electrophysiological remodeling and mitochondrial dysfunction underlying an AF-causing NPPA mutation.

Results: A mouse model of DS (NaV1.1<sup>V392I</sup>) exhibited similar Na<sub>V</sub>1.5 expression levels relative to wild type (WT); however, expression of Na<sub>V</sub>1.6 was increased in DS hearts. To investigate the structural context of increased Na<sub>V</sub>1.6 expression we used PLA (<40 nm) and STORM (<20 nm lateral resolution) to assess the density of Na<sub>V</sub>1.6 near RyR2 and NCX. PLA demonstrated higher frequency of co-localization between Na<sub>V</sub>1.6 and RyR2 and NCX in DS relative to WT. This correlated with increase in fraction of Na<sub>V</sub>1.6 clusters near (<100 nm) RyR2 in DS compared to WT as revealed by STORM. To assess functional consequences of Na<sub>V</sub>1.6 cluster remodeling, we used whole-cell I<sub>Na</sub> patch clamp recording and confocal Ca<sup>2+</sup> imaging. These studies revealed that DS cardiomyocytes evidenced enhanced late I<sub>Na</sub> coupled with increased frequency of Ca<sup>2+</sup> waves. Global suppression of Na<sub>V</sub>1.6 (DS × Na<sub>V</sub>1.6<sup>V392I</sup>) mitigated late I<sub>Na</sub> as well as aberrant Ca<sup>2+</sup> handling. Using in vivo ECG we found that during bradycardia challenge (carbachol 0.5 mg/kg intraperitoneal) DS mice exhibited higher incidence of VT relative to WT and DS × Na<sub>V</sub>1.6<sup>V392I</sup>. Importantly, VT incidence correlated with increased mortality of DS mice.

Conclusion: Remodeling within Na<sub>V</sub>1.6-rich nanodomains contributes to Ca<sup>2+</sup> mishandling and arrhythmia in DS that may underlie SUDEP. Na<sub>V</sub>1.6 may serve as a druggable target for arrhythmia and SUDEP prevention.

PO-615-05

ACACETIN, A POTENT TRANSIENT OUTWARD CURRENT BLOCKER, MAY BE A NOVEL THERAPEUTIC FOR KCND3-ENCODED KV4.3 GAIN-OF-FUNCTION-ASSOCIATED J-WAVE SYNDROMES

Dan Ye MD; Wei Zhou MD; Samantha K. Hamrick BS; David Tester BS; Changsung John Kim PhD; Hector M. Barajas-Martinez PhD, FHRS; Dan Hu MD, PhD; John R. Giudicessi MD, PhD; Charles Antzelevitch PhD, FHRS and Michael John Ackerman MD, PhD

Background: The transient outward current (I<sub>to</sub>) that mediates early (phase 1) repolarization is conducted by the KCND3-encoded Kv4.3 pore-forming α-subunit. KCND3 gain-of-function mutations have been reported previously as a pathogenic substrate for J wave syndromes (JWS), including the Brugada syndrome (BrS) and early repolarization syndrome (ERS), as well as autopsy-negative sudden unexplained death (SUD). Acacetin, a natural flavone, is a potent I<sub>to</sub> current blocker.

Objective: We hypothesize that Acacetin may be a novel therapeutic for KCND3-mediated JWS.

Methods: KCND3-V392I was identified in an 18-year-old male with JWS/ERS, and a history of cardiac arrest including ventricular tachycardia/fibrillation and atrial fibrillation/flutter. KCND3-V392I was engineered by site directed mutagenesis and expressed in TSA201 cells. Gene-edited/variant-corrected isogenic control and patient-specific pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) from the KCND3-V392I-positive patient were generated. I<sub>to</sub> currents and action potentials (APs) were recorded before and after treatment with Acacetin using whole-cell patch clamp and multielectrode array (MEA) technique. Western blot and immunocytochemistry were performed to investigate KCND3 expression.

Results: KCND3-V392I demonstrated a marked gain-of-function phenotype, increasing peak I<sub>to</sub> current density by 92% (p<0.05 vs. KCND3-WT) in TSA201 cells and by 61% in Kv4.3-V392I iPSC-CM (p<0.05 vs. isogenic control). KCND3
Control). While KCND3-WT revealed an IC50 of 7.2 ± 1.0 μM for Acacetin effect, 30 μM Acacetin dramatically inhibited KCND3-V392I peak Ito current density by 96% (p < 0.05 vs. before Acacetin). 10 μM Acacetin, a concentration approaching its IC50 value, inhibited Ito by 54% (p < 0.05 vs. before Acacetin) in patient-derived iPSC-CMs and reduced the accentuated AP notch displayed in KCND3-V392I-derived iPSC-CMs.

