Multiscale Modelling of the Effects of Temperature on Cardiac Twitches

Momcilo Prodanovic[1,2*], Srboljub M. Mijailovich[2]

[1] University of Kragujevac, Institute for Information Technologies, Department of technical and technological sciences, Kragujevac, Serbia; e-mail: momcilo.prodanovic@kg.ac.rs
[2] FilamenTech, Inc., Newton, 02458 MA, USA; e-mail: smijailo@gmail.com

* *Corresponding author*

DOI: 10.46793/ICCBI23.367P

Abstract: Functional changes in cardiac muscle, caused by mutations in sarcomere proteins, are significant for understanding cardiac pathophysiology. Experimental investigations of mechanical responses in cardiac tissue, especially in humans, are limited due to challenges in obtaining suitable samples. Trabeculae from transgenic rodent models serve as a common experimental model for studying cardiac function. However, differences in temperature between experimental settings and physiological conditions, as well as differences in myosin α and β isoform content, can complicate the interpretation and translation of findings from rodents to humans. To bridge this gap, we present a novel methodology utilizing the MUSICO computational simulation platform for multiscale modeling of cardiac twitch contractions. MUSICO integrates crossbridge cycling, calcium regulation of thin and thick filaments, explicit 3D sarcomere geometry, and species-specific mixtures of myosin isoforms. In this study, we quantitatively estimated the impact of temperature variations on twitch transients in rat trabeculae using MUSICO simulations. Model predictions were compared with a consistent set of experimental data from rat trabeculae. Our results demonstrated that the temperature of the experiments plays a significant role in force generation during cardiac muscle twitch, since it affects intracellular calcium concentrations, but also influences several crossbridge cycle kinetic rates which had to be adjusted in simulations for accurate predictions of twitch responses. By accounting for species-specific physiological variations and the temperature sensitivity of cardiac responses, this approach offers insights into a more comprehensive understanding of cardiac dynamics, ultimately leading to the prediction of human cardiac muscle responses under physiological conditions. Through improved predictive capabilities, MUSICO will open new opportunities for the development of novel therapeutics and treatments targeting cardiomyopathies.

Keywords: cardiac muscle, rat trabecula, temperature effect, twitch contraction, MUSICO simulation

1. Introduction

The complexities of cardiac muscle function, modulated by sarcomere proteins, are pivotal for understanding cardiovascular health. Mutations in these proteins can lead to significant functional changes, with profound implications for cardiac pathophysiology.

Experimental models like rodent trabeculae offer insights into heart mechanics, yet translating these findings to human physiology requires considering factors such as temperature dependence and species-specific protein isoforms.
Investigating cardiac mechanical responses requires a comprehensive approach. Temperature, often overlooked, fundamentally influences biochemical reactions and protein function. The significant study by Janssen et al. [1] points out the connection between temperature, muscle tension and intracellular calcium concentrations in cardiac muscle, emphasizing the need for precise temperature control in experiments.

Computational models, such as MUSICO (Muscle Simulation Code) platform [2], complement multiscale experiments and provide a comprehensive framework for understanding cardiac function. Recent studies by Mijailovich et al. [2] emphasize the significance of temperature in accurately characterizing mechanical responses in rat cardiac tissue. This study showed that temperature has the effect of changing several acto-myosin crossbridge cycle kinetic rates. However, the simulations included a single (equivalent) myosin isoform, instead mixture of 75% α and 25% β myosin isoforms observed in rat ventricular muscles. In our following study, Prodanovic et al. [3], we included the observed mixture of the isoforms, however simulation were done at single temperature of 25°C exclusively using dataset acquired from Chung et al. [4].

In this study we investigate implications of a range of temperatures on rat cardiac twitch contractions. By synergizing experimental data with computational simulations we aim to unravel the relationship between temperature and cardiac twitch dynamics.

