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Mechano-Electric Feedback and Arrhythmogenic Current Generation in A Computational Model of Coupled Myocytes

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Heterogeneous mechanical dyskinesis has been implicated in arrhythmogenic phenotypes. Strain-induced perturbations to cardiomyocyte electrophysiology (EP) may trigger arrhythmias *via* a variety of mechano-electric feedback (MEF) mechanisms. While the role of stretch-activated ionic currents (SACs) has been investigated intensively using computational models, experimental studies have shown that mechanical strain can also trigger intra- and inter-cellular calcium waves. To investigate whether the inherent strain dependence of myofilament calcium affinity may promote arrhythmogenic intra- and inter-cellular calcium waves under conditions of pathologic mechanical heterogeneity, we coupled a mathematical model of excitation-contraction coupling (ECC) in rabbit ventricular myocytes to a model of myofilament activation and force development. In a one-dimensional (1D) compartmental analysis, multiple myocytes were electrically and mechanically coupled in series, each myocyte consisting of fifty bi-directionally coupled sarcomere models. Calcium diffusion and strain transfer were permitted between adjacent sarcomeres. The resulting model was fitted to calcium alterations during homogeneous mechanical perturbation. The addition of end-to-end mechanical interactions of sarcomeres enabled the model to capture: (1) the effects of MEF on intracellular calcium dynamics at the sarcomeric scale; and (2) the effects of mechanical heterogeneities on calcium dynamics at the cellular scale.

The model results showed that, under conditions of calcium overload, sarcomere length heterogeneity increases the vulnerable window of stretch release that trigger suprathreshold delayed afterdepolarizations (DADs). Furthermore, sarcomere heterogeneity could modulate the susceptibility threshold for DADs and the aftercontraction wave propagation velocity non-monotonically. Meanwhile, in larger scale multi-cellular constructs coupled *via* gap junctions, mechanically-induced waves may contribute to synchronizing arrhythmogenic calcium handling and afterdepolarizations. These results suggest that feedback from heterogeneous sarcomere mechanics to intracellular calcium dynamics may increase susceptibility to proarrythmic intra- and inter-cellular calcium wave propagation.

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