Simulation of Cardiac Contractility Modulation with Single Cell Action Potential Human Models

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Cardiac contractility modulation (CCM) has emerged as a promising therapeutic approach for patients with heart failure (HF) who remain symptomatic despite traditional therapies, offering the potential to enhance myocardial contractility and improve clinical outcomes.

In this work, we have used two single-cell action potential models: the new model of human ventricular cardiomyocytes electromechanics, BPSLand (Bartolucci et al. 2022), and the novel electromechanical hiPSC-CM model, hiPSC-CM-CE (Forouzandehmehr et al. 2021) to test their response to a CCM-like stimulation. The stimulation was implemented following the protocol proposed by Feaster et al. (2021). First, the models started at 1Hz steady state, then for other 5s the same stimulus was applied. After that, the CCM starts: square wave electrical pacing pulses (i.e., monophasic) were generated and the models paced at 1 Hz (2ms stimulus pulse duration; amplitude of -26.5μA/μF and 6A/F for BPSLand and hiPSC-CM-CE respectively). CCM stimulation was delivered as four biphasic pulses of 5ms duration with amplitude -13.25μA/μF and 3A/F for BPSLand and hiPSC-CM-CE respectively, zero interphase interval. The delay between pacing pulses and CCM stimulation was 30ms.

For the first CCM beat, in both models, there was an increase in contraction amplitude which remained stable during the CCM. Then when it was removed the amplitude decreased following the results reported by Feaster et al. In addition, only the BPSLand model has shown that on the first CCM beat, the $[Ca^{2+}]_i$ amplitude was increased relative to before CCM. Additionally, the effects of CCM on intracellular calcium handling remained for the entire duration of CCM stimulation and were eliminated ate the end of CCM. These results demonstrate acute CCM stimulation modifies intracellular calcium handling properties *in silico*.

With this work, we wanted to support the investigation of this new intracardiac therapy on the scale of single-cell behavior with the help of computational models.