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COMPARATIVE SIMULATIONS OF INTACT CARDIAC MUSCLE RESPONSES FROM MICE, RATS AND HUMANS: THE EFFECT OF MYOSIN ISOFORMS

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The functional changes of cardiac muscle, often precipitated by mutations in sarcomere proteins, are usually assessed using mouse trabeculae because of the ease in manipulating genes to produce animal models of disease. Quantitative observations of mechanical responses to intracellular calcium are usually reported as force-pCa relations in demembranated cardiac muscle or transient twitch contractions in intact cardiac muscle. However, these studies are quite distinct from the observations of human cardiac muscle diseases and cannot be simply extrapolated. A key reason for this difference is the myosin isoform content: mice predominantly contain α-myosin and humans the slower β-myosin isoforms. Because human cardiac muscle tissue is not readily available, the translation of data from the abundant rodent studies to humans is necessary but challenging. The MUSICO platform [1] is well suited as a tool to translate between mice and human because it contains details of crossbridge cycling, thin and thick filament regulation by calcium, an explicit 3D geometry of the sarcomere and incorporates spatially randomly distributed mixture of myosin isoforms and structural features specific for each of the species. Using MUSICO simulations, tightly coupled with experiments, we quantitatively estimated the contributions of myosin isoforms to contraction and relaxation of cardiac muscle in mice, rats and humans. The crossbridge cycle parameters of each myosin isoform were assessed from the kinetic analysis of proteins in solution [2, 3] and the calcium and tension transients obtained from twitch contractions [4-6]. The simulations show strong correlation between active tension and ratio of myosin isoforms populations across the species. The predicted twitch responses, matched with the experimental observations, provide the matrix for translation of parameters between species. The established methodology can be used in MUSICO simulations to predict human cardiac muscle functional changes in diseases.

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REFERENCES

[1] S. M. Mijailovich, B. Stojanovic, D. Nedic, M. Svicevic, M. A. Geeves, T. C. Irving, *et al.*, "Nebulin and Titin Modulate Crossbridge Cycling and Length Dependent Calcium Sensitivity " *J Gen Physiol,* vol. 151, pp. 680-704, 2019.

[2] C. A. Johnson, J. Walklate, M. Svicevic, S. M. Mijailovich, C. Vera, A. Karabina, *et al.*, "The ATPase cycle of human muscle myosin II isoforms: Adaptation of a single mechanochemical cycle for different physiological roles," *J Biol Chem,* vol. 294, pp. 14267-14278, Sep 27 2019.

[3] S. M. Mijailovich, D. Nedic, M. Svicevic, B. Stojanovic, J. Walklate, Z. Ujfalusi, *et al.*, "Modeling the Actin.myosin ATPase Cross-Bridge Cycle for Skeletal and Cardiac Muscle Myosin Isoforms," *Biophys J,* vol. 112, pp. 984-996, Mar 14 2017.

[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.

[5] R. Coppini, C. Ferrantini, L. Yao, P. Fan, M. Del Lungo, F. Stillitano, *et al.*, "Late sodium current inhibition reverses electromechanical dysfunction in human hypertrophic cardiomyopathy," *Circulation,* vol. 127, pp. 575-84, Feb 5 2013.

[6] C. Ferrantini, J. M. Pioner, L. Mazzoni, F. Gentile, B. Tosi, A. Rossi, *et al.*, "Late sodium current inhibitors to treat exercise-induced obstruction in hypertrophic cardiomyopathy: an in vitro study in human myocardium," *Br J Pharmacol,* vol. 175, pp. 2635-2652, Jul 2018.