

Non-invasive Low-level Tragus Stimulation in Cardiovascular Diseases

Yunqiu Jiang,¹ Sunny S Po,² Faris Amil³ and Tarun W Dasari²

1. Cardiac Arrhythmias Section, Heart Center, Beijing Chao-yang Hospital, Capital Medical University, Beijing, China; 2. Cardiovascular Section, Department of Internal Medicine, Heart Rhythm Institute, University of Oklahoma Health Sciences Center, Oklahoma City, OK, US; 3. College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, US

Abstract

Low-level tragus stimulation (LLTS) is a non-invasive approach of transcutaneous vagus nerve stimulation. LLTS has applications in diseases of multiple systems, including epilepsy, depression, headache and potentially several cardiovascular diseases. LLTS has shown promising results in suppressing AF, alleviating post-MI ventricular arrhythmias and ischaemia-reperfusion injury along with improving diastolic parameters in heart failure with preserved left ventricular ejection fraction (HFpEF). Preliminary pilot clinical studies in patients with paroxysmal AF, HFpEF, heart failure with reduced ejection fraction and acute MI have demonstrated promising results. The beneficial effects are likely secondary to favourable alteration of the sympathovagal imbalance. On-going exploratory work focused on underlying mechanisms of LLTS in cardiovascular disease states and larger scale clinical trials will shed more light on the non-invasive modulation of the neuro-immune axis.

Keywords

Arrhythmia, autonomic nervous system, neuromodulation, tragus

Disclosure: SSP is on the *Arrhythmia & Electrophysiology Review* editorial board; this did not influence peer review. All other authors have no conflicts of interest to declare. **Received:** 12 January 2020 **Accepted:** 2 March 2020 **Citation:** *Arrhythmia & Electrophysiology Review* 2020;9(1):40–6.

DOI: <https://doi.org/10.15420/aer.2020.01>

Correspondence: Tarun W Dasari, Cardiovascular Section, Department of Medicine, 800 SL Young Blvd, COM 5400, University of Oklahoma HSC, Oklahoma City, OK 73104, US. E: tarun-dasari@ouhsc.edu

Open Access: This work is open access under the CC-BY-NC 4.0 License which allows users to copy, redistribute and make derivative works for non-commercial purposes, provided the original work is cited correctly.

Imbalance of the autonomic nervous system (sympathetic/parasympathetic) is known to contribute to the pathophysiology of multiple cardiovascular diseases, including AF, MI (and related ventricular arrhythmias) and heart failure. The concept of neuro-immune axis has been proposed to tightly integrate the brain–heart–periphery axis, which is characterised by various pathways of the anti-inflammatory properties of the vagus nerve.^{1,2} For instance, immune responses can activate the hypothalamic–pituitary–adrenal axis through the vagal afferents and the cholinergic anti-inflammatory pathway through the vago-parasympathetic and sympathetic reflexes.³

