Sex differences in rats with heart failure with preserved ejection fraction and the effect of autonomic modulation

Authors:
S. Stavrakis¹, K. Elkholey¹, L. Morris¹, Y. Li¹, S.S. Po¹, ¹University of Oklahoma Health Sciences Center - Oklahoma City - United States of America

Topic(s):
Experimental Heart Failure

Citation:
European Heart Journal (2019) 40 (Supplement), 2122

Background: Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for 50% of HF and sudden death is the leading cause of mortality. There are considerable sex differences in cardiac structure and function, which may be related to outcomes in HFpEF. Transcutaneous vagus nerve stimulation (tVNS) is antiarrhythmic.

Purpose: To describe sex differences in mortality, autonomic tone and ECG parameters in rats with HFpEF and examine the effect of tVNS on these outcomes.

Methods: Dahl salt sensitive (DS) rats of either sex were randomized into high salt (HS, 8% NaCl) or low salt (LS) diet (0.3% NaCl) at 7 weeks of age. After 6 weeks of LS or HS diets, HS rats were randomized to receive active or sham tVNS, 30min daily (20Hz, 3mA) for 4 weeks. The rats were monitored daily for 4 weeks for the development of HFpEF. ECG and echocardiogram were performed at 13 weeks (baseline) and 17 weeks (endpoint). Heart rate variability (HRV) was calculated at the respective time points. ECG and HRV parameters were analyzed in a blinded fashion. Logistic regression analysis was performed to identify independent predictors of mortality.

Results: A total of 58 rats were included (5 male LS, 6 female LS, 22 male HS and 25 female HS). HS rats developed significant hypertension and signs of HFpEF, while 24% of females and 53% of males died (P=0.004). There were 4 sudden cardiac deaths in males (with ventricular tachycardia documented in 1 rat), whereas all the females died of HF or stroke. Corrected QT (QTc) at baseline significantly prolonged in HS compared to LS rats (250.5±14.4ms vs. 226.8±13.9ms, respectively, p=0.0007), while all other ECG parameters did not differ significantly between groups. In HS rats, QTc prolongation was significantly more pronounced in males compared to females (259.4±20.6ms vs. 243.8±14.5ms, respectively, P=0.002). In univariate analysis, prolonged baseline QTc (OR=1.04; 95% CI 1.01–1.06, p=0.003) and male sex (OR=3.21, 95% CI 1.19–8.66, p=0.016) predicted mortality. However, in multivariate analysis, QTc was the only significant predictor of mortality (OR=1.04; 95% CI 1.01–1.06, p=0.003). After 4 weeks of treatment, active tVNS significantly decreased QTc compared to sham (244.6±13.8ms vs. 255.8±14.0ms, respectively, p=0.017) in both male and female rats in a similar manner. The low frequency to high frequency ratio (LF/HF) of HRV, which reflects sympathovagal balance, was significantly decreased in active tVNS rats compared to sham (0.21±0.13 vs. 0.54±0.14, respectively; p=0.001) in both male and female rats in a similar manner.

Conclusions: Male rats with HFpEF exhibit worse survival compared to females and are at higher risk for sudden death. QTc prolongation accounts for the increased risk of sudden death in males compared to females. Autonomic modulation with tVNS attenuates the unfavorable changes in QTc and HRV induced by HS diet and may be used to prevent ventricular arrhythmias in patients with HFpEF.