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Using mathematical modeling to unmask the concealed nature of long QT-3 syndrome

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Long QT-3 (LQT3) syndrome, a cardiac disease that can lead to arrhythmias and sudden cardiac death, is associated with gain-of-function mutations in the cardiac voltage-gated sodium channel. This gain-of-function generates a late sodium current, which can trigger ectopic electrical activity, known as early-afterdepolarizations (EADs). However, LQT3 can be a concealed disease, requiring some other etiology to unmask it, as EADs are often rare in tissue, suggesting that cell-to-cell coupling conceals the LQT3 phenotype in patients. Mathematical models have shown that narrow intercellular separation can support an alternative form of cell-to-cell coupling known as ephaptic coupling. Critically, ephaptic coupling models predict that decreasing intercellular separation slows electrical conduction due to reduced *peak* sodium current, termed “self-attenuation.” We test the novel hypothesis that self-attenuation “masks” the LQT3 phenotype and suppresses EADs by reducing the *late* sodium current.

Using a mathematical model of cardiac tissue that incorporates ephaptic coupling and an LQT3-associated sodium channel mutant model, simulations predict that for wide intercellular clefts, cells with the sodium channel mutation consistently produce EADs, while for small intercellular clefts, EADs are suppressed. Critically, the model demonstrates that for narrow clefts, ephaptic coupling provides negative feedback that reduces the late sodium current and suppresses EADs. Further, simulations show that EAD suppression does not depend on species or the specific sodium channel mutation. Importantly, experiments in isolated guinea pig hearts reproduce these computational predictions. Simulations demonstrate that ephaptic self-attenuation can provide a critical protective mechanism and conceal the LQT3 phenotype.