Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

The Influence of Activation Time on Contraction Force of Myocardial Tissue: a Simulation Study

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Abstract— **The efficiency of heart pump function greatly depends on synchronized contraction of myocardial muscle. In this work, contraction simulation of an excitable ventricular tissue cable was constructed to study the influence of excitation patterns on tissue contraction. The tissue cable is composed of elements which contract when excited by an external stimulus. In each calculation step, contraction force of each element is determined by a ventricular cell model. The mechanical deformation is then solved by finite element method and states of cells are updated accordingly. Several factors such as the starting position of the stimulation signal and the conduction velocity of gap-junctions affect contraction behavior. Simulation results show that the activation time, i.e. the time period the stimulation signal needs to spread over the tissue, is a dominant parameter for determining tissue contraction force. Contraction force of myocardial tissue increases monotonically with a decrease in activation time. This result suggests that minimization of activation time might be important for achieving effective tissue contraction.**

Index Terms— **myocardial tissue contraction, activation time, heart simulation, bio-simulation**

I. Introduction

Blood circulation in the human body is the result of a rhythmic contraction and expansion of the myocardial muscle. For an efficient pump function, all ventricular cells must contract in a synchronized way. Therefore, it is important to clarify the relationship between the contraction force of myocardial tissue and the degree of synchronization of ventricular cell contraction. However, to properly control excitation propagation of myocardial tissue in biological experiments is very difficult. To our knowledge, there is no experimental report at tissue level about the relationship between contraction force and the synchronization degree.

System biology [1], [2], which uses model based simulation techniques to achieve in-depth understanding of biological functions, is attracting increasingly attention especially in the field of complex organ functions such as human heart. Due to dificulties in performing experiments, it is even more important to construct a computational cellular model including activation and contraction behaviors for analyzing the relationship between contraction force and synchronization. Several ventricular cell models are now available for excitation and contraction research [3], [4], [5], [6]. However, excitation propagation [7], [8] and mechanical contraction [9], [10], [11], [12] are mainly studied independently. The influence of excitation on mechanical contraction is still an open question.

In this work, a one dimensional myocardial tissue was constructed using elements arranged in an end-to-end line style. Each element consists of several cells, however the behaviors of all cells in one element was assumed to be identical so that one element contracts like one cell. Mechanical deformation of tissue was calculated based on contraction force of each element using the finite element method. Contraction forces under different activation conditions were analyzed. We show that activation time (AT), i.e. the time period that the stimulation signal needs to spread over the tissue, is an important factor for the determination of the contraction force. Contraction force of myocardial tissue increases monotonically with a decrease in AT. How an increase in stimulating points effects the contraction force of tissue cable is also demonstrated.

II. Method

The tissue cable model is composed of elements each contracting according to a cell model. First, a brief explanation of the cross-bridge dynamics of the cell contraction model is given. Then the detailed description of the calculation for the coupling of mechanical tissue deformation and biological cell behavior follows.

A. Ventricular Cell Contraction Model

The behavior of each ventricular cell of the tissue cable is calculated by the Kyoto Model (KM) [6]. KM combines membrane excitation with ventricular contraction and includes many important ion channels and transporters. Here we give a brief overview of the contraction model (NL model) [9] included in KM.

When a cell is activated by an external stimulating current, the intracellular Ca^{2+} concentration increases rapidly. Ca^{2+} induced formation of cross-bridges (xb) causes the ventricular cell to contract. Fig. 1 shows the four-state diagram of the contraction model. First, Ca^{2+} binds to troponin (TnC) on thin filament to form TCa. This allows myosin heads of

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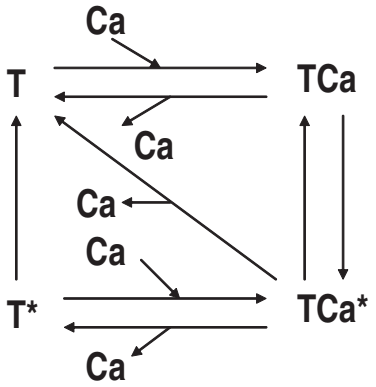


