

Investigation of the Arrhythmic Mechanisms in Hypertrophic Cardiomyopathy under Beta-adrenergic Stimulation

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Introduction: Hypertrophic cardiomyopathy (HCM) is the most common cardiac genetic disorder and the leading cause of sudden cardiac death in young adults. HCM patients often present an enhanced arrhythmogenicity that can lead to lethal arrhythmias, especially during exercise. Recent studies have shown an abnormal response of HCM cardiomyocytes to β -adrenergic stimulation (β -ARS), with prolongation of their action potential duration (APD). The mechanisms underlying this aberrant response to sympathetic stimulation and their implication in the generation of arrhythmias remain unknown.

Aims: To investigate the key ionic mechanisms underlying the HCM abnormal response to β -ARS and the resultant repolarisation abnormalities using human-based experimental and computational methodologies.

Methods: The latest models of human ventricular electrophysiology and β -ARS were integrated and calibrated using experimental measurements of human adult cardiomyocytes from control and HCM patients. In-silico populations of control and HCM cardiomyocytes were constructed by varying the maximal conductances of 11 main ionic currents, and used to evaluate the role of β -ARS on the action potential and on the generation of early after depolarisations (EADs).

Results: The developed in silico models of β -ARS replicated the behaviour observed in the experimental data. The smaller increase of potassium currents under β -ARS in HCM was identified as the main cause of APD prolongation. EADs under β -ARS were more frequent in the HCM population; 51% (HCM) vs 20% (Control) at 1 Hz pacing. Models presenting EADs were characterized by low I_{Kr} and I_{NaK} conductances whereas inward currents (I_{CaL} , I_{NaL} and I_{NCX}) were up-regulated.

Conclusions: Our modelling results suggest that the reduction of the increase of potassium repolarising currents under β -ARS is the main mechanism underlying the APD prolongation in HCM cardiomyocytes. Down-regulation of potassium currents was also present in the models that developed EADs, suggesting a relationship between the HCM phenotype and its arrhythmogenic response to β -ARS.

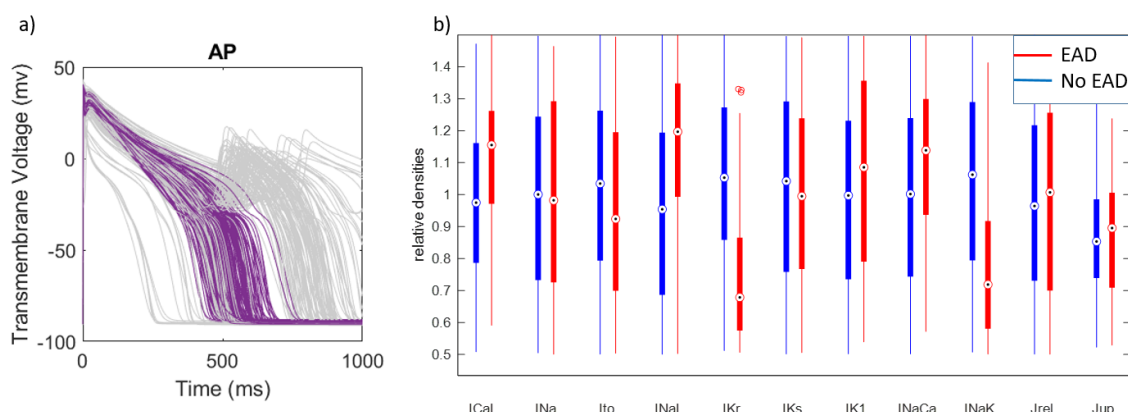


Figure 1: a) Representative AP traces for simulated HCM cell models under β -ARS. Models that developed EADs are represented in grey. b) Normalised distributions of ionic properties for the 11 conductances varied within the population of HCM myocytes under β -ARS.