Three-Dimensional Constitutive Model of Cardiac Muscle taking into account Contraction Mechanism

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Abstract

A three-dimensional transversely isotropic constitutive model of cardiac muscle is formulated by taking account of the mechanism of excitation-contraction coupling. For this purpose, stress in cardiac muscle is assumed to be the sum of passive and active parts. The passive part is represented by a nonlinear elastic material expressed by a strain energy density function of exponential type. The active part, on the other hand, is modeled by a series of evolution equations that represents the process of excitation-contraction coupling. Comparison of simulation results with experimental results in the literature shows that this model can describe the behavior of isotonic contraction as well as isometric contraction. The model can also represent inotropic effects because it includes the evolution equations describing the change in the concentration of intracellular calcium ions.

1 Introduction

Recently, several efforts have been reported to diagnose a heart disease by using finite element simulations of a left ventricle. One of the most crucial factors governing the accuracy of these simulations is the adequacy of a constitutive model describing the mechanical behavior of cardiac muscles.

In this situation some constitutive models have been proposed so far for the description of cardiac muscles. For instance, elastic models [1, 2] disregarding the activation of the cardiac muscles, or one-dimensional models [3, 4] for the active state have been discussed. However, few models capable of describing three-dimensional behavior of cardiac muscles for both passive and active states with sufficient accuracy have been formulated. In particular, there is no model

which takes into account the excitation-contraction coupling [5] explicitly and can represent the change of contractility of cardiac muscles, i.e., inotropism [5]. Thus, it will be necessitated to formulate a constitutive model which can simulate both physiological and pathological conditions of cardiac muscles, and can examine the effect of a drug dosage in medical treatment.

In the present paper, a transversely isotropic three-dimensional constitutive model of cardiac muscles which can describe the mechanical behavior of cardiac muscles in both passive and active states is proposed by taking into account the excitation-contraction coupling. Then the simulations of experiments of isometric contraction and isotonic contraction are performed to examine the applicability of the proposed model. The applicability of the model to inotropism is also discussed.

2 Formulation of a constitutive model of cardiac muscles

2.1 Basic assumptions

Cardiac muscles show large deformation. Significant anisotropy is observed between the direction of muscle fibers and the direction perpendicular to the fibers. Viscoelastic properties such as creep, stress relaxation, stress-strain hysteresis loops with strain rate dependency are also observed. The electric excitation activates cardiac muscles, and its properties differ from the passive to the active state. It is difficult to incorporate all these properties into the model. Thus we will make the following basic assumptions:

A. Cardiac muscles are incompressible.
B. Mechanical properties in the plane perpendicular to muscle fibers are isotropic, i.e., cardiac muscles have transversely isotropic properties.
C. Mechanical properties of cardiac muscles are passive in the directions perpendicular to muscle fibers. In other words, the active properties are observed only in the fiber direction.
D. Viscoelastic properties of cardiac muscles can be neglected.
E. The stress acting on the cardiac muscles is expressed as the sum of passive and active stress.

On the basis of the last assumption we express the second Piola-Kirchhoff stress $\boldsymbol{T}$ as the sum of the passive part $\boldsymbol{T}^p$ and the active part $\boldsymbol{T}^a$:

$$\boldsymbol{T} = \boldsymbol{T}^p + \boldsymbol{T}^a \tag{1}$$

In the following, we will use $\boldsymbol{T}^p$ to model the passive properties. However, the Lagrange stress is more rational to represent the active properties, because the active force is governed by the number of fibers in the cross section of muscles. Thus we introduce the active stress $\boldsymbol{S}^a$ given by

$$\boldsymbol{S}^a = \boldsymbol{F}\boldsymbol{T}^a \tag{2}$$

where $\boldsymbol{F}$ is the deformation gradient.