2. Methods

The experimental data for examining the temperature dependence of cardiac twitches were obtained from the study by Janssen et al. [1]. In this study, temperature was gradually increasing between 22.5°C and 37.5°C in 2.5°C intervals, while simultaneously recording force and calcium transients during twitches in rat trabeculae preparations at 0.5 Hz stimulating frequency.

The computational simulations were conducted using the MUSICO platform, which enables simulation of cardiac muscle twitch contractions by accounting for all interactions between sarcomere proteins in the explicit 3D sarcomere geometry. The crossbridge model contains five biochemical states of the chemomechanical cycle, and a "parked" state associated with thick filament regulation by calcium [2]. The model of thin filament regulation by [Ca^{2+}] consists of four states [2]. Furthermore, model accounts for species-specific mixtures of myosin fast (α) and slow (β) isoforms [3]. Simulation parameters were primarily derived from the studies of cardiac muscle contractions in rodents and humans by [3], while [Ca^{2+}] transients were taken from the experimental observations [1]. However, due to differences in experimental conditions in Janssen et al. [1] and Chung et al. [4], a few adjustments of the crossbridge cycle kinetic rates from [3] were essential to obtain good match with the observations in Janssen et al. [1] at 25°C. Particularly, myosin binding and detachment to actin rates, k_{+A} and k_{-A} respectively, were increased 1.5 times, myosin reverse powerstroke cap rates, k_{-Pi}^{cap}, for fast and slow

myosin isoforms were increased 2-fold, while ADP release rates, k_{+D}, for both myosin isoforms were decreased 2-fold compared to the values reported in Prodanovic et al. [3].

These adjusted parameters, alongside the observed patterns of temperature-induced changes in crossbridge kinetic rates used in simulations of rat trabeculae with a single myosin isoform [2], served as a basis for creating a translation matrix (Figure 1). This matrix enables quantitatively connecting the effects of temperature on twitch contractions in rat cardiac trabeculae allowing simulation of cardiac muscle behavior at physiologically relevant temperatures, as well as cross-species translation.

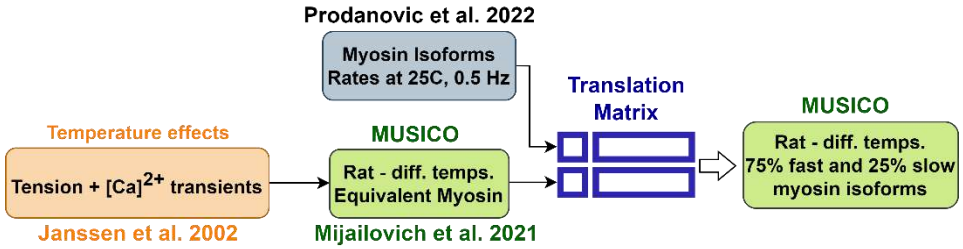

Figure 1. Workflow for predicting twitches in rat cardiac muscle at various temperatures.

3. Results

Using MUSICO platform and translation matrix, the proposed workflow for predicting twitches at various temperatures demonstrated good simulation fits to the experimental twitch data (Figure 2A). As observed, increase of temperature affects calcium transients (inset in Figure 2A) which consequently increases twitch responses.