Fig. 1. 4-state contraction model

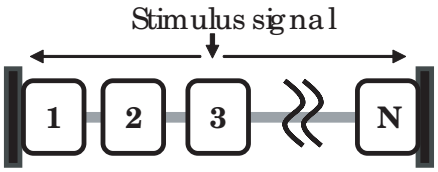


Fig. 2. Cable tissue model consisting of N elements

the thick filament to attach to thin filament sites to form strong xbs (TCa*). T* represents a strong xb with Ca^{2+} being released from TnC. Each strong xb (TCa* and T*) acts as an independent force generator. The active contraction force is determined as

$$F = A\left([TCa^*] + [T^*]\right)h \tag{1}$$

where A is a scaling constant and h is the xb elongation which is related to the half sarcomere length (L) as

$$h = L - X, \tag{2}$$

where X is the inextensible part of L besides h. When mechanical deformation takes place, an instant change in h causes the cross-bridge out of its steady state h_c. The return to steady state is a much slower process expressed by the following differential equation:

$$dX/dt = B(h - h_c) \tag{3}$$

where B is the speed parameter.

B. The Cable Tissue Model

A tissue cable of hexahedral elements in an end-to-end arrangement is used to investigate isometric contractions (Fig. 2). The initial size of one hexahedral element is 0.1x0.1x$0.1mm$. Each element is a set of ventricular cells, and the long axis of each cell is assumed to be in the direction of the cable. The behaviors of all cells in one element are assumed to be identical. When one element is activated, excitation propagates to the adjacent elements on both left and right sides. The conduction velocity (CV) of the excitation depends on the state of the gap-junctions connecting adjacent cells. In this model, several elements are stimulated first and the excitation times of the other elements are determined according to the CV and their distances from the element where the stimulation has started. The AT of a myocardial tissue is defined as the time period between the excitation of the first and the last element. Ventricular cells are assumed to contract and elongate only in the long axis when they are excited. To simulate isometric contractions, both ends of the cable were fixed. The Neumman boundary condition which assumes the spatial difference of the electrical potential to be zero was used in the finite element model. Young's modulus of each element was set to $20kPa$ according to experiments [13].

C. Calculation for the Coupling of the Cell Model and the Mechanical Deformation

The mechanical deformation of each element is calculated as follows,

$$F = Ku \tag{4}$$

where F is the external force vector, K the material matrix, and u the result displacement vector. Since the force-length relation of myocardial cell show different contraction forces at different sarcomere lengths, the calculation of the cell model and the mechanical deformation must be coupled with each other. For a cable of N elements, the calculation steps are as follows:

1) Obtain the contraction force for each element i ($i = 1, 2, \ldots, N$) from the ventricular cell model.
2) Solve the mechanical deformation according to equation (4).
3) Calculate the new sarcomere length of each cell model proportional to the mechanical deformation of the corresponding element as follows,

$$L'_e = L_e + u_c \quad L' = LL'_e/L_e \tag{5}$$

where L_e, L'_e are the length of elements, L, L' the sarcomere length of the corresponding cell models before and after deformation respectively, u_c the displacement in long axis.
4) Update the cell model using the new sarcomere value L'.
5) Iterate the step 1) and 4) till specified time duration is reached.

The differential equations of the ventricular cell model (KM) are solved using the Euler method with fixed time step. The time step was determined to be $0.025ms$ by trial. Further decrease in time step resulted in little improvement. To activate the cells, an external stimulating current of $-4000pA$ was applied for $2ms$ for each cycle period of $400ms$. DynaBioS [14], a platform for multiphysical simulator development, was used in the implementation of the coupled calculation of KM model and mechanical deformation. simBio [15], a java package of ventricular cell modeling, was used to calculate the ventricular model. For the finite element solver the commercial software Marc was used.

