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FUNCTIONAL CHARACTERIZATION AND IDENTIFICATION OF A THERAPEUTIC FOR A NOVEL SCN5A-F1760C VARIANT CAUSING TYPE 3 LONG QT SYNDROME REFRACTORY TO ALL GUIDELINE DIRECTED THERAPIES

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Background: Long QT syndrome (LQTS) stems from prolongation of the cardiomyocyte’s action potential duration (APD). Pathogenic variants in the SCN5A-encoded Nav1.5 sodium channel cause type 3 LQTS (LQT3). Here, we present a now deceased infant with severe LQT3 (QTc of 680-1200 ms) who was refractory to left cardiac sympathetic denervation and pharmacological treatments with either lidocaine (Lido) or mexiletine (Mex). The decedent had a novel variant, F1760C, involving a critical residue of the Nav1.5’s local anesthetic (i.e., Lido/Mex) binding domain.

Objective: To functionally characterize and assess treatment options for an infant with a SCN5A-F1760C variant using TSA-201 and patient-specific induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs).

Methods: TSA-201 cells were transfected with SCN5A wildtype (WT) and F1760C-associated sodium currents with/without 10μM Lido, flecainide (Flec), and the antiepileptic drug, phenytoin (Phen). Patient-specific SCN5A-F1760C iPSC-CMs and CRISPR-Cas9 gene/variant corrected isogenic control (IC) iPSC-CMs were generated. FluoVolt voltage dye was used to measure APD with/without 5μM Phen.

Results: V1/2 of inactivation was right-shifted significantly in F1760C cells (-72.2±0.7 mV) compared to WT cells (-86.3±0.9 mV; p<0.0001) resulting in a marked increase in window current. F1760C increased sodium late current 2-fold from 0.18±0.04% of peak in WT to 0.49±0.07% of peak in F1760C (p=0.0005). Treatment with Lido, Flec, and Phen rescued the V1/2 of inactivation -3.86, -3.08, and -3.86 mV, respectively. However, Lido, Flec, and Phen treatment resulted in a gain-of-function shift in V1/2 of activation -8.34, -12.02, and -5.90 mV, respectively. Baseline APD to 90% repolarization (APD90) was increased significantly in F1760C iPSC-CMs compared to IC iPSC-CMs (IC:423±15 ms; F1760C: 601±4 ms; p<0.0001). 4-hour treatment with Phen significantly decreased APD90 of F1760C iPSC-CMs (5μM: 453±6 ms; p<0.0001).

Conclusion: Phenytoin rescued electrophysiological phenotype and APD of a novel SCN5A-F1760C variant. The antiepileptic drug, phenytoin, may be an effective alternative therapeutic for the treatment of LQ3, especially for variants that disrupt the lidocaine binding site.

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PERIODIC REPOLARIZATION DYNAMICS (PRD) AS A POTENTIAL BIOMARKER TO PREDICT SUDDEN CARDIAC DEATH DURING ACUTE MYOCARDIAL INFARCTION IN A PRECLINICAL PIG MODEL

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Background: Ischemic heart failure (IHF) predisposes to arrhythmogenesis and sudden cardiac death (SCD). The ECG-derived biomarker periodic repolarization dynamics (PRD) is linked to sympathetic activity-driven modulations of repolarization and is a risk predictor of SCD in heart failure patients.

Objective: To validate PRD as biomarker for proarrhythmic autonomic innervation in pigs.

Methods: Acute myocardial infarction (AMI) was induced in 20 pigs by balloon occlusion of the LAD for 90 min. PRD were measured using high-resolution ECG in Frank-lead configuration. 30 days after AMI left ventricular (LV) tissue samples were collected for histologic assessment and expression analysis.

Results: 30 days after AMI, PRD levels were significantly increased compared to baseline (2.13 deg² vs. 3.65 deg²; Fig 1A) indicating an enhanced sympathetic activity mediated repolarization instability due to autonomic remodeling. Immunostaining revealed a higher density of sympathetic...