ALG10B (p.G6S: 0.7±0.18, n=8 vs. control: 1.25±0.16, n=9, p<0.05); 2) significant retention of Kv11.1 in the endoplasmic reticulum (p<0.0005); and 3) a significantly prolonged action potential duration (APD) confirmed by both patch clamp (p.G6S: 531±38 ms, n=15 vs. control: 324±22 ms, n=13, p<0.001) and MEA (p<0.0001). Lumacaftor, a compound known to rescue Kv11.1 trafficking, shortened the pathologically prolonged APD of ALG10B-G6S iPSC-CMs by 11% (n=31 cells, p<0.001).

Conclusion: Here, we demonstrate that p.G6S-ALG10B down-regulates ALG10B resulting in defective Kv11.1 trafficking and APD prolongation. As such, ALG10B is a novel LQTS-susceptibility gene that serves as the pathogenic substrate for the LQT2-like phenotype observed in a multi-generational pedigree of previously genetically elusive LQTS. Inclusion and analysis of ALG10B to the LQTS genetic test may be warranted, especially in genotype-negative patients with an LQT2-like phenotype.

PO-630-05

A NOVEL MECHANISM OF SMALL-CONDUCTANCE CA2+-ACTIVATED K+ CHANNEL ACTIVATION VIA NEURONAL NITRIC OXIDE SYNTHASE INHIBITION IN RAT ATRIA

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Background: The presence of atrial fibrillation (AF) is associated with electrical remodeling processes that promote a substrate for the maintenance of AF itself. Small-conductance Ca2+-activated K+ (SK) channel is a key factor in the atrial electrical remodeling. However, the mechanism of its activation is unclear. A recent study showed that neuronal nitric oxide synthase (nNOS) expression and activity are reduced in AF patients and that nNOS depletion causes the abbreviation of APD, leading to increased AF vulnerability in animals. Decreased NO production, especially in the SK channel, is a key factor in the pathogenesis of atrial fibrillation. A recent study showed that neuronal nitric oxide synthase (nNOS) expression and activity are reduced in AF patients and that nNOS depletion causes the abbreviation of APD, leading to increased AF vulnerability in animals. Decreased NO production, especially in the SK channel, is a key factor in the pathogenesis of atrial fibrillation.

Objective: We aimed to evaluate the potential of SK channel blocking to mitigate abnormal electrophysiological properties and the inducibility of atrial tachyarrhythmia which was induced by neuronal nitric oxide synthase (nNOS) depletion, and to describe the related mechanism.

Methods: Atrial tachyarrhythmia (ATA) induction and optical mapping were performed on perfused rat hearts. nNOS was pharmacologically inhibited by S-methylthiocitrulline (SMTC, 100mM). The influence of the SK channel was examined by a specific channel inhibitor, apamin (100nM). Action potential duration (APD), conduction velocity, and calcium transient (CaT) parameters (CaT1/2, Rise time, T 1/2, Tau) were evaluated by voltage and calcium optical mapping. Dominant frequency was examined in the analysis of APD dynamics.

Results: SMTC increased the inducibility of ATA and apamin mitigated the nNOS inhibition-induced arrhythmogenicity. SMTC caused the abbreviation and enhanced spatial dispersion of APD, which was reversed by apamin. In contrast, conduction velocity was not affected by SMTC or apamin. Moreover, apamin reduced the dominant frequency of SMTC-induced ATA. In voltage and calcium optical mapping, SMTC and apamin does not altered parameters associated with CaT, however, SMTC caused abbreviation APD, which was reversed by apamin.

Conclusion: Acute nNOS inhibition abbreviated APD via activating SK channels. A specific SK channel blocker mitigated APD abbreviation without alteration of CaT, implying an underlying mechanism of post translational modification of SK channels.
PO-630-08

INFLUENCE OF TWO NARCOSIS REGIMENS ON CARDIAC ELECTROPHYSIOLOGY IN MICE

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Background: Mouse models are commonly used to study arrhythmia mechanisms in vivo. Different narcosis regimens have proven feasibility in rodents with medetomidine (0.5 mg/kg), midazolam (5 mg/kg) and fentanyl (0.005 mg/kg) (MMF) and isoflurane (1-3 %)/fentanyl (0.05 mg/kg) (IF) among the most commonly used regimens, but little data is available regarding their effects on cardiac electrophysiology.

Objective: To investigate the effects of MMF and IF narcosis in C57BL/6 wildtype mice on cardiac electrophysiology in vivo.

Methods: Telemetry transmitters were implanted in 4 C57BL/6 mice which served as controls for ECG analysis without narcosis. In 22 mice ECG and invasive electrophysiology studies were performed under narcosis (n=10 MMF, n=12 IF). We assessed ECG, heart rate variability (HRV), sinus node recovery time (SNRT), atrioventricular and ventricular refractory periods (AERP, AVERP and VERP), Wenckebach point, VA conduction and arrhythmia inducibility by burst stimulation.

Results: MMF causes significant bradycardia (452 bpm baseline vs. 271 bpm MMF, ****p < 0.0001), affects HRV indicated by increased pRR50 (1.6 % baseline vs. 67.4 % MMF, ****p < 0.0001), reduced LF/HF ratio (0.62 baseline vs. 0.16 MMF, *p = 0.019) and both increased SD1 (15 ms baseline vs. 94 ms MMF, ****p < 0.0001) and SD2 (19.6 ms baseline vs. 48.5 ms MMF ****p < 0.0001). MMF prolongs SNRT (at 120 ms basic cycle length 234 ms MMF vs. 145 ms IF, ***p < 0.0001), and prolongs QRS duration (8.1 ms baseline vs. 11.6 ms MMF, *p = 0.015) and QT interval (50 ms baseline vs. 68 ms MMF, ****p < 0.0001). MMF prolongs SNRT (at 120 ms basic cycle length 234 ms MMF vs. 145 ms IF, ***p < 0.0001), antegrade and retrograde conduction in the AV node (118 ms MMF vs. 89 ms IF, ****p < 0.0001), AVERP (67 ms MMF vs. 50 ms IF, *p < 0.01) and ultimately leads to increased susceptibility for ventricular arrhythmias (1.3 % MMF vs. 0 % IF, **p < 0.01) compared to IF.

Conclusion: Our results highlight a significant impact of MMF narcosis on cardiac electrophysiology in mice. While IF only moderately reduces heart rate, MMF leads to significant bradyarrhythmia, QRS/QT prolongation and HRV alterations as well as impaired sinus node and AV node function, ultimately resulting in an increased inducibility of ventricular arrhythmias. Based on these effects we suggest using IF narcosis to study cardiac electrophysiology in mice.