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A Study on the Relationship between Electrical Transmural Heterogeneity and Ventricular Energetics

Yuki Hasegawa, Mitsuharu Mishima, Takao Shimayoshi, Akira Amano, Tetsuya Matsuda

Abstract— **In this study, we use cardiovascular simulation to gain new insights on the correlation between electrical heterogeneity and ventricular energetics. Although there are numerous *in vivo* and *in vitro* studies on the electrical heterogeneity within the ventricular myocardium, not much attention has been directed to its correlation to cardiovascular mechanics, because of difficulties in simultaneously observing and analyzing multiple spatial scales(the cell, the organ, and the system). We performed simulations with two cardiovascular simulation models, one which uses different myocardial cell models for the epicardial, endocardial, and mid-myocardial cells, and another which uses a homogeneous model throughout the entire myocardium. The epicardial, endocardial, and mid-myocardial cell models were created by parametrically tuning a homogenous cell model. From the cardiovascular simulation we obtained pressure-volume loops which were used to calculate cardiovascular energetic efficiency and myocardial contractility. We found that energetic efficiency is higher in the electrically heterogeneous model.**

I. Introduction

The main function of the cardiovascular system is to keep the blood flowing through our body, in order to circulate the necessary nutrients to keep it active. The blood is kept flowing by an organic pump, or the heart, which is stimulated by an electrical propagation. The electrical activation starts a sequence of ionic transactions within the cells. The cells convert chemical energy into mechanical contraction through a phenomena known as excitation-contraction coupling. Blood is pumped out of the heart into the circulation system, which is the system of blood vessels that carries the liquid to the ends of our body and back to the heart. Each of the described components, the heart, the myocardial cells, and the circulatory system, are well connected and changes in one component will interactively effect the others. Crucial mechanisms such as length dependent contractile force[1] and electro-mechano feedback[2] are examples of the iterations between components. Therefore, properties like electrical heterogeneity of the myocardium will not only affect the mechanics of the heart but will also affect the hemodynamics of the circulation system, as well.

Electrical heterogeneity of the myocardium is the electrophysiological differences between the epi, mid, and endo myocardial cells[3], [4], [5]. The electrophysiological differences result in different contraction characteristics in isolated cells[6]. However, these studies are limited to isolated cells and its effect on the cardiovascular system is not well known. The difficulty of observing and analyzing the cardiovascular system in *in vivo* and *in vitro* experiments, lies in the fact that its components and the resulting phenomena belong in different spatial scales.

In silico experiments can be used to overcome this difficulty by providing a medium to easily and simultaneously analyze the multiple components of the system. Multi-scale cardiovascular simulation models are composed of multiple models, each describing a phenomena that occur at different spatial scales such as electrical propagation, myocardial cell electrophysiology, ventricular deformation, circulatory hemodynamics. The resulting cardiovascular models describe the aforementioned interactions between the spatial scales.

Some *in silico* studies have hypothesized that the electrical heterogeneity combined with the aforementioned electrical propagation delay and ventricular loading helps maintain a uniform strain throughout the myocardium during systole[7], [8]. On the contrary, Ashikaga et al.[9] found *in vivo* myocardial shortening is transmurally dispersed. However, this study was limited to the mid-anterior wall of the ventricle. Therefore, the role of transmural heterogeneity in terms of cardiac mechanics remains controversial.

Furthermore, non-heterogeneous myocardial function has been observed in hearts undergoing acute ischemia[10]. Ischemia can affect cardiac contractility and energetic efficiency, which are indexes used to evaluate the cardiac function[11]. The maximum elastance E_{max} has been used as a measure for ventricular contractility and pumping capability[12]. E_{max} is the slope of the linear line formed by connecting the end systolic pressure-volume points for each pressure-volume loop with different hemodynamic load. The line formed by the end systolic points is known as End-Systolic Pressure Volume Relationship (ESPVR). E_{max} is load independent, and it increases with positive inotropic intervention and decreases with negative inotropic intervention. Note that, because E_{max} is calculated from PV loops, it represents contractility of the myocardium as a whole and not of the individual myocardial cells.

The ESPVR and PV loops can be used to calculate mechanical work done by the left ventricle[12]. Mechanical work is calculated by summing the area inside the PV loop and the area of the triangle under the ESPVR line. The former describes work energy, or the mechanical energy used for ejection and filling, and the latter describes the potential energy, or the energy that is maintained at the end of the ejection phase and released during isovolumic relaxation. The combined area is known as Pressure Volume Area (PVA). The linear relation between left ventricular ATP consumption (V_{ATP}) and PVA describes energetic efficiency.

