

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:

- We examined the effects of chronic, intermittent LLTS on inflammation, fibrosis and diastolic dysfunction 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.
- The animals were monitored, for development of HFpEF, daily.
- After 6 weeks of LS or HS diets, HS rats were randomized into 3 groups: active LLTS (n=37), sham LLTS (n=38) and LLTS plus methyllycaconitine (MLA) (n=31), a specific blocker of the $\alpha 7$ -nicotinic acetylcholine receptor ($\alpha 7$ nAChR), which mediates the anti-inflammatory effects of LLTS.
- Stimulation was delivered for 30min daily (20Hz, 3mA) for 4 weeks
- ECG and echocardiogram were performed at 13 weeks (baseline) and 17 weeks (endpoint) and parameters were analyzed in a blinded fashion.

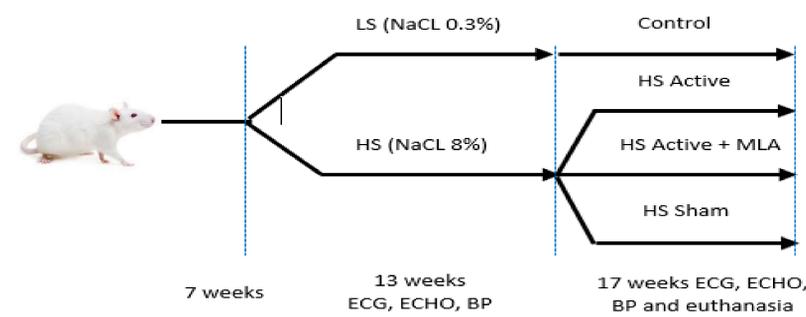


Figure (A). Study protocol

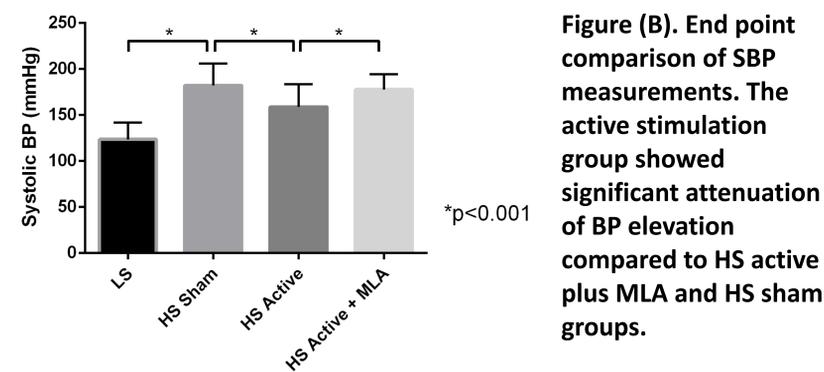


Figure (B). End point comparison of SBP measurements. The active stimulation group showed significant attenuation of BP elevation compared to HS active plus MLA and HS sham groups.

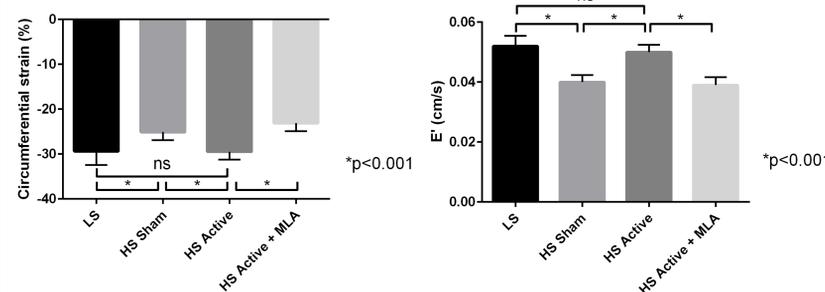


Figure (C). End point comparison of echocardiographic parameters. Left panel: Circumferential strain. Right panel: e'. Active stimulation resulted in a significant amelioration of echocardiographic parameters compared to HS sham and this effect was attenuated in the presence of MLA.

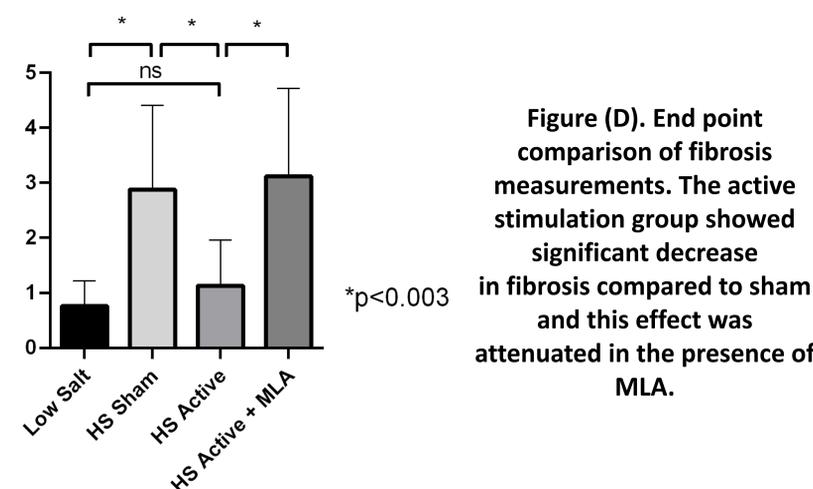


Figure (D). End point comparison of fibrosis measurements. The active stimulation group showed significant decrease in fibrosis compared to sham and this effect was attenuated in the presence of MLA.

Results:

- HS rats developed significant hypertension and signs of HFpEF but there was no difference in LV ejection fraction among the groups.
- 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.
- At endpoint systolic and diastolic blood pressure (BP) were elevated in the HS groups compared to LS group (133±25mmHg), but the BP elevation was attenuated in the active LLTS group (159±30mmHg), compared to both LLTS sham (177±24mmHg; p=0.003) and LLTS active plus MLA groups (171±29mmHg; p=0.01).
- 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 (1.1±0.8%) compared to sham LLTS rats (2.9±1.5%; p=0.001). This effect was attenuated in the presence of MLA (3.1±1.6%), suggesting that the anti-inflammatory effect of LLTS is necessary to prevent fibrosis in this model.

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