III. Results

A. Analysis of Peak Force with Varied CV and Cable Length

In this simulation study the stimulating current was always applied to the element on the left end of the cable. Excitation propagated from the left to the right end. The AT of the cable was determined by the ratio of cable length and the CV of the excitation. First, simulation was performed with a normal CV as found in human myocardial tissue which is around $0.5m/s$. Then simulations at CV= $0.2m/s$ and CV= $0.1m/s$ were also performed to study the effect of delayed CV on tissue contraction. Fig. 3 shows the membrane action potential, half sarcomere length and contraction force of element 1, 25 and 50 at CV= $0.1m/s$ employing a cable with 50 elements. Contraction force of the cable is also shown in Fig. 3C. The excitation starts at element 1 and propagates from left to right, i.e., the action potential of element 50 is delayed for almost 50 ms compared to element 1 (Fig. 3A). Elements stimulated late are slightly stretched before they start contracting (Fig. 3B). For example element 50 is stretched during the initial 100 msec by elements stimulated earlier and attains a stronger contraction force (Fig. 3C). This result is in agreement with the force-length relation for myocardial tissue, i.e. a ventricular cell of longer initial sarcomere length produces stronger contraction forces.

To further evaluate the influence of AT on the contraction force, cables of different lengths were used for three different CVs. Starting from a 3 element cable (0.3mm in length), for every simulation one element was added until a 50 element cable (5mm in length) was reached. A total of 48 results were obtained for each CV. Fig. 4A shows the peak force (PF) and Fig. 4B the half duration (HD) of each contaction time course at 3 different CVs respectively. HD is the time duration in which contraction force is above the half of peak force. PF values are normalized to the maximum value measured for all simulations (3 element cable at 0.5m/s), and HD values to the minimum value (3 element cable at 0.5m/s). As elucidated in Fig. 4, AT determines PF and HD regardless of the cable length and CV. For a cable of 50 elements, when the CV decreases from a normal value of $0.5m/s$ to $0.1m/s$, AT increases from $9.8ms$ to $49.0ms$, PF decreases by 3.4%, and HD increases by 1.1%.

B. Effect of Multisite Stimulation

In the following simulation, the number of stimulation site was increased from 1 to 4, and PF of the isometric contraction was evaluated. For a given number of stimulation sites (n), the position for the initial stimulation was chosen so that the AT of the tissue cable was minimized. For example, in case $n = 2$, elements of number 25 and 75 were initially stimulated. Fig. 5 shows the results. PF value was normalized by the PF at $n = 1$. With an increasing in number of stimulation sites, AT of the tissue cable decreases and PF increases.

C. Discussion

Many parameters concerning muscle activation are known to influence contraction. However, simulation results in section III-A and III-B show that the AT is a dominant modulator. It suggests the importance of shortenning the AT in order to obtain an efficient contraction in artificial pacing. Under the assumption that the force of individual elements remains unchanged with different stimulation conditions, the cable contraction force decreases with increasing AT. However as shown in Fig. 3C, the force of a stretched element increases. This results suggest that the negative effect of asynchronous contraction is more dominant under this condition. Though the efficiency of tissue contraction dependents on many factors, this simulation provides a new point of view from the AT of tissue excitation.

