

ABSTRACT BS-512: Contribution of Neuromodulation to Arrhythmias

Friday, April 29, 2022

9:15 AM - 10:15 AM

BS-512-01

PHARMACOLOGICAL SYMPATHETIC REINNERVATION AFTER MYOCARDIAL INFARCTION PREVENTS ARRHYTHMIAS IN THE MOUSE HEART

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Background: Sympathetic control of the heart plays a key role in modulating cardiac function and electrophysiology. Sympathetic hypo-innervation following myocardial infarction (MI) increases risk for development of ventricular arrhythmias. We have previously shown that chondroitin sulfate proteoglycans (CSPGs) play a role in post-MI hypo-innervation by signaling through the neuronal protein tyrosine phosphatase receptor σ (PTP σ), and that genetic deletion of PTP σ from the sympathetic neurons of mice restores innervation and prevents arrhythmias post-MI.

Objective: To investigate the effects of pharmacological modulation of PTP σ by the novel Intracellular Sigma Peptide (ISP) on cardiac sympathetic innervation and electrophysiology in the post-MI mouse heart.

Methods: MI was carried out in male and female mice (C57Bl6, 12-18 weeks old) with 45 min of ischemia followed by reperfusion. Blinded treatment with either vehicle (VEH: 5% DMSO/saline IP) or ISP (10mg/kg IP) was administered on days 3-10 post-MI. Hearts were dissected and Langendorff-perfused 14 days post-MI for electrophysiological studies (performed after 15 min of equilibration, N=4/group). Additional hearts (N=5/group) were used for immunohistochemistry studies to assess infarct size and sympathetic innervation (via tyrosine hydroxylase [TH] staining).

Results: ISP treatment had no effect on infarct size compared to VEH. VEH-treated hearts showed significant loss of TH+ fibers in the infarct, whereas ISP-treated hearts did not. Ex vivo heart rate was significantly higher in the ISP-treated compared to VEH hearts (300.3 ± 34.9 vs. 180.3 ± 37.7 BPM, $p=0.003$). Premature ventricular contractions (PVCs) occurred in all 4 VEH-treated hearts; bigeminy and ventricular tachycardia (VT) occurred in 1 VEH heart each. None of the ISP-treated hearts developed any kind of ventricular arrhythmias, resulting in a significantly lower arrhythmia score in ISP compared to VEH (0 ± 0 vs. 1.75 ± 0.96 , $p=0.01$).

Conclusion: Pharmacologic intervention by daily injection of ISP post-MI prevents arrhythmias in the mouse heart, despite no change in infarct size. These data suggest that restoring sympathetic innervation to the infarct is anti-arrhythmic.

BS-512-02

AUTONOMIC NEUROMODULATION FROM RENAL SYMPATHETIC DENERVATION PREVENTS ATRIAL FIBRILLATION VULNERABILITY CAUSED BY CHRONIC OBSTRUCTIVE SLEEP APNEA IN A RABBIT MODEL

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Background: Obstructive sleep apnea (OSA) has been reproducibly identified as an important risk factor for AF. Chronic

OSA (COSA) induces a sympathetic overactivity and plays a critical role in the initiation and maintenance of AF.

Objective: The aim of this study was to evaluate the autonomic modulation effect of renal artery denervation (RDN) in the treatment of AF in COSA.

Methods: Eighteen rabbits, randomized to sham control, COSA and COSA receiving RDN groups. All rabbits were injected at the tongue base under endoscopic guidance with normal saline (sham control) or liquid silicone (COSA and COSA-RDN) 1 month prior to the experiment. Combined surgical and chemical RDNs were approached through bilateral retroperitoneal flank incisions in COSA-RDN two months prior to the experiment. The atrial effective refractory period (ARP) and window of vulnerability (WOV), the difference between the longest and shortest coupling interval of the premature stimulus that induced AF) during sleeping were measured. Immunoblots and immunohistochemistry were evaluated after experiment.

Results: During sleep, the arterial P_{CO2} was higher in COSA (69.3 ± 3.4 mmHg), when compared to sham control (50.5 ± 8.0 mmHg, $p=0.006$) and COSA-RDN (47.6 ± 2.9 mmHg, $p=0.004$) respectively. There were no differences of ARPs of biatria among 3 groups (Fig A). Spontaneous initiation of AF (Fig B) was found in 2 of 6 rabbits in COSA, but not in other rabbits during sleep. The AF WOV was elevated in COSA (33.8 ± 8.8 ms), when compared to sham control (5.7 ± 3.0 ms, $p=0.01$) and COSA-RDN (9.3 ± 4.1 ms, $p=0.04$), respectively. There was an increase of tyrosine hydroxylase nerve innervation in left atrium in COSA, compared to sham control and COSA-RDN, whereas renal catecholamine was decreased in COSA-RDN, compared to sham control and COSA groups (Table). There were no ionic channel protein expression differences among groups (Fig C).

Conclusion: COSA increases the AF vulnerability with spontaneous AF initiation. RDN attenuates the cardiac sympathetic overactivity and catecholamine spillover, which in turns ameliorates the atrial arrhythmogenesis.

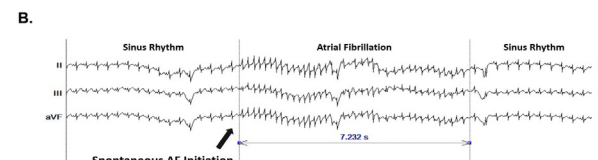
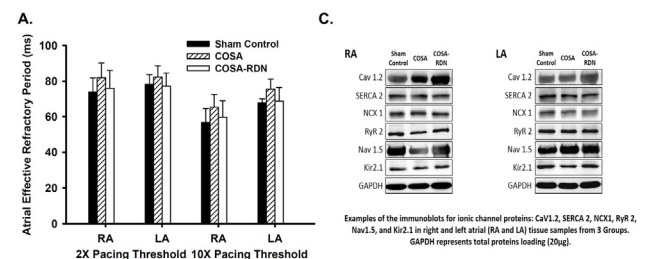


Table. Immunohistochemistry and Renal Catecholamine Data among three groups.

	Sham Control	COSA	COSA-RDN	p Value
Tyrosine Hydroxylase Nerve Density (Sympathetic)				
RA ($10^2 \mu\text{m}^2/\text{mm}^2$)	1.270 \pm 0.118	1.572 \pm 0.251	0.948 \pm 0.205	0.18
LA ($10^2 \mu\text{m}^2/\text{mm}^2$)	0.985 \pm 0.230	1.301 \pm 0.105	0.643 \pm 0.129	0.04
Choline Acetyltransferase Nerve Density (Parasympathetic)				
RA ($10^2 \mu\text{m}^2/\text{mm}^2$)	0.448 \pm 0.260	0.690 \pm 0.290	0.479 \pm 0.182	0.16
LA ($10^2 \mu\text{m}^2/\text{mm}^2$)	0.232 \pm 0.104	0.202 \pm 0.077	0.355 \pm 0.197	0.24
Catecholamine From Kidney				
Noradrenaline (ng/dl)	2.15 \pm 0.17	2.26 \pm 0.04	0.67 \pm 0.26	<0.001
Adrenaline (ng/dl)	0.16 \pm 0.01	0.17 \pm 0.05	0.02 \pm 0.01	0.03

COSA: chronic obstructive sleep apnea; COSA-RDN: chronic obstructive sleep apnea with renal artery denervation; LV: left ventricle; RV: right ventricle.