2.2 Constitutive relation for the passive state

In the passive state, the strain in the muscles is induced by externally applied forces. We will describe this response by nonlinear elastic materials. On the basis of the experimental results [6], we express the passive stress $\boldsymbol{T}^p$ by

$$\boldsymbol{T}^p = \partial \rho_0 W / \partial \boldsymbol{E} \tag{3}$$

where $\rho_0 W$ is the strain energy density function of exponential type [7]

$$\rho_0 W = a(\exp Q) + (H/2)\{\det(2\boldsymbol{E} + \boldsymbol{I}) - 1\} \tag{4}$$

where ρ_0 denotes the mass density in the undeformed configuration, a is a material constant and H is Lagrange's multiplier related with the incompressible condition. The variables $\boldsymbol{E}$ and $\boldsymbol{I}$ are Green's strain tensor and the identity tensor, respectively. Furthermore, Q is the quadratic form with respect to the components of $\boldsymbol{E}$ that represents the transverse isotropy, and is expressed as

$$Q = \nu \operatorname{tr}^2 \boldsymbol{E} + 2\mu \operatorname{tr} \boldsymbol{E}^2 + 2\xi \operatorname{tr} \boldsymbol{E} \operatorname{tr} \boldsymbol{M}\boldsymbol{E} + 4\eta \operatorname{tr} \boldsymbol{M}\boldsymbol{E}^2 + \zeta \operatorname{tr}^2 \boldsymbol{M}\boldsymbol{E} \tag{5}$$

where ν, μ, ξ, η and ζ are material constants. In this equation, $\boldsymbol{M}$ is the structural tensor of the transverse isotropy with respect to the unit vector $\boldsymbol{h}$ which represents the direction of muscle fiber in the undeformed configuration, and thus the tensor $\boldsymbol{M}$ is defined by

$$\boldsymbol{M} = \boldsymbol{h} \otimes \boldsymbol{h} \tag{6}$$

By using the above equations (3), (4) and (5), the passive stress $\boldsymbol{T}^p$ is expressed by the following equation:

$$\begin{aligned} \boldsymbol{T}^p = {} & 2a(\exp Q)[\nu(\operatorname{tr} \boldsymbol{E})\boldsymbol{I} + 2\mu\boldsymbol{E} + \xi\{(\operatorname{tr} \boldsymbol{E})\boldsymbol{M} + (\operatorname{tr} \boldsymbol{M}\boldsymbol{E})\boldsymbol{I}\} \\ & + 2\eta(\boldsymbol{M}\boldsymbol{E} + \boldsymbol{E}\boldsymbol{M}) + \zeta(\operatorname{tr} \boldsymbol{M}\boldsymbol{E})\boldsymbol{M}] + H(\boldsymbol{I} + 2\boldsymbol{E})^{-1} \end{aligned} \tag{7}$$

2.3 Constitutive relation for the active state

The activation of cardiac muscles induces the contraction of muscle fibers and/or the generation of additional tension. According to the basic assumption C, the active stress $\boldsymbol{S}^a$ can be expressed by

$$\boldsymbol{S}^a = \tau^a \boldsymbol{R}\boldsymbol{h} \otimes \boldsymbol{h} \tag{8}$$

where τ^a denotes the activated stress caused by the activation, and $\boldsymbol{R}$ is the rotation tensor in the polar decomposition of $\boldsymbol{F}$. In the following, we will formulate the evolution equation of τ^a.

In general, an extent of active tension of muscles depends on the concentration of free calcium ions in cardiac cells. The attachments of free intracellular calcium ions to troponins on thin filaments enable actin sites to react with myosin heads; these attachments form cross-bridges, and they generate active tension in cardiac muscles. Hence, we begin to formulate the equation to express the concentration β of free calcium ions in the cells. With referring to the reference [8] and by examining the experimental results of Sonnenblick [6] we represent β by

$$\beta = \beta_0 \left[(1+\chi)t\right]^k \exp\left[-(1+\chi)\ell t\right] \tag{9}$$

where t denotes time, and β_0, k and ℓ are constants. Furthermore the parameter χ is defined by

$$\chi = \left[c_1 + c_2 \exp\left\{c_3\left(S_h - c_4\right)\right\}\right]\gamma \tag{10}$$

where c_1, c_2, c_3 and c_4 are constants. The parameter S_h expresses the nominal stress component in the direction of muscle fibers, which is represented by

$$S_h = \boldsymbol{S}\boldsymbol{h} \cdot \boldsymbol{R}\boldsymbol{h} \tag{11}$$

