A Human-Based Computational Investigation Into Sarcomeric and Ionic Remodelling in Hypertrophic Cardiomyopathy

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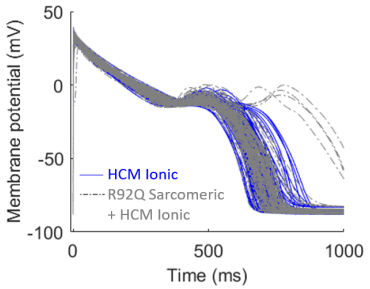
Introduction: Hypertrophic cardiomyopathy (HCM), an inherited cardiac disease, is one of the leading causes of sudden cardiac death in the young. Remodelling of ion channels and sarcomeric proteins occurs, but their relative contributions to the cellular pro-arrhythmic phenotype is unclear. Troponin T (TnT) sarcomeric mutations are particularly arrhythmogenic.

Methods: The Tomek-Rodriguez-O'Hara-Rudy-Land computational electromechanical model of the human ventricular cardiomyocyte was used as baseline. A population of 1000 models, with varying ion channel conductances, was calibrated to human experimental data, giving 440 models. Three additional populations of 440 models were generated by varying cellular parameters to simulate HCM ionic remodelling, R92Q TnT mutation sarcomeric remodelling and a combination of the two. Blocks from 0–60% for late Na^+, L-type Ca^{2+} and Na^+/Ca^{2+} exchanger (I_{NCX}) currents were applied. Key biomarkers and early afterdepolarisation (EAD) frequencies were measured.

Results: There were no EADs in the baseline or sarcomeric remodelling populations. A greater frequency of EADs was observed in the combined sarcomeric and HCM ionic remodelling populations compared to ionic alone (7.3% vs 5.5%). Calcium transient decay time was prolonged in the combined remodelling relative to ionic remodelling (median: 556 ms vs 483 ms); I_{NCX} was also prolonged. Targeting this arrhythmogenic pathway, a simulated activator of a calcium-handling protein, sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), reduced EAD frequency from 7.3% in the combined remodelling population to 3.0%.



Greater early afterdepolarisation severity in combined sarcomeric & ionic remodelling

Conclusions: Sarcomeric remodelling worsens EADs by prolonging calcium transient decay and I_{NCX}. A specific SERCA activator could provide a novel, mutation-specific, anti-arrhythmic therapeutic for HCM patients.