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Age Dependent Regulation of Cardiac Sodium Channel Gain of Function

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Age dependent Regulation of Cardiac Sodium Channel Gain of Function

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Action potentials (AP) in the heart are initiated by sodium (Na+) ion influx via voltage-gated Na+ channels. Gain-of-function mutations in the gene encoding the Na+ channel associated with the long QT type-3 (LQT3) syndrome can produce a “late” Na+ current, producing pro-arrhythmic early-afterdepolarizations (EADs), and prolonging AP duration (APD). High-resolution imaging has shown that Na+ channels are clustered at the intercalated disc (ID), facilitating the formation of Na+ nanodomains in the intercellular cleft. We recently showed in simulations and ex-vivo guinea pig experiments that narrow clefts suppressed APD prolongation in LQT3- associated models, which simulations predict is mediated by changes in cleft Na+ concentration (Greer-Short, et al., Circ AE, 2017). LQT3 is a cardiac disease that often does not manifest symptoms until later in life, suggesting age-dependent factors influence the formation of EADs and APD prolongation. Here, we performed new simulations to predict how intercellular cleft width regulation depends on key cellular and tissue properties that vary with age, specifically cell size, gap junctional coupling, and Na+ channel expression density and subcellular localization. Cardiac tissue is modeled by a 50-cell strand of electrically and ephaptically coupled cardiomyocytes, with each cell discretized into axial and ID patches to account for nonuniform Na+ channel subcellular localization. Consistent with our prior work, across all age dependent conditions, wider cleft width prolonged APD due to enhanced late Na^+ current. We find that properties increasing total cellular Na+ channels expression (increased Na^+ channel density, increased cell size) promoted longer APDs, but with a complex dependence on Na^+ channel localization and gap junctional coupling. Our works predict that intercellular cleft Na^+ as well as cell size and Na^+ channel conductance are key regulators of cardiac repolarization. Specifically, increasing cell size and Na^+ channel conductance increases EAD formation. Ongoing ex-vivo imaging and optical mapping studies will be compared with model predictions.