Transcutaneous Vagus nerve stimulation ameliorates the phenotype of heart failure with preserved ejection fraction through its anti-inflammatory effects

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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:

• 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 α7-nicotinic acetylcholine receptor (α7nAChR), 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.

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.

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