The comparison between two mathematical contractile elements Integrated to an hiPSC-CM *in silico* Model

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Introduction: Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CM) are a valuable model for drug testing and disease studies, since they retain the same genetic information as the donor.

Aim: Exploring the effects of hiPSC-CM Ca^{2+} dynamics on the contraction force and obtaining a realistic understanding of hiPSC-CM pro-arrhythmic risk assessments, require a comprehensive mathematical hiPSC-CM model. We aim to complete in mechanical terms the recently published Paci2020 model of the hiPSC-CM action potential (AP).

Methods: We integrated two contractile element (CE) models, namely Rice2008 and Negroni2015, in the Paci2020 model. Secondly, we assessed the CE impact on hiPSC-CM electrophysiology in terms of AP and Ca^{2+} transient (CaT) biomarkers and compared the capabilities of the two CEs in recapitulating in vitro hiPSC-CM force-Ca^{2+} data.

Results: The simulated force-Ca^{2+} relationships, revealed a rather close pCa50 values for both CEs: 6.17 and 6.10, respectively for Rice2008 and Negroni2015. Also, Hill's coefficients for the two curves were 7.30 and 3.6. The relationships were in agreement with in vitro data from human engineered heart tissues. Most of the biomarkers measured from simulated spontaneous APs and CaTs showed good agreement with in vitro data for both CEs. Unlike the hiPSC-CM with Negroni2015 CE, the model with Rice2008 CE replicated also the AP shape factor biomarkers of ventricular like hiPSC-CMs within the experimental range. The active peak force observed at 1.8 mM external [Ca^{2+}], in paced conditions (1 Hz), was 0.011 mN/mm^2 for Paci2020+Rice2008 and 0.57 mN/mm^2 for Paci2020+Negroni2015. These values match, qualitatively, the 0.26 mN/mm^2 in vitro peak force reported previously for 1.8 mM external [Ca^{2+}].

Conclusion: Our work represents a first attempt to move beyond electrophysiology in in silico descriptions of hiPSC-CMs, through evaluating two of contractile machinery models.