May 31st, 6:30 PM - 7:00 PM

Intercellular sodium nanodomain signaling regulates repolarization in cardiac tissue

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Ventricular fibrillation (VF) is a life-threatening condition caused by irregular electrical signals generated in the heart. In cardiac cells, action potentials (AP) are initiated by an influx of sodium (Na^+) ions via voltage-gated Na^+ channels. In the presence of gain-of-function Na^+ channel mutations, Na^+ influx can persist, prolonging AP duration (APD). Recent imaging studies have shown that Na^+ channels are highly clustered at the cell intercalated disk, facilitating formation of Na^+ nanodomains in the intercellular space between cells. Simulations from our lab have recently predicted that modulating intercellular cleft width can alter APD in the presence of Na^+ channel mutations, due to a decreased Na^+ driving force at the intercalated disk. In this work, we performed new cardiac tissue simulations to determine the effects of changing both intercellular cleft and interstitial space widths on APD and conduction velocity (CV). We also investigate changes in the bulk extracellular Na^+ concentration in both the nanodomain and interstitial spaces and pacing basic cycle length (BCL). Consistent with our prior work, we found that APD increases while CV decreases with increasing cleft width, with significant APD prolongation for slow pacing rates (i.e., long BCL values). Interestingly, due to the high density of Na^+ clustered at the intercalated disk, we found that APD and CV did not depend on interstitial widths. Future directions include varying the Na^+ channel density in the intercellular cleft, which we expect will influence the dependence on interstitial width. Overall, our model predicts that intercellular nanodomain formation is a critical regulatory of cardiac repolarization, in particular in the setting of defective Na^+ channel function.