Modeling and Simulation of Developmental Changes in Contractile Apparatus of Ventricular Cells

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Abstract

During development, ventricular cells utilize different isoforms of both myosin heavy chain (MHC) and troponin I. The differences in these isoforms affect Ca^{2+} sensitivity, ATPase activity, and velocity of contraction. In order to consider the differences in isoforms, we integrated a new contraction model with the Kyoto model. Briefly, the new model considered tropomyosin, which inhibits formation of a cross-bridge between actin and myosin filaments. We varied the level of Ca^{2+} sensitivity in order to obtain similar traces for contractile force between the original Kyoto model and the modified model. We also modified the new contraction model to consider ATP consumption by myosin-ATPase in order to simulate the changes in ATPase activity caused by the difference in MHC isoforms. The modified model enabled us to compare the contribution of developmental changes in ATP consumption via contraction to excitation-contraction coupling, which is regulated differently in fetal and adult guinea pigs.

1. Introduction

The heart develops and acquires new functions while continuously pumping blood. Furthermore, abnormalities that develop early in this process progress to congenital heart malformations. Accordingly, the developmental processes of the heart, including expression of genes encoding ion channels, are likely to be tightly regulated. In our previous study [1], we modeled developmental changes in the action potentials (AP) in rodent ventricular cells by integration of quantitative changes in ionic components of cell membrane and sarcoplasmic reticulum (SR) throughout the course of development using the Kyoto model, a comprehensive model of guinea pig ventricular cells [2].

During development, the ventricular cells utilize different isoforms of both myosin heavy chain and troponin I. The differences in these isoforms affect Ca^{2+} sensitivity, ATPase activity, and velocity of contraction in fetus [3]. Here, we further modified the model constructed in our previous study [1] to represent and simulate the developmental changes in the contractile apparatus of ventricular cells. Our simulation showed that representation of contractile apparatus in embryonic ventricles, higher sensitivity to intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$), and smaller amount of troponin I, contribute to enhance cross-bridge tensions.

2. Methods

As listed in Table 1, the quantitative changes in various ionic components were presented as the densities of the components in late embryonic (LE) stage relative to those in the adult stage. We defined the LE stage as 1-7 days before birth in rodents.

Table 1. Relative current densities of ionic components representing rodent ventricular cells at late embryonic (LE) and adult stages utilized in our previous study [1]

Ionic components	Late Embryonic	Adult
L-type Ca^{2+} channel	0.78	1.0
T-type Ca^{2+} channel	4.5	1.0
Delayed rectifier K^+ channel, rapid component	2.0	1.0
Delayed rectifier K^+ channel, slow component	0.01	1.0
Transient outward current	0.27	1.0
Na^+/Ca^{2+} exchange current	1.74	1.0
ATP-sensitive K^+ current	0.88	1.0
RyR channel	0.40	1.0
SR Ca^{2+} pump	0.21	1.0
SR-related components	0.3	1.0
CICR factor	-60	-150

The original Kyoto model [2] utilized Negroni-Lascano (NL) model [4] to simulate the dynamic

behavior of sarcomere shortening in response to transient changes in $[Ca^{2+}]_i$. In this study, we replaced the NL model with the contraction model established by Niederer et al. [5] in order to simulate developmental changes in the contractile apparatus of rodent ventricular cells.

In the modified model, we varied the following two parameters: (1) sensitivity of troponin to $[Ca^{2+}]_i$, and (2) amount of troponin I, which inhibits attachment of myosin heavy chain (MHC) to actin.

All models were first simulated for 600 s in order for all glycolytic intermediates to reach a quasi-steady state, and then externally stimulated by potassium ions at a frequency of 2.5 Hz for 600 s to pace the model. All simulations were based on the Dormand–Prince method, as implemented in E-Cell Simulation Environment (SE) version 3 [6].

3. Results and discussion

Representation of the quantitative differences in various ionic components (Table 1) between LE and adult stages with the Kyoto model resulted in longer action potential duration (APD) and smaller amplitude of $[Ca^{2+}]_i$ transient in the LE ventricular cell model than in the adult ventricular cell model (Figure 1). APD at 90% repolarization (APD_{90}) was 146 ms in the LE model and 133 ms in the adult model. In response to the small amplitude of $[Ca^{2+}]_i$ transient in the LE ventricular cell model, the maximum value of cross-bridge tension decreased in the simulation with the LE model.