The γ, on the other hand, expresses the parameter describing the effects of contraction rate of muscle fibers on the deformation behavior. The evolution equation of γ is formulated as follows:

$$\dot{\gamma} = \dot{\lambda}_h - c_5\gamma \tag{12}$$

where c_5 is a constant, and $\dot{\lambda}_h$ is the rate of extension ratio in the fiber direction expressed by

$$\dot{\lambda}_h = \frac{\dot{\boldsymbol{E}}\boldsymbol{h} \cdot \boldsymbol{h}}{\sqrt{1 + 2\boldsymbol{E}\boldsymbol{h} \cdot \boldsymbol{h}}} \tag{13}$$

Then we note that during twitch there is a gradient of intracellular calcium ion concentration in the muscles, and that only calcium ions near the filaments have chances to attach to troponins. Thus, we introduce a variable α in addition to β to express these chances. The evolution of α is formulated as follows:

$$\frac{d\alpha}{dt} = \begin{cases} c_6\left[1+\left\{g_1+g_2\exp(g_3 S_h)\right\}\gamma\right](\beta-\alpha) \\ \qquad\qquad \text{when} \quad \beta \geq \alpha \\ c_7\left[1+\left\{g_4+g_5\exp(g_6 S_h)\right\}\gamma\right](\beta-\alpha) \\ \qquad\qquad \text{when} \quad \beta < \alpha \end{cases} \tag{14}$$

where c_6, c_7, g_1 through g_6 are constants.

By use of this α, the rate of the proportion $A_c(t)$ of the number of actin sites available to react with myosin heads to the total number of actin sites in muscles is determined by the equation [9]

$$\frac{dA_c(t)}{dt} = c_8\alpha^n\left[1-A_c(t)\right] - c_9 A_c(t) \tag{15}$$

where c_8, c_9 and n are constants.

For the rate of the proportion $n(t)$ of the number of action sites having formed cross-bridges to the total number of actin site we represent as follows:

$$\frac{dn(t)}{dt} = f(\gamma)\left[F(\lambda_h)A_c(t) - n(t)\right] \tag{16}$$

In this equation $f(\gamma)$ and $F(\lambda_h)$ are functions defined by

$$f(\gamma) = \begin{cases} f_0\exp\left[-\left(\dfrac{\gamma}{f_1}\right)^2\right] & \text{when} \quad \gamma \leq 0 \\ f_0\exp\left[-\left(\dfrac{\gamma}{f_2}\right)^2\right] & \text{when} \quad \gamma > 0 \end{cases} \tag{17}$$

$$F(\lambda_h) = \left\langle F_1\exp\left\{-\left(\frac{\lambda_h-\lambda_{h0}}{\Delta\lambda_h}\right)^2\right\} - F_0\right\rangle \tag{18}$$

Here f_0, f_1 and f_2 are constants, and λ_{h0} is the value of λ_h at the maximum tension, $\Delta\lambda_h$ is the half of the range of λ_h generating the tension, and F_0 and F_1

are constants. The symbol $\langle\ \rangle$ represents Macauley bracket which is defined as $\langle x\rangle = x$ (when $x \geq 0$) and $\langle x\rangle = 0$ (when $x < 0$).

Finally, the rate of active tension in cardiac muscles is proportional to the number of cross-bridges, which gives

$$\frac{d\tau^a}{dt} = c_{10}\left[1 + c_{11}|\gamma|\right]\frac{dn(t)}{dt} \tag{19}$$

where c_{10} and c_{11} are constants.

3 Examination of the applicability of the proposed model

3.1 Simulation results and discussion

We performed numerical simulations of the proposed model in order to evaluate the accuracy of the description of mechanical behavior of cardiac muscles. For comparison we selected the experimental results by Sonnenblick [6]. He soaked the papillary muscles excised from the right ventricle of a cat into Krebs-Ringer liquid at 21-23 $^{\circ}C$, and measured the time variation of the tension under the isometric contraction and the shortening under the isotonic contraction.

