Regional and Frequency Dependencies of Force Development in Myocardium: A Simulation Study

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Abstract

Heart models are used to simulate the electro-mechanical behavior of the myocardium. The simulations improve the comprehension of physiology and pathologies. A model of an anisotropic and inhomogeneous myocardial area is introduced, in which simulations of electrical excitation and force development are performed. The model is based on a modified Noble-Varghese-Kohl-Noble model of electrophysiology, the bidomain model for excitation propagation and the force model of Rice, Winslow and Hunter. Simulations with this myocardial model show the dependencies of the force development on frequency and on regional differences in the heart wall.

1. Introduction

For diagnosis, therapy and education, the comprehension of physiological and pathological behavior of myocardium as well as the influence on the cardiovascular system is of importance. The propagation of electrical excitation and the subsequent development of force in myocardium are main components in this system. Information about these components can be acquired e.g. with simulations based on heart models. Therefore, different models are combined describing the anatomy, electrophysiology, excitation propagation and force development.

A complex three-dimensional model of a ventricular wall is presented in this work. With this model simulations of electrical excitation propagation and force development are achieved in realistic manner. The electrophysiologic model is derived from the Noble-Varghese-Kohl-Noble (NVKN) model. This model describes the concentration and flow of ions as well as the resistor of cellular structures and the transmembrane voltage. The electrical coupling of cells is achieved with the bidomain model, which considers electrical conductivity of gap junctions as well as of the intra- and extracellular space. To calculate the intra- and extracellular current flow, Poisson's equation for electrical current fields is used. The electrophysiological model is coupled with a model of cellular force development presented by Rice et al.

2. Modeling

Accurate modeling of the electro-mechanical behavior of myocardium is the basis for complex and realistic simulations. The different approaches that are combined to the heart wall model are presented in the following sections. A detailed description can be found in [1].

2.1. Electrophysiology

The electrophysiological behavior of cells is modeled with a modified NVKN model of a guinea-pig ventricular cell [2]. The model describes the electrophysiological state of a cell with a set of coupled differential equations. These equations represent ionic concentrations, which are changed by passive and active transport mechanisms. The transport of ions is time dependent and influenced by gradients of concentrations and the electrical field.

Modern models like this include also detailed descriptions of the behavior of intracellular structures as well as of the pharmaceutical and deformational influence.

The time derivative of the transmembrane voltage V_m is defined by:

$$\frac{\partial V_m}{\partial t} = -\frac{1}{C_m}\left(I_{mem} - I_{stim}\right)$$

with the membrane capacity C_m, the sum of the transmembrane currents I_{mem} and the stimulus current I_{stim}.

Figure 1 shows the transmembrane voltage and the concentration of intracellular calcium for this model after stimulation with a frequency of 1 Hz.

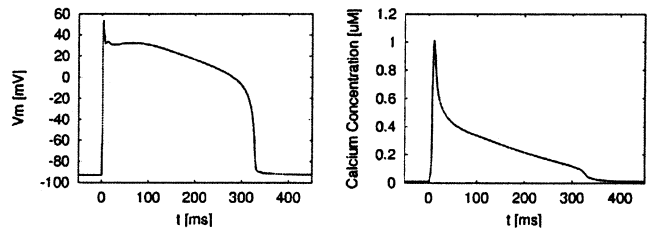

Figure 1. Transmembrane voltage (left) and intracellular calcium concentration (right) of the NVKN model.

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2.2. Excitation propagation

Myocardium consists primarily of discrete myocytes, arranged in an oriented and laminated structure [3, 4]. Myocytes are enclosed by the sarcolemma, which delimits extra- from intracellular space. Myocytes are of irregular shape, but a dominant principal axis can be assigned.

The intracellular space of myocytes is coupled by gap junctions, located by bundle at the intercalated disks. Longitudinal and transversal gap junctions can be distinguished, leading to a macroscopic anisotropic electrical conductivity.

The bidomain model treats the electrical behavior of tissue in two domains, in the intra- and extracellular space, separated by the cell membrane [5]. In each domain Poisson's equation for fields of stationary electrical current is fulfilled:

$$\nabla(\sigma_i \nabla \phi_i) = \beta I_m - I_{si}$$
$$\nabla(\sigma_e \nabla \phi_e) = -\beta I_m - I_{se}$$

where ϕ_i and ϕ_e are the intra- and extracellular voltages, resp. , σ_i and σ_e are the corresponding conductivity tensors, I_m is the transmembrane current density, β is the surface to volume ratio of the membrane and I_{si} and I_{se} are externally applied current sources. The intracellular conductivity σ_i consists of conductivities for the intracellular components and for the gap junctions.

