Computational modeling identifies the cellular electromechanical effects of disrupted intracellular calcium handling in arrhythmogenic cardiomyopathy patients

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Background: Patients with arrhythmogenic cardiomyopathy (ACM), an inherited progressive cardiac disease, mostly remain asymptomatic until the occurrence of life-threatening arrhythmias. Previous research identified disturbed calcium handling as a potential disease-initiating mechanism [1], but how this translates to arrhythmogenesis and cardiac mechanical dysfunction remains unknown.

Purpose: To characterize disturbed molecular regulators of intracellular calcium (Ca2+) handling in patients with ACM and predict their effects on action potential (AP), calcium transient (CaT) and tension development in both left and right ventricles (LV, RV) using a computer model of cellular electromechanics.

Methods: We performed gene expression (qPCR) and protein level (Western blot) analysis using LV and RV tissue samples obtained from 5 ACM patients who underwent heart transplant and 5 controls with no history of cardiac disease. Changes in protein levels were implemented in our recent human electromechanical cardiomyocyte computer model [2]. CaT, AP and tension traces were simulated and compared to control. Clinical data (age, sex, genetics, ECG, echocardiography) were related to the simulation outcome.

Results: Measured protein levels varied significantly between the 5 patients and between individual LV and RV samples. Exemplary results for one ACM patient are shown in the figure below. In the LV, AP duration was shorter than control (221ms vs. 255ms), CaT peak was increased (0.52µM vs. 0.39µM) but CaT amplitude was reduced due to increased diastolic Ca2+ (0.26µM vs. 0.060µM). Relaxation was also impaired, as shown by a longer CaT and tension duration (965ms vs. 640ms), and an increased diastolic tension (10mN vs. 4.8mN). In the RV, AP duration was shortened, and CaT and tension peak were lower than in the LV (0.37µM and 13.6mN). Diastolic levels were elevated compared to control, and CaT and tension development were prolonged. This can be related to the measured Ca2+ changes: in the LV, a lower activity of the sodium-calcium exchanger (NCX) (22% of control) and SERCA pump (52%) combined with an increased ryanodine receptor (RyR) activity (96%) may impair the extrusion of Ca2+, leading to accumulation of Ca2+ and increased diastolic Ca2+ levels. In the RV, milder changes in NCX (48% of control) and RyR (11%) may explain the larger Ca2+ extrusion, leading to lower CaT peak and diastolic levels. The patient showed a normal LV size, a severely dilated RV, as well as a poor LV fractional shortening suggesting increased ventricular stiffness, in line with the potential impaired relaxation shown by the simulations.

Conclusion: By integrating protein level data from ACM patients into a computational model of cellular electromechanics, we quantified the electromechanical effects of patient-specific Ca2+ handling changes. Future whole-heart extensions of this work have the potential to identify and understand proarhythmic mechanisms in ACM patients.