Transcutaneous vagus nerve stimulation restores the cardiac phenotype in heart failure with preserved ejection fraction by modulating the immune cell profile

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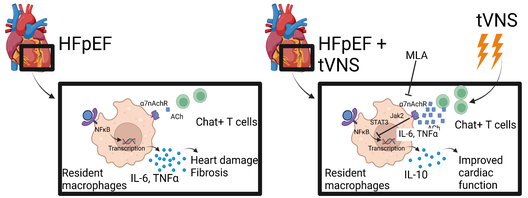
INTRODUCTION/ HYPOTHESIS

- A proinflammatory state plays a central role in heart failure with preserved ejection fraction (HFpEF) but the role of specific immune cells remains unclear.
- Transcutaneous vagus nerve stimulation (tVNS) modulates immune responses via the cholinergic anti-inflammatory pathway, which involves acetylcholine-dependent activation of α7 nicotinic acetylcholine receptors (α7nAchR) on macrophages.
- tVNS reverses the HFpEF phenotype by reducing resident macrophage number and pro-inflammatory cytokine production in an acetylcholine-α7nAchR-dependent manner (Figure 1).

Figure 1 . Conceptual framework of our work



METHODS

- We induced HFpEF in male C57BL/6 CCR2-RFP mice with nitric oxide synthase blocker (L-NAME) and a high-fat diet for 5 weeks.
- C57BL/6 CCR2-RFP mice fed with standard chow diet served as controls (n=7).
- We randomized the mice to sham, or tVNS with or without the α7nAchR inhibitor methyllycaconitine (MLA) (n=6 in each group) for 4 weeks, followed by euthanasia (Figure 2).
- Cardiac macrophages were analyzed using flow cytometry.
- Resident macrophages were further subdivided based on MHC2 and CCR2 expression (Figure 3).

Figure 2. Schematic representation of the experimental design.

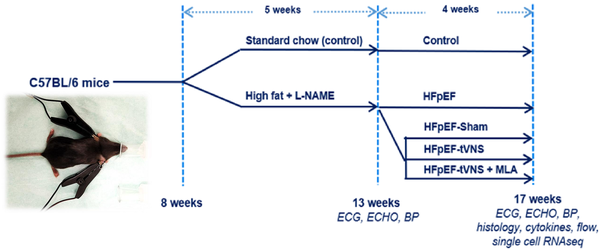
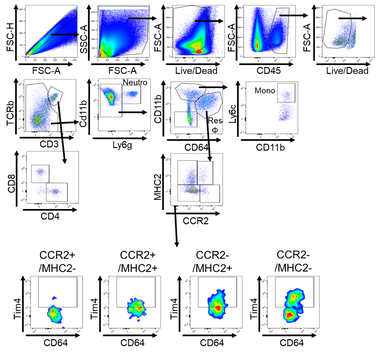


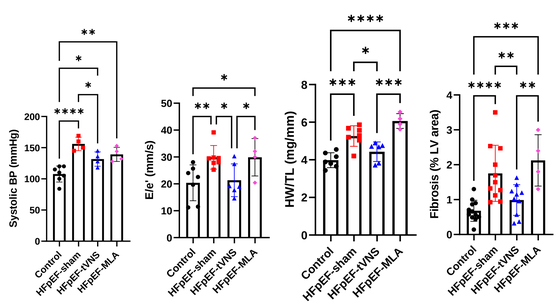
Figure 3. Flow cytometry gating strategy

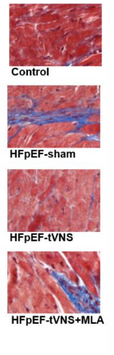


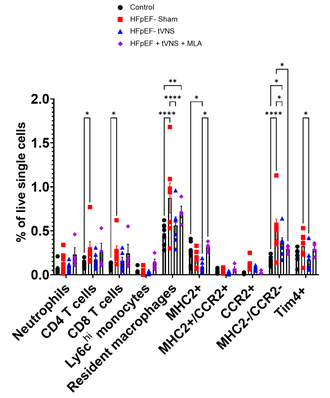
RESULTS

- HFpEF mice exposed to sham developed hypertension, diastolic dysfunction, increased heart weight normalized to tibia length, and left ventricular fibrosis compared to the control mice, while tVNS restored these parameters towards the control values.
- MLA partially reversed the protective effect of tVNS in these parameters (Figure 4).

Figure 4. tVNS improves cardiac and immune cell phenotype in HFpEF mice







- Flow cytometry data revealed a significant increase in resident macrophages in HFpEF sham compared to control hearts, mainly driven by the MHC-/CCR2- subtype.
- Notably, tVNS restored the numbers of resident macrophages to the control levels, while MLA partially attenuated this effect (Figure 4).

CONCLUSIONS

- tVNS improves the cardiac phenotype in HFpEF mice by modulating cardiac resident macrophages, in an acetylcholine-α7nAchR-dependent manner.