The domains are coupled by the current density I_m through the cell membrane and by the definition of the transmembrane voltage:

$$V_m = \phi_i - \phi_e$$

This leads to an equation calculating the stimulus current from the transmembrane voltage:

$$\nabla(\sigma_i \nabla V_m) + \nabla(\sigma_i \nabla \phi_e) = \beta(C_m \frac{\partial V_m}{\partial t} - I_{ion}) - I_{si}$$

This method bases on the iterative solving of Poisson's equation with numerical techniques.

2.3. Force development

The development of force in the contractile elements of myocytes is provoked by the increase of the concentration of intracellular calcium $[Ca^{2+}]_i$resulti ng from an electrical excitation. Therefore, $[Ca^{2+}]_i$ is used to define rate coefficients, which depict the interaction between states. The states describe e.g. the bounding of intracellular Ca^{2+} to the troponin complex and the cross-bridge cycling. Further, the model is influenced by the sarcomere length and the state variables.

A foundation of this work is the 3rd Rice-Winslow-Hunter model of cardiac muscle [6]. This model consists

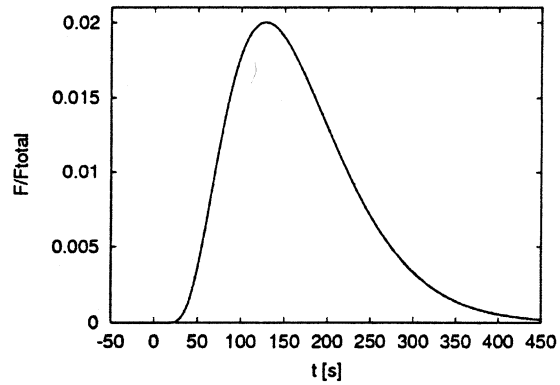

Figure 2. Force development simulated with calcium input of the electrophysiologic model.

of 6 states, $N0$, $N1$, $P0$, $P1$, T and TCa with $N0 + N1 + P0 + P1 = 1$ and $T + TCa = 1$. The interaction between the states of the model is described by a system of 1st order differential equations:

$$\frac{\partial}{\partial t}\begin{pmatrix} N0 \\ N1 \\ P0 \\ P1 \\ T \\ TCa \end{pmatrix} = R \begin{pmatrix} N0 \\ N1 \\ P0 \\ P1 \\ T \\ TCa \end{pmatrix}$$

with the 6×6 matrix R consisting of rate coefficients. Some rate coefficients are dependent on the sarcomere length SL and $[Ca^{2+}]_i$. The normalized force F is determined by:

$$F = \frac{\alpha(P1 + N1)}{F_{max}}$$

with sarcomere overlap function α and maximal force F_{max}. The states $P1$ and $N1$ are the force generating states.

Figure 2 shows the simulated force development provoked by changes of $[Ca^{2+}]_i$ of the NVKN model with a stimulation frequency of 1 Hz.

2.4. Simulation environment

The force is simulated in an inhomogeneous and anisotropic three-dimensional region of the left ventricular heart wall (figure 3). The lattice includes 150 x 150 x 125 voxels with a voxel size of 0.2 mm x 0.2 mm x 0.2 mm. The orientation of the fibers varies from the subepicardial (-70°) via the midmyocardial (0°) to the subendocardial myocardium (70°) [3], which leads to the anisotropic behavior. Inhomogeneities are integrated by modification of the K^+ depolarizing current I_{to} of the electrophysiological model. The current is contingent on the distance to the endocardial border [7]. The conductivity

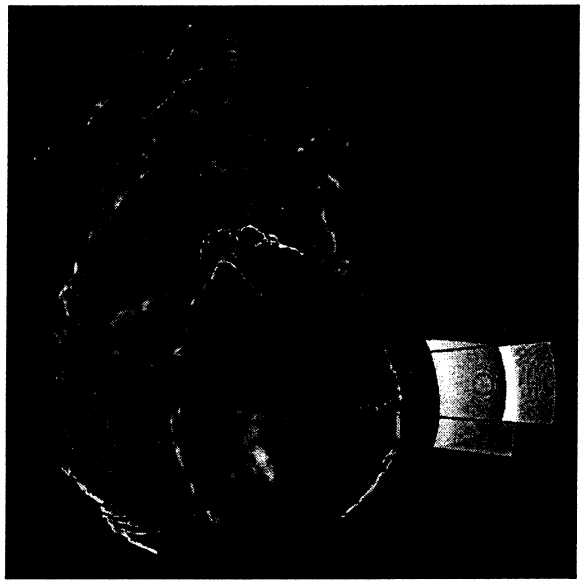

Figure 3. Anisotropic and inhomogeneous model of the left ventricular wall in anatomical context of the heart.