Figure 1 shows the time variation of the tension in the isometric contraction. The values of 1.12, 1.18, 1.21 are taken as the specified extension ratio λ_h of cardiac muscles. In the figure, the various symbols denote the experimental results, while the solid lines are the results calculated by the model. We see that the

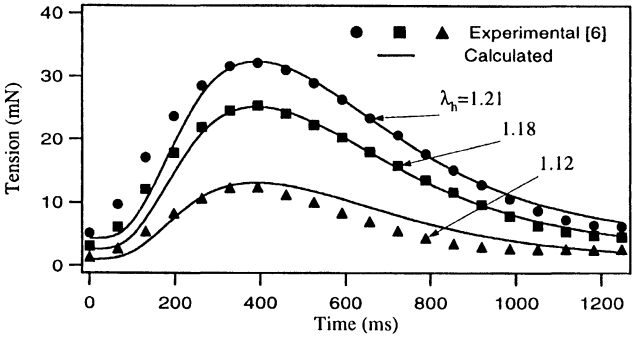
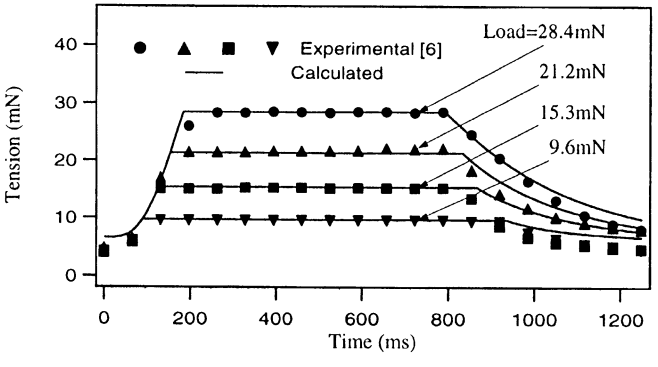


Figure 1 Simulations of isometric contraction

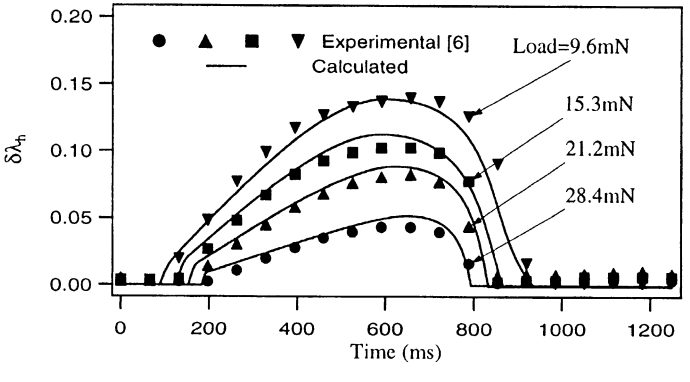
model can reasonably reproduce the experimental data.

Figure 2 (a) and (b) show the time variation of the tension and the decrease in extension ratio under the isotonic contraction. A value of λ_h=1.20 (corresponding to 3.9 mN) is chosen as the prestrain for every case. The afterloads are 11.4, 17.3 and 24.5 mN, respectively. From these figures we see that this constitutive model can describe the behavior of cardiac muscles.

Figure 3 shows the simulation and experimental results [10] for a quick-stretch test at peak tension during isometric contraction. Because the area of cross-section of the specimen is unknown, we cannot evaluate the two results quantitatively. But the simulation describes the experiment qualitatively well.

