Mutation-specific hypertrophic cardiomyopathy and Mavacamten: a mechano-energetic *in silico* study

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Introduction: Associated with pathogenic variants in sarcomere genes, hypertrophic cardiomyopathy (HCM) represents the most prevalent genetic cardiac disorder. Mavacamten is known as the first drug with proven efficacy for obstructive HCM. To obtain safe and effective patient-specific solutions, in-depth knowledge of the Mavacamten mode of action in the mechanoenergetic cardiomyocyte machinery is required.

Methods: We started from our previous electromechanical model of human induced pluripotent stem cell-derived cardiomyocyte (hiPSC-CM) and incorporated a metabolic-sensitive component describing the effects of MgATP, MgADP, inorganic phosphate, and ATP hydrolysis-derived proton on the tension development. Our goal was to investigate the pathophysiology of the R403Q HCM mutation and the capability of Mavacamten to ameliorate the cellular mechano-energetics.

Results & Discussion: Our metabolic sensitive model of hiPSC-CM electromechanics recapitulates key biomarkers of active tension (AT), fractional shortening (FS), action potential (AP), and calcium transient (CaT) within the experimental ranges as simulated by our previous model. Markedly, our results suggest that the prolonged contractile relaxation duration, observed in vitro, due to R403Q mutation (~33%) can be simulated by an impaired mechano-energetic regulation in the contractile element without assuming an additional flux to the thin filaments. Furthermore, our HCM model could correctly predict the unaltered ATPase activity and ~40% increase in FS in R403Q mode. In HCM R403Q mode, our model simulates the improved FS, contractile relaxation, and ATPase rate due to 0.5 µM Mavacamten 14.6%, 21%, and 19.3%, respectively, consistent with the experimental reports.

Conclusion: This work is a step towards metabolic-sensitive robust computational models of cardiac electromechanics suitable for pharmacological investigations on sarcomeric cardiomyopathies.