Noninvasive Neuromodulation Via Tragal Stimulation
Time to Lend an Ear?*
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The tight link between the cardiac autonomic nervous system and arrhythmogenesis is well established (1). After cardiac injury, remodeling occurs at various nexus points in the cardiac neural hierarchy (2–5). The degree of remodeling at these centers demonstrated in animal models and in humans with ischemic and nonischemic cardiomyopathy underscores the potential that neuromodulatory therapies hold for treating arrhythmias, and preserving cardiac function.

Currently, clinical therapies (existing or under study) that modulate cardiac autonomic function after cardiac injury include pharmacological agents (beta-blockers and renin-angiotensin-aldosterone antagonists), bilateral cardiac sympathetic (6,7) and renal denervation (8), and electrical stimulators of the vagus nerve (VN) and spinal cord. Arrhythmias develop in many patients while on pharmacotherapy, in part because these agents only modulate a few of the neurotransmitters used by the cardiac autonomic nervous system (for example, neuropeptide Y and galanin are unmitigated) (9). Bilateral cardiac sympathetic denervation and renal denervation require invasive procedures, as do electrical stimulators for the VN or spinal cord. In addition, a poorly understood concept is that VN stimulation (VNS) activates both efferent and afferent fibers, and the latter can actually result in withdrawal of central parasympathetic drive to the heart, an unintended effect (10). Whether beneficial effects of VNS are seen depend critically on the balance between afferent and efferent activation, determined by stimulation parameters (10).

Transcutaneous electrical stimulation of the auricular branch of the VN, also known as tragus or tragal stimulation, holds promise as a noninvasive method of VNS. This branch is accessed at the tragus (the anterior protuberance of the outer ear), a region known to be rich in nerve fibers positive for acetylcholinesterase (11). These fibers mainly project to the nucleus tractus solitarius (NTS), as do most visceral afferent fibers (12,13).

Thus far, tragus stimulation has largely been explored in atrial fibrillation (AF). Low-level tragus stimulation (LL-TS) reversed acute atrial remodeling induced by rapid atrial pacing (i.e., shortening of atrial end-refractory period [AERP] and increased AERP dispersion) (11). Others demonstrated that LL-TS inhibited stellate ganglion (SG) neural activity and reduced sinus node heart rate acceleration during sympathetic stimulation (14). LL-TS was also shown to prolong AF cycle length and reduce AF duration, in part by preventing connexin down-regulation (15,16). In humans, LL-TS acutely increased AERP and decreased AF induction, duration, and inflammatory cytokine levels (17). Similar to low-level VNS (18), LL-TS reduces sympathetic tone in humans, as indicated by heart rate variability and muscle sympathetic nerve activity (19).

In a canine myocardial infarction (MI) model, 90 days of intermittent LL-TS reduced infarct size and interstitial fibrosis, down-regulated profibrotic proteins, and attenuated the impairment of cardiac function (20). However, whether LL-TS had any
impact on neural remodeling in MI model was not well understood.

In this issue of *JACC: Clinical Electrophysiology*, Yu et al. (21) report on the mitigation of adverse neural remodeling after MI by LL-TS. In a canine MI model, 2 months of daily LL-TS (2 h) suppressed left stellate ganglion (LSG) activity, decreased intraganglionic nerve sprouting, down-regulated protein levels of nerve growth factor and up-regulated neuronal small conductance calcium-activated potassium channel type 2. It also decreased arrhythmogenesis with a flattening of the restitution curve slope. These findings are similar to VNS effects (22,23). This work is novel in its demonstration that LL-TS reduces SG neuronal activity (along with sprouting and synaptic density) in this post-MI model. It is unclear whether the entire population or a subset of SG neurons or nerve fibers (efferent post-ganglionic, afferent, or local circuit neurons) demonstrates this decrease.

Although LL-TS shows promise for clinical use, a number of points should be carefully considered. First, pharmacological therapies now established to be the standard of care for MI were not used in this study. The efficacy of LL-TS may therefore be less in a clinical setting if implemented as an adjunctive measure. Further, the long-term efficacy of LL-TS is not well understood; whether there is tachyphylaxis and its effects can be eliminated by bilateral vagal transection (11). Retrograde tracer and functional magnetic resonance studies suggest that the NTS is activated by LL-TS. The downstream effects of this activation are, however, not well understood. From the NTS, there are projections to cortical and subcortical areas (including the hypothalamus and preganglionic efferent parasympathetic and sympathetic neurons in the brainstem and spinal cord) and to other medullary centers involved in integrating sensory afferent information from the viscera to regulate cardiovascular function and reflexes (24). LL-TS has been shown to decrease sympathetic tone. The mechanisms are not understood, but presumably involve withdrawal of central sympathetic and/or enhanced central parasympathetic drive. As discussed previously, VNS activates afferent and efferent fibers, with complex stimulation-dependent effects. LL-TS may avoid the adverse effects seen with VNS, induced by the potentially conflicting effects of simultaneous afferent and efferent vagal activation. VNS also concomitantly activates sympathetic fibers running along or within the VN itself.

LL-TS is an attractive form of neuromodulation because it could be implemented with ease and flexibility. It could be used during and after MI to prevent remodeling or arrhythmias, as early as when emergency personnel diagnose acute MI in the field, to post-discharge therapy along with pharmacological agents. It may also acutely increase coronary blood flow and reduce angina.

In summary, LL-TS is promising but needs further careful investigation in long-term studies in conscious humans to determine feasibility, tolerance, and efficacy. More importantly, it is crucial to tease out the central pathways affected by LL-TS to better understand mechanisms of action and to minimize risk and loss of efficacy in the long term. As such, much remains to be learned before LL-TS can be declared a therapeutic strategy in humans.

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