Y. Hasegawa, M. Mishima and T. Matsuda are with Graduate School of Informatics, Kyoto Univerisity, Kyoto, 606-8501, Japan (phone:+81-75-753-3373; fax:+81-75-753-3375; e-mail:yhasegawa@sys.i.kyoto-u.ac.jp)

T. Shimayoshi is with ASTEM RI, Kyoto, 600-8813, Japan

A. Amano is with Department of Bioinformatics, Ritsumeikan University, Kyoto, 611-0031, Japan

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The purpose of this study is to investigate the effects of transmural heterogeneity on ventricular energetics from a theoretical standpoint. A simple multiscale cardiovascular simulation model is used to study the effects of transmural heterogeneity on E_{max} and V_{ATP} - PVA relationship.

II. Cardiovascular Simulation Model

In this paper, we used the cardiovascular simulation model introduced in [13] and [14], which can replicate linearity of ESPVR and linearity of V_{ATP} - PVA. The cardiovascular simulation model has three components: the myocardial excitation-contraction model, the left ventricular structural dynamic model, and the circulatory model. The myocardial excitation-contraction model and the circulatory model are both strongly coupled to the left ventricular structural dynamic model. The component models will be briefly explained in this section.

A. Myocardial Excitation-Contraction Model

The electrophysiology of myocardial cells are simulated by the Kyoto model[15]. The Kyoto model explains myocardial cellular function including excitation contraction coupling, membrane excitation, intracellular ion changes, and ATP production and consumption. The model uses the contraction model proposed by Negroni and Lasconi[16]. The contraction model describes cross-bridge dynamics of the thick and thin filaments and calcium kinetics of the binding of calcium and troponin. Both the cross-bridge dynamics and calcium kinetics are length and velocity dependent. The force can be represented as a function of half sarcomere length L: $F_b(L)$.

B. Left Ventricular Structural Dynamic Model

The left ventricular structural dynamic model (LVFEM) is a finite element model which represents the structural deformation of the ventricular wall. The active stress for each of the elements are calculated from the myocardial excitation-contraction model. The passive stress is modeled as a mooney-rivlin solid, which is a hyperelastic material model. Structural deformation is calculated by a balance equation which contains active and passive stresses for each element and LV pressure on the inner wall. The finite element method (FEM) is used to solve for the balance equation and meet the requirements for the boundary condition of LV volume which is defined by the circulatory model. For simplicity, the balance equation will be written as an implicit function:

$$0 = H(\mathbf{L}, \mathbf{F_b}, P_{lv}, V_{lv}), \tag{1}$$

where $\mathbf{F_b}$ and $\mathbf{L}$ respectively stand for vectors of myocardial forces and half sarcomere lengths of representative cells for finite elements, and P_{lv} and V_{lv} are LV pressure and volume respectively.

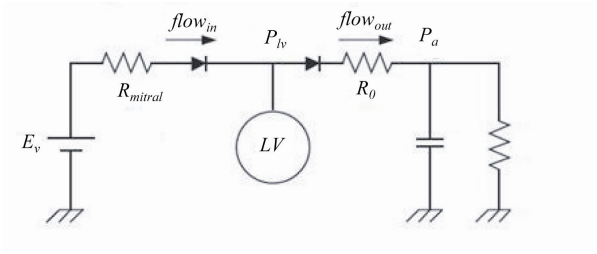

Fig. 1. Windkessel Model

TABLE I
Ratio for changed parameters

	epi	mid	endo
I_{Na} membrane capacitance	0.555414013	1	0.677707006
I_{NaCa} convert factor	0.84874273	1	0.670116319
I_{Kr} membrane capacitance	2.378109453	1	1.188343994
I_{Kr} convert factor	2.378109453	1	1.188343994
I_{Ks} membrane capacitance	2.082007412	1	1.99505089
I_{to} membrane capacitance	0.884146341	1	0.170426829
I_{K1} membrane capacitance	0.396850394	1	1
I_{K1} convert factor	0.396850394	1	1

C. Circulatory Hemodynamic Model

The circulatory model calculates hemodynamics and the resulting change in LV volume. Circulatory hemodynamics of pulmonary preload and aortic afterload were modeled using the Windkessel model. We adopted the 3-element windkessel model to simulate the afterload and added a single element for the simulation of the preload. The schematics for the model is shown in Fig. 1. The resulting equation for the model uses LV pressure as the input variable for the calculation of blood flow.

$$\frac{dV_{lv}}{dt} = Q_{in}(P_{lv}) - Q_{out}(P_{lv}), \tag{2}$$

where the function Q_{in} represents inflow governed by preload which consists of mitral resistance and pulmonary venous pressure, and Q_{out} is outflow governed by the afterload which consists of aortic compliance, aortic resistance and resistance of the aortic valve.