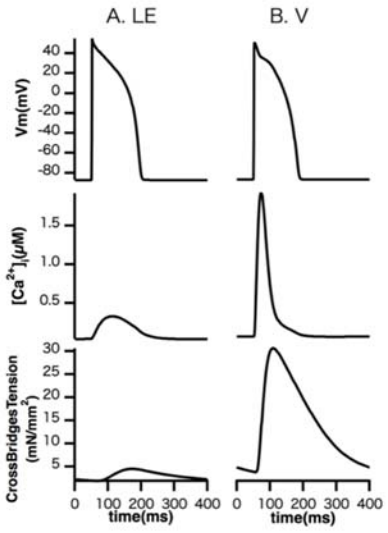

Figure 1. Simulated action potential (mV), intracellular Ca^{2+} concentration (μM), and cross-bridge tension (mN/mm^2) using the late embryonic (LE) ventricular cell model (A) and adult ventricular cell model (B)

In Figure 2, we varied the parameter that represents the sensitivity of troponin to $[Ca^{2+}]_i$. The lightest line is the simulated result when the parameter was multiplied by 0.5 to represent low Ca^{2+} sensitivity. In contrast, the darkest line is the simulated result when the parameter was multiplied by 2.0 to represent high Ca^{2+} sensitivity. Figure 2A shows the reaction velocity of changes in the state of troponin (TRPN); positive velocity represents the dissociation of Ca^{2+} from troponin, and negative velocity represents the binding of Ca^{2+} to troponin. As we increased the $[Ca^{2+}]_i$ sensitivity in the model, both cross-bridge tension and ATP consumption velocities.

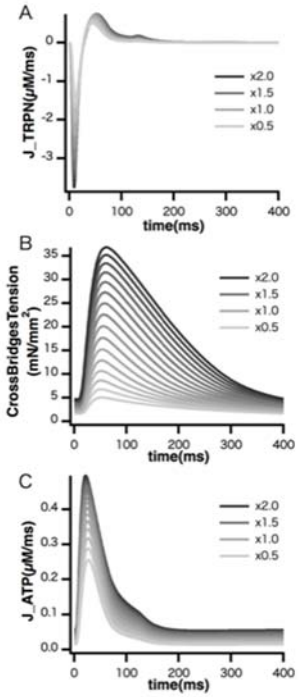

Figure 2. Simulated results of varying the parameter representing sensitivity of troponin to $[Ca^{2+}]_i$. (A) Reaction velocity of changes in the state of troponin (μM/ms). (B) Cross-bridge tension (mM/mm^2). (C) Estimated reaction velocity of ATP consumption (μM/ms)

In Figure 3, we simulated the decrease in the amount of troponin I by varying the parameter to increase the fraction of actin sites available for MHC to bind. The lightest line is the simulated result when the parameter was multiplied by 0.5 to represent large amounts of troponin I. Furthermore, the darkest line is the simulated result when the parameter was multiplied by 2.0 to represent a small amount of troponin I. The cross-bridge tensions (Figure 3B) increased as the fractions of available actin sites (Figure 3A) increased. In contrast to the simulated effects of increasing Ca^{2+} sensitivity (Figure 2), varying the parameter to increase the fraction of actin sites available had hardly any effect on ATP consumption rate (Figure 3C).

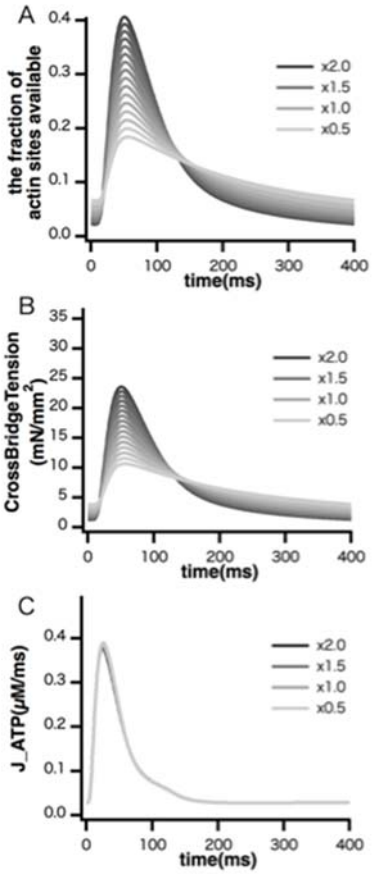

Figure 3. Simulated results of varying the parameter representing the amount of troponin I. (A) Changes in ratio of actin sites available for troponin to bind. (B) Cross-bridge tension (mM/mm^2). (C) estimated reaction velocity of ATP consumption (μM/ms)

