simulation, we consider that once the fibroblast points reach to a certain number, the elasticity of the fibroblasts area drops rapidly. Therefore, the grids of mechanical elements in the fibroblast areas were considered as a visco-elastic tissue with a large fibroblast elastic modulus. With this assumption, local strains were very tiny within the fibroblast regions, and they can still be displaced by forces acting from the surrounding myocardium. If the detailed model of fibroblast mechanics has been fully worked out, it can be coupled to the myocyte mechanics model to simulate the more precise mechanisms of cardiac electromechanical coupling.

5. Summary

In conclusion, a cubic strongly coupled myocardial-fibroblastic electromechanical model has been developed. The simulation results suggest that fibroblasts will slow down wave propagation and increase mesh contraction. The effect proves that fibroblasts are an important mechanism in electromechanical coupling and should be valued in cardiac electromechanical modeling.

Acknowledgements

This project is supported by the National Natural Science Foundation of China (81171421, 61101046).

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