III. Experiment

A. Methods

The Kyoto model was fitted to match the action potentials and unloaded shortening of the epicardial, mid-myocardium, and endocardial cells in Campbell et al.[8]. The parameters changed in the model are based on the parameters used in [17] and experimental data from [5]. The ratios for the changed parameters are listed in Table I. The resulting epicardial, mid-myocardium, and endocardial cell models were used in the heterogeneous model, while the generic Kyoto model was used in the homogeneous model. The width of the 3 layers in the heterogeneous model were set equal for simplicity.

Both of the heterogeneous and homogeneous model used a ring model for the LVFEM. The specifications for the ring model were 3 ring layers and 8 elements per layer, which is a total of 24 elements. Electrical activation timings

TABLE III

CONTRACTILITY AND ENERGETIC EFFICIENCY INDEXES

	hetero	homo
E_{max}	6.0276	6.5191
correlation	0.99999	0.99999
slope of V_{ATP}-PVA	0.014423	0.011437
y-intercept	14.117	15.944
correlation	0.98819	0.99259

were calculated in a prior simulation[14], and are within physiological range[18]. Activation timings were were set for the center of each element, and were distributed between 54.70 ms to 63.95 ms, where 0 ms is defined as the start of the simulation for the first cycle and every 400 ms thereafter.

At each timestep, the non-linear system of equations were solved by Broyden's method. Simulations were performed for 4000 timesteps with 0.1 ms step size, which is one cardiac cycle for the Kyoto model. DynaBios[19], which is a simulation platform that includes simBio[20] to calculate the myocardial cell model and commercially produced FEM solver MSC Marc, is the software used for the simulations.

B. Results

Table II shows the single cell simulation results of parameter tuning for the epicardial, mid-myocardial, and endocardial cells. It also includes the resulting values for each layer in the heterogeneous and homogeneous cardiovascular simulations. There were no significant differences in shortening and relaxation onsets in the heterogenous and homogeneous models.

Fig. 2 shows the pressure-volume loops and ESPVR lines for both models. The PV loops were drawn by taking pressure and volume values at each timestep. Each ESPVR was calculated by linear regression of the end systolic pressures and volumes. In the simulation, end-systole was defined as the timestep in which aortic pressure reached left ventricular pressure. PVA was calculated from the pressure-volume loops and ESPVR line. Fig. 3 shows the V_{ATP} - PVA relationship for both models. Table III lists E_{max}, correlation of the end systolic points, slope of V_{ATP} - PVA, y-intercept V_{ATP} - PVA, and correlation of the V_{ATP} - PVA points. The slope of the V_{ATP} - PVA line represents PVA dependent V_{ATP}, or the ability to generate mechanical energy per ATP. The y-intercept of the V_{ATP} - PVA line represents V_{ATP} cost for contractility, or E_{max}. The slope of V_{ATP} - PVA was slightly higher for the heterogeneous model. E_{max} and y-intercept of V_{ATP} - PVA was slightly lower for the heterogeneous model compared to the homogeneous model.