**Conclusion:** This pre-clinical study provides pharmacological and functional evidence to suggest that Acacetin may be a novel therapeutic for patients with KCND3 gain-of-function-associated JWS by inhibiting Ito and abolishing the accentuated AP notch in patient-derived iPSC-CMs.

**PO-615-06**

**OUTPATIENT REFERRAL REDUCES THE LENGTH OF HOSPITALIZATION FOR PATIENTS UNDERGOING NONINVASIVE CARDIAC RADIOABLATION**

Kaitlin Moore BS; Clift Robinson MD; Daniel H. Cooper MD; Pamela Samson MD; Geoffrey Hugo PhD; Carlos Conteras BA and Phillip Cuculich MD

**Background:** Noninvasive cardiac radioablation (CRA) is an emerging therapy for ventricular tachycardia (VT), but it requires a complex coordination of care to obtain necessary cardiac imaging and pre-planning. Little is known about the length of hospitalization for patients undergoing CRA.

**Objective:** To quantify the length of hospital stay, testing completed before treatment, and hospitalization status for patients at the time of referral for CRA.

**Methods:** Retrospective analysis of hospitalization status, length of stay, and cardiac imaging from single-referral center for cardiac stereotactic body radiotherapy (SBRT). Patients were either referred for CRA while hospitalized or while outpatient. Necessary pre-treatment cardiac testing included a combination of chest CT, cardiac MRI, myocardial perfusion imaging (PET/CT and/or SPECT), cardiac echo, 12-lead ECG in VT, noninvasive programmed stimulation (NIPS), and SBRT simulation. A contemporary cohort of similar patients undergoing catheter ablation for refractory VT were analyzed for comparison length of stay.

**Results:** 102 patients were referred for CRA between 4/2015 and 12/1/2021. 54 patients underwent CRA and were included in the analysis. 27 patients (50%) were referred while inpatient and completed pre-treatment testing before hospitalization. 27 patients (50%) were referred as outpatient and completed pre-treatment testing during a pre-arranged expedited hospitalization. 21 patients served as the catheter ablation comparison arm. Duration of hospital stay for inpatient CRA referral (mean 14 days, range 2-43 days) was similar to the catheter ablation group (mean 12 days, range 1-103 days). Outpatient CRA referral resulted in a considerably shorter length of stay (mean 3 days, range 0-13 days) (Figure 1).

Of the inpatient CRA referral group, after the cardiac work up, 48.1% remained inpatient until the time of treatment. Of the outpatient referral group, after the expedited hospital stay, 100% left the hospital and received treatment as an outpatient. Differences of workflow and frequency of cardiac pre-testing for the entire CRA cohort is shown in Figure 2.

**Conclusion:** An expedited outpatient referral is feasible and dramatically reduces the duration of hospitalization for patients undergoing CRA.

**PO-615-07**

**USE OF A REMOTE ASSISTANCE DEVICE TO GUIDE CARDIAC IMPLANTABLE DEVICE PROGRAMING IN RURAL AREAS: RESULTS OF A FEASIBILITY STUDY**

Juan C. Diaz MD; Felipe Cañas; Jorge Romero MD, FHR; Julian M. Aristizabal MD; Jorge Marin; Isabella Alviz MD; Marta Lorente-Ros; Daniel Rodriguez MD; Mohamed Gabr MD; Luigi Di Biase MD, PhD, FHR; Oriana Bastidas; Alejandro Velasco MD, CCDS and Mauricio Duque MD, FHR

**Background:** Remote monitoring has been proven to increase the rate of arrhythmia and device malfunction detection. However, it is not widely available in underdeveloped regions and changes in device programming are not possible and require office visits, which may be difficult for patients living in distant rural areas.

**Objective:** To describe our experience with the use of the Realwear HTM-1 (Realwear, Vancouver, WA) to provide remote assistance for patients with cardiac implantable electronic devices (CIEDs) living in rural areas. Briefly, the Realwear allows the user to be directed through on-screen prompts and signals placed by the recipient. By freeing the user’s hands, the device allows for expert-guided intervention.

**Methods:** Between September 2020 and September 2021, patients requiring CIED follow-up in a distant rural population (Apartado, Colombia) were seen in a local facility by a primary care physician using the Realwear HTM-1 guided by an electrophysiologist. CIEDs were interrogated and changes in device programming were guided by the electrophysiologist. The primary objective was the incidence of clinically significant CIED alerts (including arrhythmias or device malfunction). Secondary objectives included initiation of oral anticoagulation (OAC) for atrial fibrillation (AF) and interventions for non-CIED related medical conditions (including changes in medical treatment or need for additional testing).