In Figure 4, we compared the differences in the effect of changing the parameter that represented the sensitivity of troponin to $[Ca^{2+}]_i$ and that of changing the fraction of actin sites available for troponin to bind. Figure 4A shows the effect of increasing the parameter that represents $[Ca^{2+}]_i$ sensitivity from 0.5 to 2.0 at increments of 0.1. In the simulation with the model that represented low Ca^{2+} sensitivity through multiplication of the parameter by 0.5, the amount of ATP consumed was 17 μM per beat. Conversely, in the simulation with the model that represented low Ca^{2+} sensitivity through multiplication of the parameter by 2.0, the amount of ATP consumed was 28 μM per beat. As such, although increasing the sensitivity of troponin to Ca^{2+} enhances cross-bridge tension (Figure 2B), it also increases the amount of ATP consumed per beat. However, our simulation showed that increasing the fraction of actin sites available for MHC to bind had hardly any effect on ATP consumption (Figure 4B).

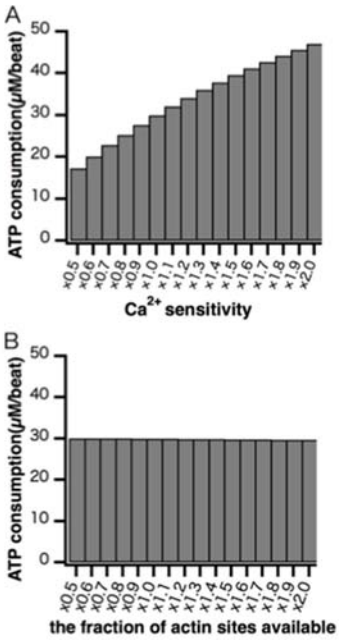

Figure 4. Changes in the predicted amount of ATP consumed via binding of Ca^{2+} to troponin per beat (μM/beat) when Ca^{2+} sensitivity of troponin was increased (A) and when the fraction of actin sites available for MHC to bind was increased (B).

Here, we made 16 combinations of the model parameters (Figure 5). In both Figure 5A and 5B, the horizontal axis shows the increase in values multiplied to the parameter that represents Ca^{2+} sensitivity and the vertical axis shows the increase in the fraction of actin sites available for MHC to bind. In Figure 5A, changes in the amplitudes of cross-bridge tension are indicated in color. Our simulation showed that increase in the fraction of actin sites (vertical axis) had a large effect on the enhancement of cross-bridge tension when the sensitivity of troponin to Ca^{2+} was high. In Figure 5B, the color scale illustrates the changes in the predicted amount of ATP consumed by Ca^{2+} binding to troponin. In contrast, changes in the fraction of actin sites available for MHC to bind had hardly any effect on the predicted amount of ATP consumed per beat, regardless of the changes in Ca^{2+} sensitivity.

In summary, we simulated the isoformal switch in the contractile apparatus of rodent ventricular cells using a comprehensive mathematical model of the cells by changing two different parameters: (1) sensitivity of troponin to $[Ca^{2+}]_i$ and (2) the fraction of actin sites available for MHC to represent small amount of troponin I. Although the changes in both parameters contributed to enhance cross-bridge tension, increase in the fraction of actin sites available for troponin had hardly any effect on the predicted amount of ATP consumed in the binding of Ca^{2+} to troponin. Further modification of the contraction

model is necessary for a more detailed discussion of isoformal switch in the contractile apparatus during the development of ventricular cells.

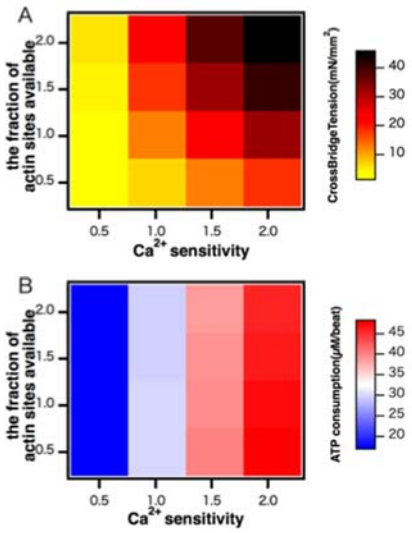

Figure 5. Simulated results of 16 combinations of the model parameters. (A) Changes in the amplitude of cross-bridge tension (mN/mm^2) and (B) predicted amount of ATP consumed via binding of Ca^{2+} to troponin (μM/beat).

4. Conclusion

Integration of the contraction model established by Niederer et al. [5] with our previous model enabled us to assess the effects of differences in the characteristics of the contractile apparatus in LE and adult ventricular cells. Our simulation showed that representation of high sensitivities of troponin to $[Ca^{2+}]_i$ and small amount of troponin I both contributed to enhance cross-bridge tension.

Acknowledgements

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