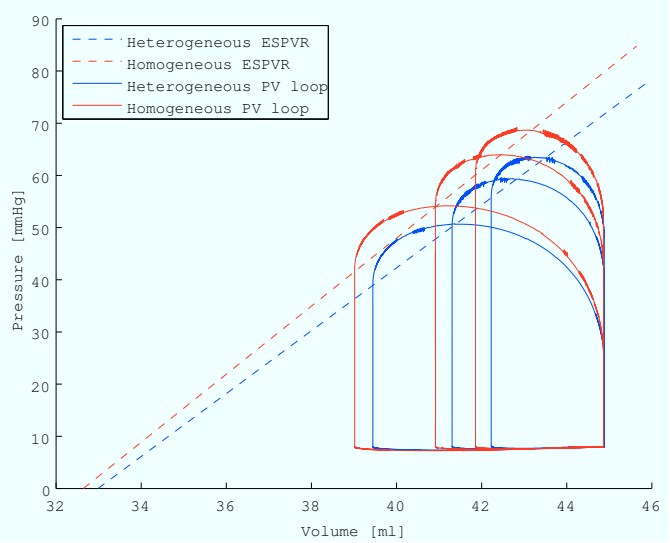

Fig. 2. Pressure-volume loop and ESPVR line

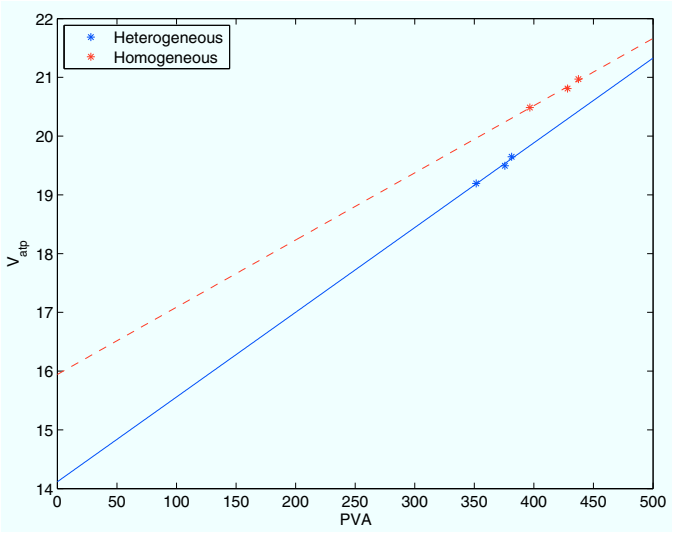

Fig. 3. V_{ATP} - PVA relationship

IV. DISCUSSION

A. Transmural Dispersion of Shortenning

Our heterogeneous simulation results showed that onsets of contraction and relaxation occur in uniform despite transmural heterogeneity, which is in agreement with past simulations[7], [8]. However, we did not see any significant difference in contraction and relaxation timing between the homogeneous and heterogeneous models. Therefore, this is not in agreement with the hypothesis that myocyte electrical heterogeneity and electrical activation delay reduces heterogeneity of myocyte shortening.

It has been reported that *in vitro*[21] and *in vivo*[9] experiments show different results for heterogeneity of myocyte shortening. Therefore, this topic remains controversial, and a more detailed analysis is required.

B. Cardiac Contractility and Energetic Efficiency

The E_{max} for the heterogeneous model was only slightly less than that for the homogeneous model. The lower E_{max} is most likely due to the lower contraction force in the epicardium for the heterogeneous model.

The results showed that the heterogeneous model has higher generation of PVA per V_{ATP} compared to the homogeneous model. This was caused by a downward shift in the V_{ATP} - PVA line for the heterogeneous model, which indicates lower cost for E_{max}. It is also important to note

TABLE II

TIMINGS AND PEAK FORCE

	single cell			heterogeneous			homogeneous		
	epi	mid	endo	epi	mid	endo	epi	mid	endo
onset shortening [ms]	53.5	53.5	53.5	69.5	60.4	60.4	69.0	59.7	59.7
onset relaxation [ms]	134.3	136.3	135.8	172.3	167.5	165.9	171.0	167.5	165.4
peak force [mN/mm^2]	8.214	10.462	10.174	15.232	22.685	24.043	19.990	22.092	24.630
time to peak force [ms]	134.3	136.3	135.8	128.3	139.1	143.9	127.6	138.3	145.3

that the slope of the linear line of V_{ATP} - PVA was of higher value in the heterogeneous model. However, overall energy efficiency was higher in the heterogeneous model because of the downward shift.

One of the potential explanations for this outcome from our results is the closer peak force times between the 3 layers in the heterogeneous model as shown in Table II.

C. Model Limitations

The cardiovascular simulation model uses a 2 dimensional finite element model for the structural dynamics of the left ventricle. Phenomena such as longitudinal displacement, 3 dimensional torsion, and apex to base heterogeneities are not included in our calculation. The major differences between of myocyte relaxation and contraction onset between *in vivo* experiments[9] and our experiment suggests that further studies using a finer 3 dimensional model may be useful.

The circulatory model does not include a left atrium, which is responsible for pumping blood into the left ventricle during the filling phase. The absence of the left atrium is the main reason for the lack of ejection volume in our model. Therefore, this model is limited to simulating the contractility and energetics of the isolated left ventricle, which may be different in the whole heart case.

V. CONCLUSION

We evaluated the energetic efficiency of an electrically heterogeneous and homogeneous heart by simulation. The heterogeneous model showed lower E_{max}, but higher PVA generation per V_{ATP}. Therefore, results indicated that the electrically heterogeneity contributes to the energetic efficiency of the heart. The improvement in energetic efficiency may be attributed to the decrease in variance of time to peak force.

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