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## **Messages from the auricle - limiting progression of heart failure with preserved ejection fraction through transcutaneous nerve stimulation of nerves in the external ear**

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Heart failure is a common syndrome, affecting 2% of adults (up to 10% of people over the age of 65 years; >1 million people in the UK and around 5.7 million adults in the USA). Despite optimal therapy, annual mortality is ~7%. Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of all heart failure patients and outcomes are poor as no treatment has been shown to decrease morbidity and mortality. Effective treatments are therefore urgently required. Now, Stavrakis et al. (2018) provide evidence that a simple, non-invasive and inexpensive neuromodulatory procedure can ameliorate the development of HFpEF in a rat model.

To establish a model of HFpEF, 7 week old Dahl sensitive rats were fed high salt (4% NaCl) diet for 6 weeks, and cardiovascular function in these rats compared with those maintained on a low salt diet. High, but not low, salt diet resulted in increased blood pressure, left ventricular hypertrophy and deterioration in diastolic function. Whilst animals did not develop heart failure per se, symptoms mimicked early stage of HFpEF in humans. Potential explanations for the observed deteriorations were revealed when the authors detected increased infiltration of inflammatory cells and expression of genes encoding inflammatory cytokines in the left ventricle in the high salt diet rats.

Strikingly, in this study the detrimental changes in cardiac function, inflammation and gene expression in the high salt fed rats were ameliorated by low-level transcutaneous stimulation of the concha of the external ear (LLTS). This important finding builds on previous reports that mild electrical stimulation of the external auricle influences the cardiovascular system and can ameliorate disease in both humans and animal models. For example, electroacupuncture in the auricular concha reduced symptoms in patients with coronary artery disease, possibly by reducing sympathetic nerve output to the heart and vessels (Zamotrinsky et al., 2001). Support for a sympatholytic action was obtained when stimulation at the tragus reduced sympathetic nerve activity in humans (Clancy et al., 2014). Since HF is accompanied by an increase in sympathetic nerve activity, reducing it via LLTS may be one approach to further examine for mechanistic understanding.

Another potential explanation may lie in the observation in this current study that gene expression of inflammatory cytokines was reduced in the left ventricle of LLTS treated rats. The current hypothesis is that such anti-inflammatory actions are mediated by stimulation of the vagus nerve (Borovikova et al., 2000). Furthermore, in rats challenged with a septic stimulus, auricular stimulation suppressed serum TNF- $\alpha$ , interleukin-1 $\alpha$  and interleukin-6 (Zhao et al., 2012). Indeed, the authors of the current study have shown previously that LLTS inhibits production of TNF- $\alpha$  in patients with atrial fibrillation (Stavrakis et al., 2015). Auricular stimulation therefore appears to be a promising approach for anti-inflammatory interventions at least associated with cardiovascular diseases but potentially with other conditions that show inflammation.

What could the future hold for auricular stimulation as a treatment for HFpEF, and indeed other diseases? Since disease progression markers in the LLTS treated high salt-fed rats were still higher than those in control animals, an obvious question is whether more than 30 mins per day stimulation could have a greater effect. Other questions include whether the stimulation parameters were optimal – most studies stimulating the external auricle use similar parameters, but these seem to have been arrived at empirically. Another major discussion that has recently arisen is to ask what is actually being stimulated? Effects on sympathetic activity and/or inflammatory cytokines have been reported from stimulating the concha, cymba concha and the tragus. Since all of these sites in the external auricle apparently receive innervation from a sensory branch of the vagus nerve, effects of stimulation are often cited to be initiated by activation of this vagal branch (Deuchars et al., 2018). However, since this assumption relies on a single human cadaveric study, it has recently been questioned (Badran et al., 2018). In the current study, this was addressed by a sham arm in which stimulation of the auricular margin did not provide the same protection as concha stimulation. A greater understanding of what is actually being stimulated and the pathways underlying the effects may therefore enhance future studies. Finally, notwithstanding uncertainty in what is being stimulated, auricular stimulation (also referred to as LLTS as here or as transcutaneous vagal nerve stimulation) is undergoing intense investigation with promise as an accessible and inexpensive treatment for disorders as diverse as chronic pain, epilepsy, anxiety and tinnitus.

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