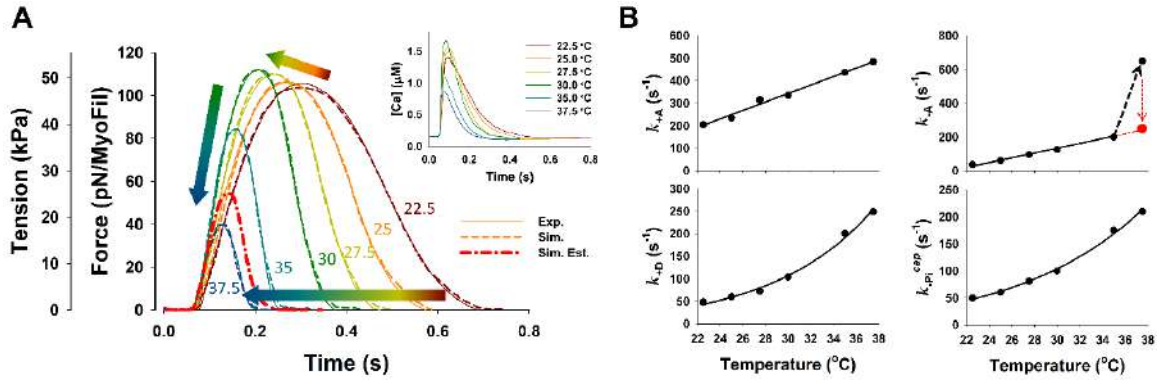

Figure 2. MUSICO simulations of temperature dependance on rat cardiac twitch. A) Simulations (dashed lines) compared to experimental observations [1] (thin lines). Inset: [Ca^{2+}] transients from [1] used as the inputs for simulations. B) Temperature dependence of acto-myosin crossbridge cycle kinetic rates in MUSICO.

Moreover, twitch duration is decreasing, while peak of the twitch is rising until temperature reaches 30°C and then progressively declines. Beside intracellular calcium transients, simulations show that temperature strongly affects kinetic rates of acto-myosin crossbridge cycle by progressively increasing myosin to actin binding and

detachment rates (K_{+A} and K_{-A}), ADP release rate (K_{+D}) and reverse powerstroke cap rates, k_{-Pi}^{cap}, (Figure 2B).

However, it should be noted that rapid decline in observed twitch tension at 37.5°C could potentially originate from inconsistencies in the recording of tension and calcium transients. This is reflected in the drastic increase in myosin detachment rate (Figure 2B). Following the pattern of twitch peak decline with increasing the temperature above 30°C, it was expected that the peak tension at 37.5°C would be between 25-30 kPa. Assuming this, simulations predicted expected physiological peak tension of 25.4 kPa for $k_{-A} = 250 s^{-1}$ (red dotted line in Figure 2A), based on the linear increase of the rate by temperature (red point in Figure 2B).

4. Conclusions

MUSICO simulation showed that temperature plays a significant role in tension generation during cardiac muscle twitch. Besides observed effects on intracellular calcium concentrations, simulations revealed that temperature affects several crossbridge cycle kinetic rates. Because numerous recorded observations fall beyond the physiological temperature range, translating data across scales and species becomes a formidable challenge. However, our translational matrix approach, as demonstrated, effectively integrates various datasets to provide valuable insights even in data-scarce scenarios. To deepen our understanding, collecting detailed experimental data across the full physiological temperature range holds promise for uncovering novel cardiac phenomena. By accounting for species-specific physiological variations and the temperature sensitivity of cardiac responses, this approach offers insights into a more comprehensive understanding of cardiac dynamics, ultimately leading to prediction of human cardiac contractions more accurately under physiological conditions.

Acknowledgment

This research is funded by the Ministry of Science, Technological Development and Innovation, Republic of Serbia, Grant: No. 451-03-47/2023-01/200378.

References

[1] P. M. Janssen, L. B. Stull, and E. Marban, "Myofilament properties comprise the rate-limiting step for cardiac relaxation at body temperature in the rat," *Am J Physiol Heart Circ Physiol,* vol. 282, pp. H499-507, Feb 2002.

[2] S. M. Mijailovich, M. Prodanovic, Poggesi, C., M. A. Geeves, and M. Regnier, "Multiscale Modeling of Twitch Contractions in Cardiac Trabeculae," *Journal of General Physiology,* vol. 153 p. e202012604, 2021.

[3] M. Prodanovic, M. A. Geeves, C. Poggesi, M. Regnier, and S. M. Mijailovich, "Effect of Myosin Isoforms on Cardiac Muscle Twitch of Mice, Rats and Humans," *Int J Mol Sci,* vol. 23, Jan 20 2022.

[4] C. S. Chung, C. W. Hoopes, and K. S. Campbell, "Myocardial relaxation is accelerated by fast stretch, not reduced afterload," *J Mol Cell Cardiol,* vol. 103, pp. 65-73, Feb 2017.