G_{to} increases from 0.013 nS in epicardial up to 0.038 in endocardial regions. This leads to a prolongation of the plateau phase in midmyocardial regions.

The excitation of the heart wall is initiated at the subendocardial myocardium by applying pointwise intracellular currents. The applying of current starts at apical points modeling myocytes with connections to Purkinje fibers and wanders basal.

3. Results

Several simulation where performed to study regional and frequency dependencies of force development in the myocardium. Some results are demonstrated in figure 4 and 5, where derivations of a single cell in the myocardial area are presented. These results show increasing force maxima when rising frequency from 0.25 to 1 Hz. Up to 2 Hz the force maxima decreases to 5% of the maximum value and vanishes with further increasing frequency. This effect is independent on regional differences. The force maxima decreases from epicardial to endocardial regions by a maximum of 80%. Figure 6 displays these effects in a three-dimensional plot.

Results in the heart wall model at physiological conditions show the effects of regional dependencies. In figure 7 the transmembrane voltage can be seen in depolarization, plateau and repolarization phase. The regional dependency is especially visible in the repolarization phase, where the repolarization front wanders to midmyocardial regions. Figure 8 shows the developed force in the heart wall. The most force is generated in subendocardial regions.

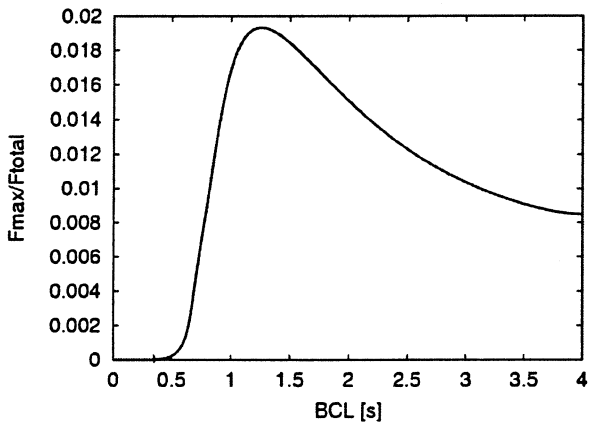

Figure 4. Force maximum dependent on the basic cycle length at a value of conductivity G_{to} of 0.013 nS.

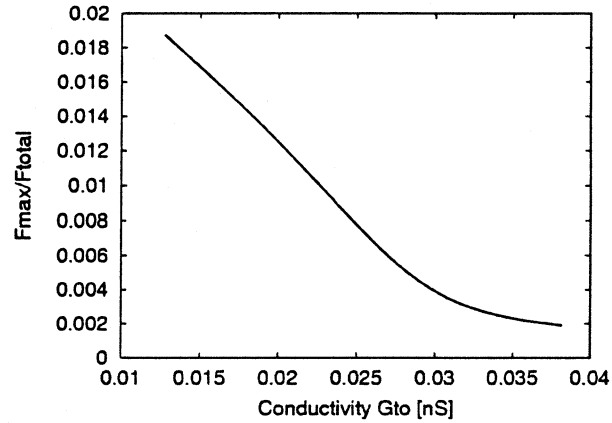

Figure 5. Force maximum dependent on the conductivity G_{to} at a frequency of 1 Hz. The values of G_{to} decrease from subendocardial to subepicardial regions.

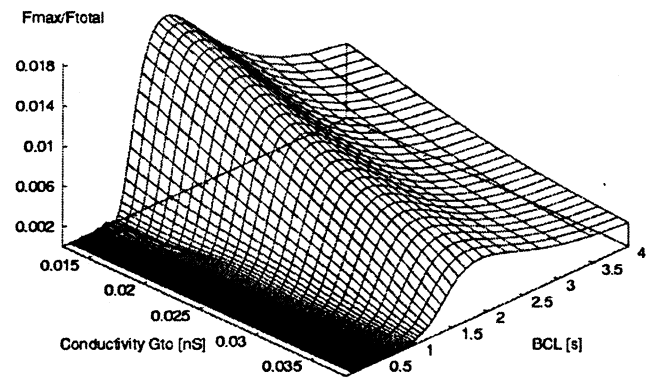

Figure 6. Three dimensional plot of force maximum dependent on basic cycle length and conductivity G_{to}.

