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Background: Tobacco smoke exposure is associated with increased risk for atrial and ventricular arrhythmias. However, the individual components of tobacco smoke that may promote arrhythmias and the underlying electrophysiological mechanisms are unknown. Nicotine (NIC) is a major component of tobacco smoke and emerging tobacco products, including e-cigarettes.

Objective: To determine the effects of chronic NIC exposure on autonomic and electrophysiological remodeling in the rabbit heart.

Methods: Male and female rabbits were exposed to NIC (21mg/day, transdermal patch, 28 days, n = 7) or control (CT, n = 4). Fully innervated hearts were optically mapped using voltage- (RH237) and calcium-sensitive (Rhod2-AM) indicators. Sympathetic innervated hearts were optically mapped using voltage- (RH237) and calcium-sensitive (Rhod2-AM) indicators. Sympathetic nerve stimulation (SNS) was performed with electrical stimulation at the first thoracic vertebrae (7 V) and frequency was increased by 0.5 Hz until a 15% increase in heart rate (HR) was achieved. B-adrenergic (B-AR) responsiveness was evaluated with norepinephrine (500nM, NE). Sympathetic nerve density was assessed by immunostaining for tyrosine hydroxylase (TH).

Results: TH+ fiber density was reduced in NIC vs. CT (7.5 ± 0.91% vs. 10.18 ± 2.45%, p < 0.05), SNS stimulation thresholds tended to be higher in NIC vs. CT (6.25 ± 5.54 Hz vs. 1.16 ± 0.56 Hz, p = NS). Ca2+ alternans tended to occur at slower pacing cycle lengths in NIC vs. CT both at baseline and during SNS (232.0 ± 16.43 ms vs. 202.5 ± 33.04 ms with SNS, p = 0.1). APD alternans thresholds also occurred at slower pacing cycle lengths for NIC vs. CT, especially with SNS (224.0 ± 25.10 ms vs. 190.0 ± 20.0 ms, p = 0.06). NIC-exposed hearts also tended to have reduced B-AR responsiveness compared to CT (33.4 ± 36.7% vs. 83.2 ± 51.2% increase in HR with NE, p = 0.12).

Conclusion: These results suggest that chronic NIC exposure may lead to a reduction in sympathetic nerve density and activity, reduced B-AR sensitivity, and potentially increased susceptibility to cardiac alternans. Findings from this study may have significant implications for young adults who represent the fastest growing group of nicotine users and the cardiac effects of nicotine on this potentially vulnerable population is unknown.

BS-526-02

ROLE OF THE SUCCINATE PATHWAY IN THE ELECTROPHYSIOLOGICAL PROPERTIES OF RIGHT ATRIA IN A PERSISTENT ATRIAL FIBRILLATION SHEEP MODEL

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Background: The progression from paroxysmal to persistent atrial fibrillation (AF) is still a poorly understood process. Succinate levels are increased in AF patients indicating a potential role for metabolic remodeling in this transition process.

Objective: To assess the impact of the succinate pathway on the electrophysiological properties of right atria (RA) in a persistent AF sheep model.

Methods: Optical mapping was performed on ex vivo RA from a burst pacing AF sheep model, including 8 sham, 7 persistent AF, and 3 resistant animals. RA were perfused by Tyrode solution with glucose (5.6mM), subsequently replaced by succinate (10mM), known to increase mitochondrial Reactive Oxygen Species (ROS). An activator of the succinate l-adrenergic receptor (GPR91), cis-epoxySucinic acid (300μM), was also used to study the GPR91 involvement in atrial electrophysiology and AF (N = 6). Action potential duration at 80% of repolarization (APD80) were assessed from 2 to 5Hz pacing frequency and during sinus rhythm (SR). We used an S1S2 pacing protocol to determine effective refractory period (ERP) and a burst pacing protocol (30Hz) to assess ex vivo AF vulnerability. Finally, an organ donation program allowed us to investigate these properties in a human RA from an AF patient.

Results: During succinate perfusion SR is decreased in Sham (1.5 vs 1.2 Hz; p = 0.03), AF (1.5 vs 1 Hz; p = 0.003) and resistant (1.3 vs 1 Hz; p = 0.01) sheep, ERP is increased in AF sheep (184 vs 344 ms; p = 0.0007) and APD80 is increased in Sham (217 vs 264 ms; p = 0.0004) and AF sheep (195 vs 275 ms; p = 0.003). We also observed an increase in amplitude alternans and decrease in frequencies at which alternans was observed. These results appear to be confirmed in a human AF RA where succinate increased APD80 (257 vs 309 ms), ERP (260 vs 330 ms) and the occurrence of spontaneous arrhythmias. Finally, in sheep, GPR91 activation led to a slowing of SR (1.7 vs 1.3 Hz; p = 0.03), a shortening of APD80 (200 vs 170 ms; p = 0.007) and an increase in spontaneous arrhythmias.

Conclusion: Succinate induces significant electrophysiological modifications, especially in persistent AF, and increases vulnerability to AF. We have shown that the GPR91 pathway is involved in atrial electrophysiology and succinate-induced arrhythmogenesis, most likely in combination with increased ROS production.

BS-526-03

RENAL SYMPATHETIC DENERVATION PREVENTS LIFE-THREATENING ARRHYTHMIAS THROUGH AUTONOMIC REVERSE REMODELING IN CHRONIC SLEEP DISORDERED BREATHING

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Background: Obstructive sleep apnea (OSA) has been associated with increased cardiovascular morbidity and mortality, including sudden cardiac death. Sympathetic overactivity has been reported in OSA.

Objective: The study aimed to investigate the effect of renal artery denervation (RDN) on OSA rabbits in preventing ventricular arrhythmias.

Methods: Eighteen rabbits, randomized to sham control (Gr1), OSA (Gr2) and OSA receiving RDN (Gr 3). All rabbits were injected at the tongue base under endoscopic guidance with normal saline (Gr 1) or liquid silicone (Gr 2 & 3) 1 month prior to the experiment (Fig A & B). Combined surgical and chemical RDNs were approached through bilateral retroperitoneal flank incisions in Gr 3 two months prior to the experiment. Electrophysiologic properties were evaluated during sleeping. Immunoblots of ionic channel protein and immunohistochernistry (IHC) were evaluated after experiment.

Results: During sleep, the arterial P<sub>CO2</sub> was higher in Gr 2 (69.3 ± 3.4 mmHg), when compared to Gr 1 (50.5 ± 8.0 mmHg, p = 0.006) and 3 (47.6 ± 2.9 mmHg, p = 0.004) respectively. There were no differences of ventricular effective refractory periods of both RV and LV among 3 groups (Table). The VF inducibility was elevated in Gr 2 (21.3 ± 3.5%), when compared to Gr 1 (8.3 ± 0.3%, p = 0.03) and 3 (8.0 ± 0.4%, p = 0.02), respectively. There was a decrease of renal noradrenaline in Gr