Low – Level Transcutaneous Vagus Nerve Stimulation Reverses Cardiac Dysfunction and Changes Left Ventricular Gene Expression in a Rat Model of Heart Failure With Preserved Ejection Fraction

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INTRODUCTION

- Heart failure (HF) currently affects an estimated 6.5 million adults in the United States, of which approximately 50% have HF with preserved ejection fraction (HFpEF).
- Despite normal or near normal left ventricular ejection fraction, HFpEF is associated with increased morbidity and mortality.
- The complex pathophysiology of HFpEF remains incompletely understood .
- Inflammation and left ventricular (LV) fibrosis play an important role in the development of HFpEF.
- We have previously shown that low level transcutaneous vagus nerve stimulation (LLTS) is antiarrhythmic and anti-inflammatory.

PURPOSE

- The goal of this study was to determine the effect of chronic intermittent LLTS on cardiac fibrosis, diastolic dysfunction, and left ventricular (LV) gene expression in a rat model of HFpEF.

METHODS

- Dahl salt-sensitive (DSS) 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 into 4 groups: HS active LLTS (n=50), HS sham LLTS (n=48), HS plus Olmesartan (n=14) and HS active LLTS plus Methyllycaconitine (MLA) (n=36), a specific blocker of the α7-nicotinic acetylcholine receptor (a7nAChR), which mediates the anti-inflammatory effects of LLTS.
- Stimulation was delivered for 30 min daily (20Hz, 3mA) for 4 weeks.
- Echocardiography was performed at 13 weeks (baseline) and 17 weeks (endpoint). At endpoint, LV histology and gene expression were examined.

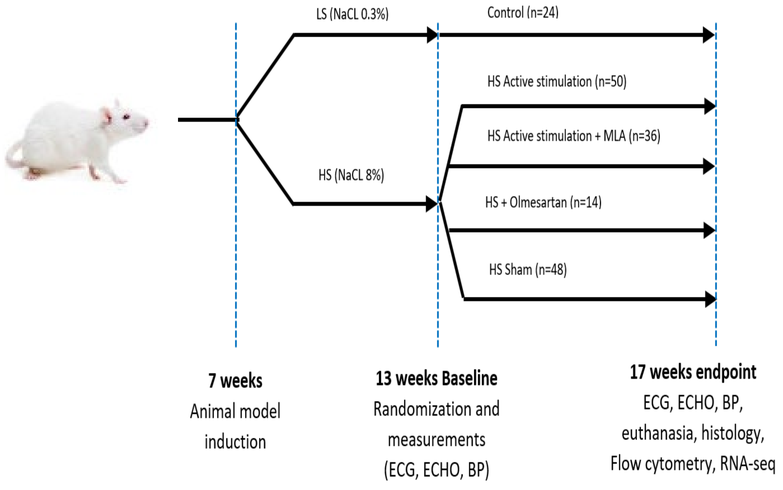

Figure 1. Study protocol.

RESULTS

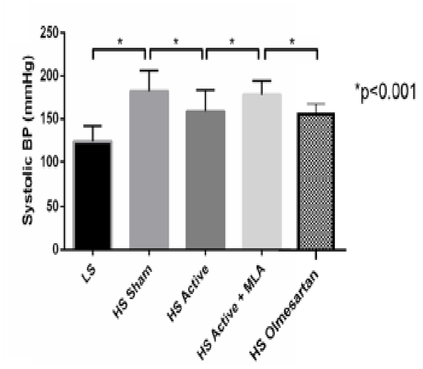

Figure 2. End point comparison of SBP measurements. The active stimulation group showed significant attenuation of BP elevation compared to HS active plus MLA and HS sham groups.

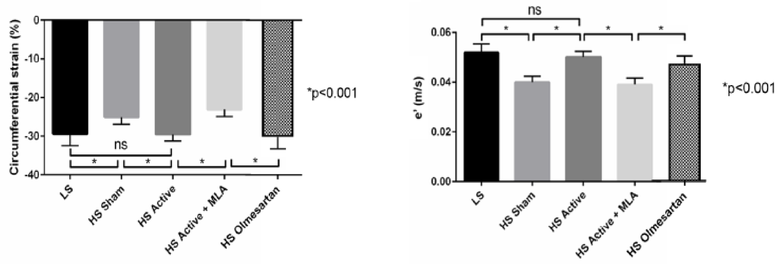

Figure 3. End point comparison of echocardiographic parameters. Left panel: Circumferential strain. Right panel: e'. Active stimulation resulted in a significant amelioration of echocardiographic parameters compared to HS sham and this effect was attenuated in the presence of MLA.

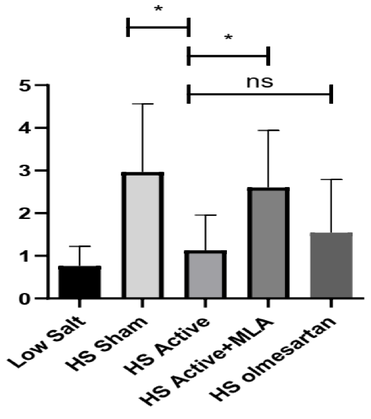

Figure 4. End point comparison of fibrosis measurements. The active stimulation group showed significant decrease in fibrosis compared to sham and this effect was attenuated in the presence of MLA.

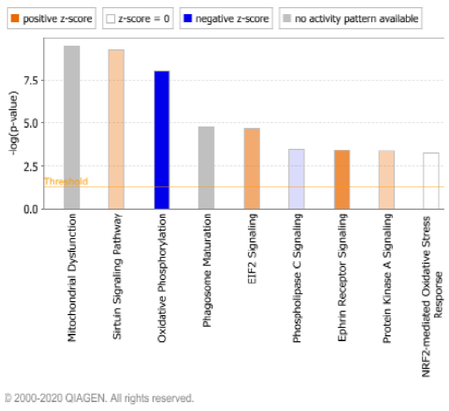

Figure 5. Effect of LLTS on myocardial gene expression – Ingenuity Pathway Analysis (IPA). LLTS significantly changed the expression of genes involved in mitochondrial dysfunction, sitruin signaling pathway and oxidative phosphorylation in comparison to HS sham.

RESULTS(cont.)

- HS rats developed significant hypertension and signs of HFpEF but there was no difference in LV ejection fraction and the heart rate among the groups.
- At endpoint systolic and diastolic blood pressure (BP) were elevated in the HS groups compared to LS group but the BP elevation was attenuated in the active LLTS group (compared to both LLTS sham and LLTS active plus MLA groups).
- Echocardiographic parameters, including e' and circumferential strain showed a similar amelioration in the presence of active LLTS compared to sham LLTS and this effect was attenuated in the presence of MLA.
- Left ventricular fibrosis was significantly decreased in active LLTS rats compared to sham LLTS rats. This effect was attenuated in the presence of MLA (suggesting that the anti-inflammatory effect of LLTS is necessary to prevent fibrosis in this model).
- RNA-seq analysis revealed that LLTS significantly changed the expression of genes involved in mitochondrial dysfunction, sitruin signaling pathway and oxidative phosphorylation.

CONCLUSIONS

- **Autonomic modulation with LLTS attenuates the unfavorable changes in and echocardiographic parameters and LV fibrosis induced by HS diet through its anti-inflammatory effects.**
- **The data support our hypothesis that inhibiting the anti-inflammatory effect of LLTS attenuates the antifibrotic effect.**
- **These results provide the basis for the examining the role of LLTS in patients with HFpEF.**
- **Further studies are required to examine the molecular mechanism of this difference**

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