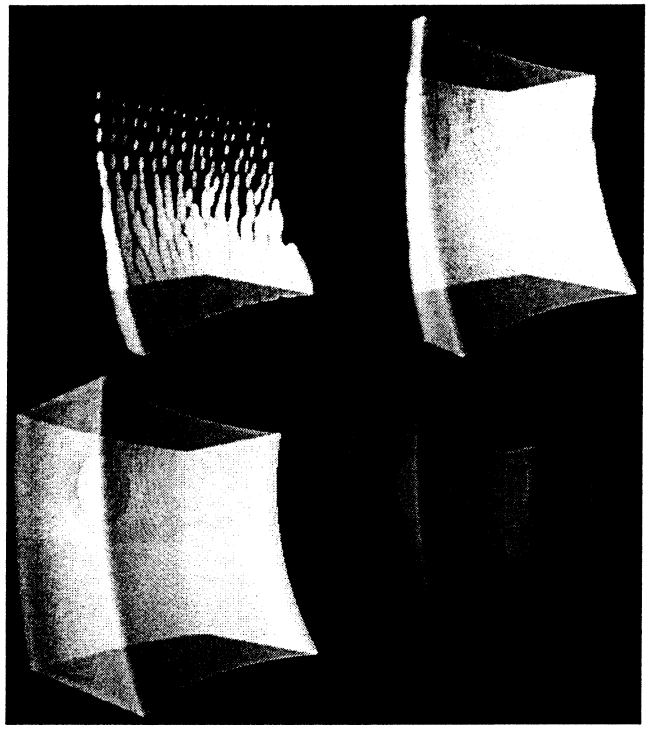

Figure 7. Transmembrane voltage in a model of left ventricular wall at different time steps (10 ms, 20 ms, 130 ms, 410 ms).

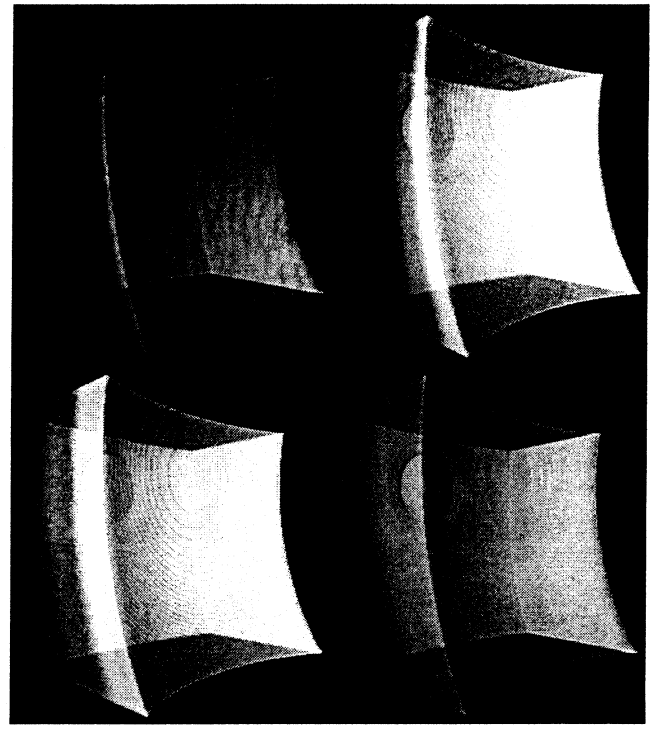

Figure 8. Force development in a model of left ventricular wall at different time steps (65 ms, 100 ms, 160 ms, 250 ms).

4. Conclusion

The presented model is suitable to simulate the general effects of the force development, but must be validated by animal experiments and adapted to human cells. Also the influence on regional dependencies must be verified. The effects of the presented dependencies to the mechanical behavior will be examined in future.

Ultimately, such models can be used to enable specific diagnosis and therapy advancements, to assist medicament development and to improve the understanding of the complex cardiovascular system.

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