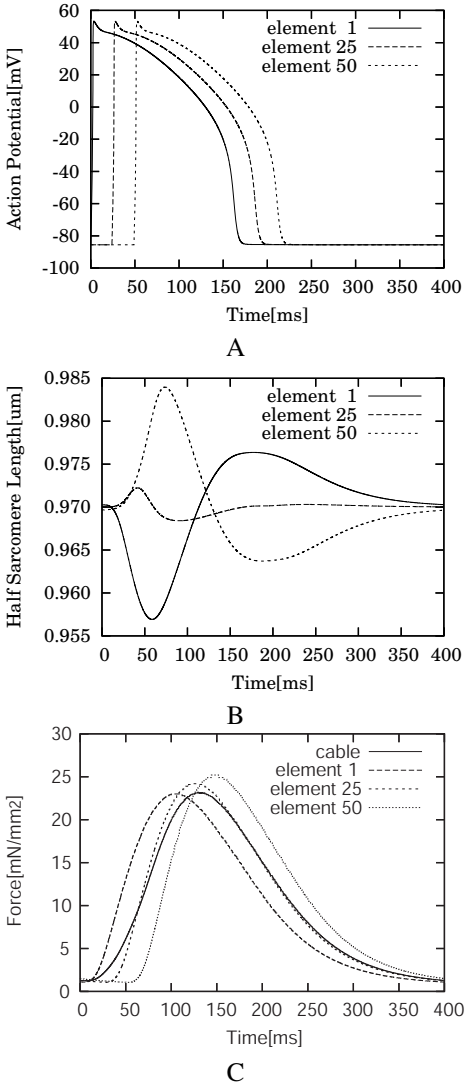
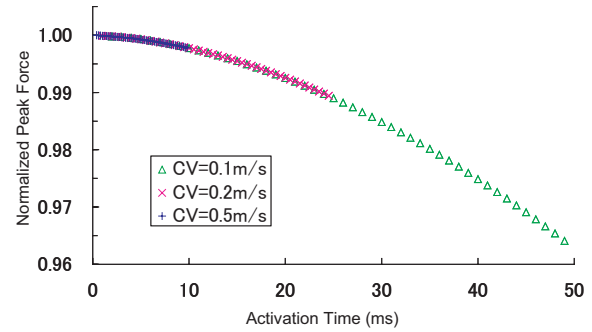


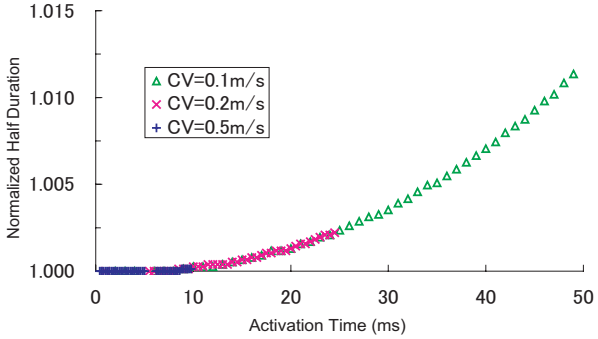
Fig. 3. Simulation results of A. membrane action potential, B. half sarcomere length , and C. contraction force of different ventricular cells.

IV. Conclusion

In this work, the influence of different stimulation conditions on contraction force was estimated using a myocardial tissue cable of excitable and contractible elements. Simulation results revealed that the activation time of a myocardial



A



B

Fig. 4. Contraction force peak and half duration versus activation time: A. peak force decreases and B. half duration increases when activation time increases.

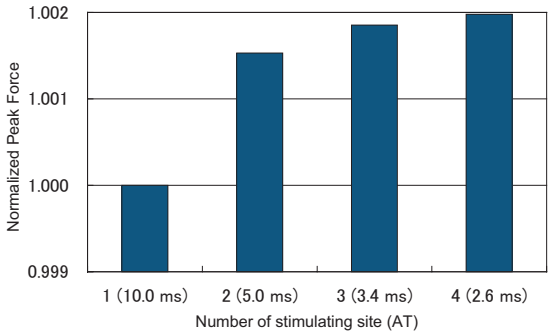


Fig. 5. Contraction force increases with the number of stimulation sites.

tissue is an important factor concerning contraction force which increases monotonically with a decrease in activation time. Future work includes the implementation of such a simulation on a three dimensional heart model to examine the effect pacing sites have on heart pump function.

ACKNOWLEDGMENTS

This work was supported by the Leading Project for Biosimulation Project and Grant-in-Aid for Scientific Research (C) No.16500186, MEXT. This work was partially supported by the Japanese Ministry of Education, Science, Sports and Culture, Grant-in-Aid for Young Scientists (B), 17700394, 2005.