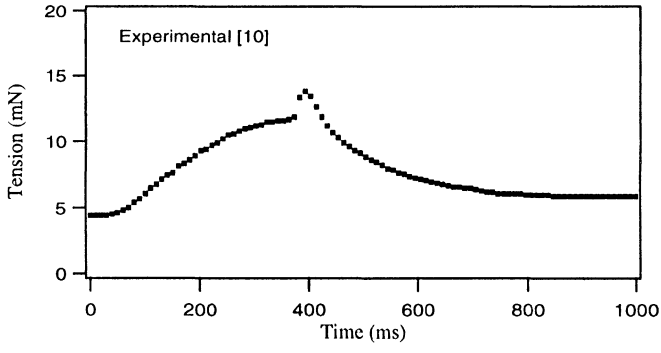


(a) Tension

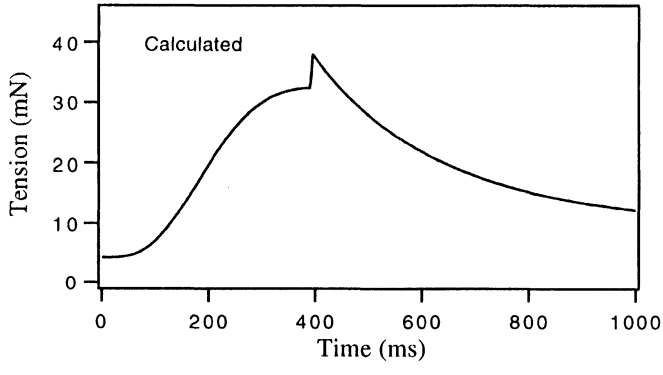


(b) Shortening

Figure 2 Simulations of isotonic contraction



(a) Experimental results



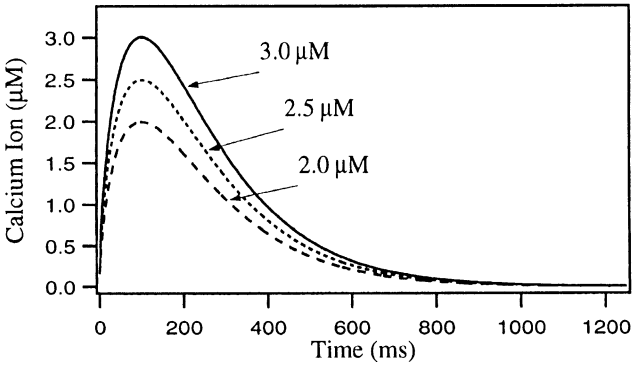
(b) Calculated results

Figure 3 Simulations of quick-stretch during isometric contraction (at peak)

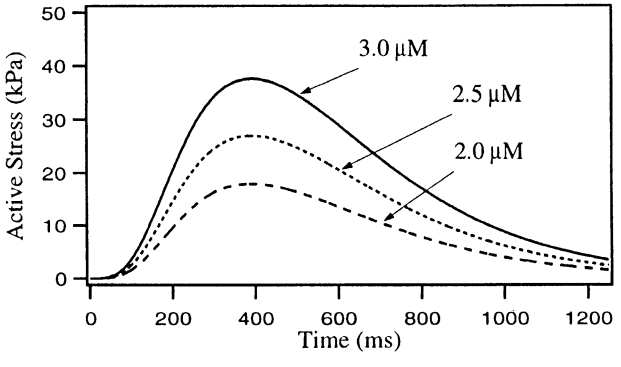
3.2 Examination of applicability to inotropism

The inotropism is defined as the change of contractility of cardiac muscles, and is caused by the change of the time variation curve of the concentration of calcium ion Ca^{2+} in the cardiac muscles by dosage of medicine, stimulation, temperature variation, etc., as well as the temperature dependence of actomyosin interaction [5]. In the following, we suppose a proper time variation curve of the Ca^{2+} concentration, and discuss the adequacy of the proposed model by comparing the typical features of the generated active stress with the literature.

The increase of the frequency of the stimulation to a cardiac muscle cell results in the rise of the maximum value of the concentration of Ca^{2+} [5], and thereby



(a) Intracellular calcium concentration



(b) Active stress

Figure 4 Effects of maximum value of intracellular Ca^{2+}

increases the maximum value of the tension, i.e., Bowditch effect. The results of the simulation are shown in Fig. 4. We see that the model can represent qualitatively the tendency of the variation of the maximum tension.

4 Conclusion

A three-dimensional transversely isotropic constitutive model for cardiac muscles was formulated. The passive behavior is represented by the nonlinear elastic material. The active behavior, on the other hand, was expressed by taking account of the excitation-contraction coupling of the cardiac muscles.

The experiments of the isometric and the isotonic contraction are simulated by this model to evaluate the adequacy of the model. The results showed that this

model can give satisfactory predictions. Furthermore, it was shown that the model has the potential to describe the inotropism.

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