REFERENCES

[1] P.J. Hunter, and T.K. Borg: "Integration from proteins to organs: the Physiome Project", Nature Reviews, Mol. Cell Biol, 4, 237-243, 2003.
[2] N. Smith, P.J. Mulquiney, M.P. Nash, C.P. Bradley, D. Nickerson, P.J. Hunter: "Mathematical modelling of the heart: Cell to organ", Chaos Solitons Fractals 13, 1613-1621, 2002.
[3] G.W. Beeler, H. Reuter: "Reconstruction of the action potential of ventricular myocardial fibres", J Physiol 268, 177-210, 1977.
[4] D. DiFrancesco, D. Nobel: "A model of cardiac electrical activity incorporating ionic pumps and concentration changes", Phils Trans R Soc Lond B Biol Sci 307, 353-398, 1985.
[5] C.H. Luo, Y. Rudy: "A dynamic model of the cardiac ventricular action potential I. Simulation of ionic currents and concentration changes", Circ Res 74, 1071-1096, 1994.
[6] S. Matsuoka, N. Sarai, S. Kuratomi, K. Ono, A. Noma: "Role of individual ionic current systems in ventricular cells hypothesized by a model study", Jpn J Physiol., 53, 105-123, 2003.
[7] F.H. Samie, J. Jalife: "Mechanisms underlying ventricular tachycardia and its transition to ventricular fibrillation in the structurally normal heart", Cardiovasc Res. 50, 242-50, 2001.
[8] F.H. Fenton, E.M. Cherry, H.M. Hastings, S.J. Evans: "Multiple mechanisms of spiral wave breakup in a model of cardiac electrical activity", Chaos 12, 852-892, 2002.
[9] J.A. Negroni, E.C. Lascano: "A cardiac muscle model relating sarcomere dynamics to calcium kinetics", J. Moll. Cell Cardiol., 81, 2278-2296, 1996.
[10] K.D. Costa, J.W. Holmes, A. D. McCulloch: "Modeling cardiac mechanical properties in three dimensions", Phil Trans Royal Soc Lond A 359, 1233-1250, 2001.
[11] M. Vendelin, P.H.M. Bovendeerd, J. Engelbrecht, T. Arts: "Optimizing ventricular fibers: uniform strain or stress, but not ATP consumption, leads to high efficiency", AM J Physiol Heart Circ Physiol 283, 1072-1081, 2002.
[12] John K-J. Li, Ying Zhu1, Xiaoming Guan, Gary Drzewiecki, and Joseph Kedem: "Cardiac Force and Muscle Shortening in Regional Ischemia:Asynchronization and Possible Uncoupling", IEEE EMB Conf., 2005.
[13] S. Nakaya, H. Kanai, K. Nakabachi, H. Honda, K. Koiwa: "Noninvasive measurement of ventricular end-diastolic pressure and myocardial elasticity by analysis of cardiac wall minute vibration", Journal of Japanese BME Society, 13, 1-8, 1999. (in Japanese)
[14] T. Shimayoshi, K. Hori, J.Y. Lu, A. Amano, T. Matsuda: "A software environment for simulators suitable for complex biological analysis2", IEEE EMB Conf., 2004.
[15] N. Sarai, S. Matsuoka, A. Noma: "simBio: a Java package for the development of detailed cell models", Prog. in Bioph. and Mol. Biol., 90, 360-377, 2006.
[16] W.T. Abraham, W.G. Fisher, A.L. Smith, D.B. Delurgio, A.R. Leon, E. Loh, D.Z. Kocovic, M. Packer, A.L. Clavell, D.L. Hayes, M. Ellestad, R.J. Trupp, J. Underwood, F. Pickering, C. Truex, P. McAtee, J. Messenger: "Cardiac resynchronization in chronic heart failure", N Engl J Med. 346, 1845-1853, 2002.