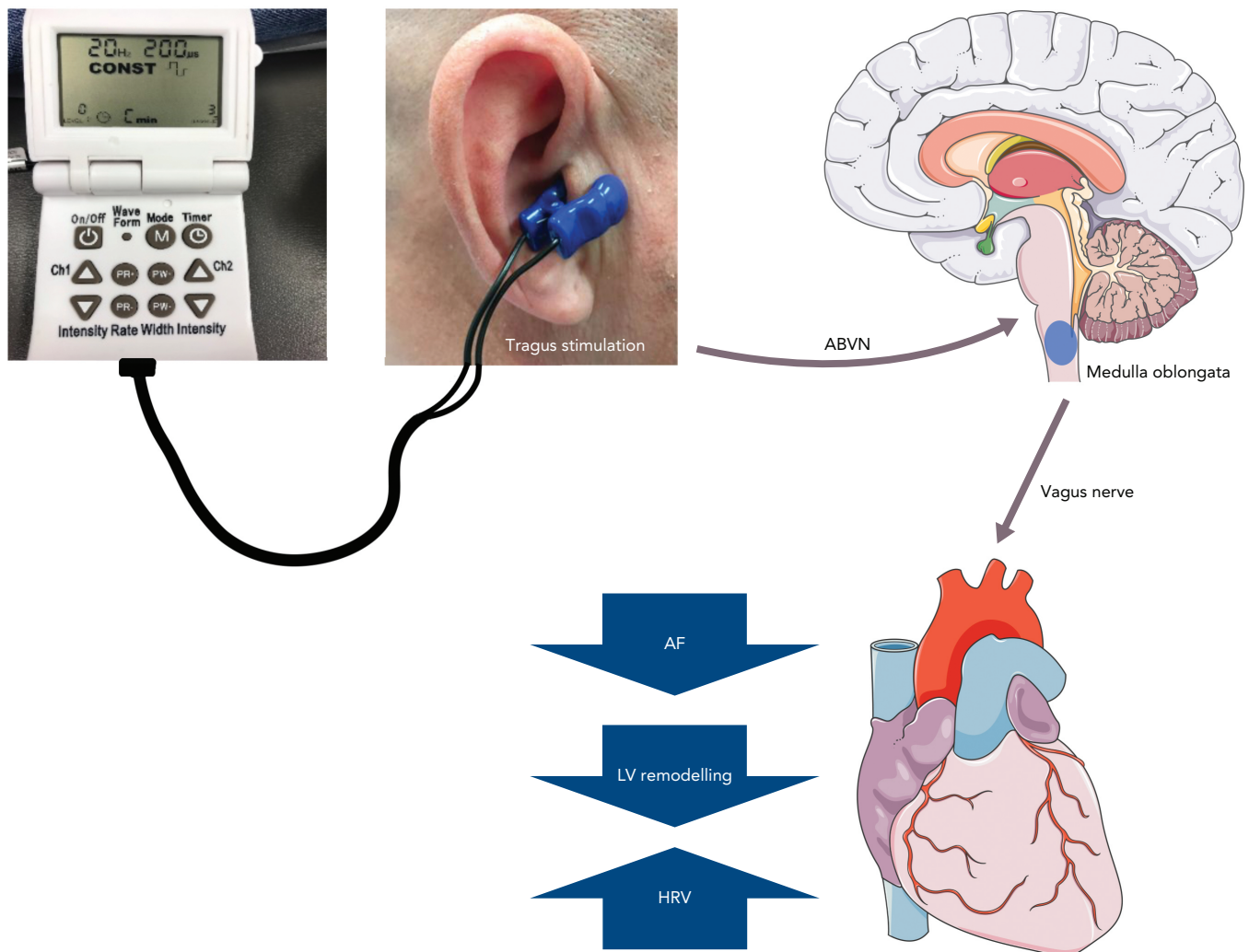
Modulating this neuro-immune axis could play a key role in the alleviation of several cardiovascular diseases. Several modalities have been developed to modulate this axis and restore a favourable balance between the sympathetic and parasympathetic system. A few examples of this include direct vagus nerve stimulation (VNS), baroreceptor stimulation, renal artery sympathetic denervation, low-level tragus stimulation (LLTS), cardiac sympathetic denervation and spinal cord stimulation.⁴ Among them, direct cervical VNS has been used in multiple diseases, including epilepsy, drug-resistant depression, migraine, angina pectoris, hypertension and impaired upper limb function after stroke.^{5–11} In patients with heart failure with reduced ejection fraction (HFrEF), three major clinical trials of direct VNS have yielded mixed results.^{12–14} One of the major drawbacks of cervical vagus stimulation is the invasive nature of this treatment with inherent surgical complications and poor patient tolerance.¹⁵

Designed to stimulate the auricular branch of the vagus nerve (ABVN), LLTS is a non-invasive transcutaneous technique of VNS that can modulate the autonomic function (*Figure 1*).¹⁶ The aim of this current review is to summarise the evidence to date pertaining to the use of LLTS in various cardiovascular disease states.

The Anatomical and Physiological Basis of Low-level Tragus Stimulation

Twenty per cent of the vagus nerve fibres are efferent fibres originating from the brainstem, providing parasympathetic control of the viscera, peripheral vasculature and heart. The remaining 80% of the nerve fibres are afferent fibres that relay sensory information from the periphery to the central nervous system. The afferent fibres distribute widely in the heart, lungs, liver, adrenal medulla and the gastrointestinal tract up to the splenic flexure of the colon.¹⁷ The vagus nerve contains three fibre types: highly myelinated A fibres, which have low activation thresholds; lightly myelinated B fibres; and unmyelinated C fibres, which have high activation thresholds.^{18,19} The ABVN is the cutaneous branch of the vagus nerve which innervates the antihelix, tragus and cavity of the concha.²⁰ The innervation of the auricle is shown in *Figure 2*. Currently, how the external auricle is innervated remains controversial. In an anatomical study, ABVN was able to be observed in 94% of cases (17/18). All of the ABVN were observed to distribute to the external acoustic meatus and auricle. Cutaneous branches from the facial nerve were observed to innervate the external acoustic meatus as well.²¹ The nerve branches around the auricle and the acoustic meatus have

Figure 1: Low-level Tragus Stimulation

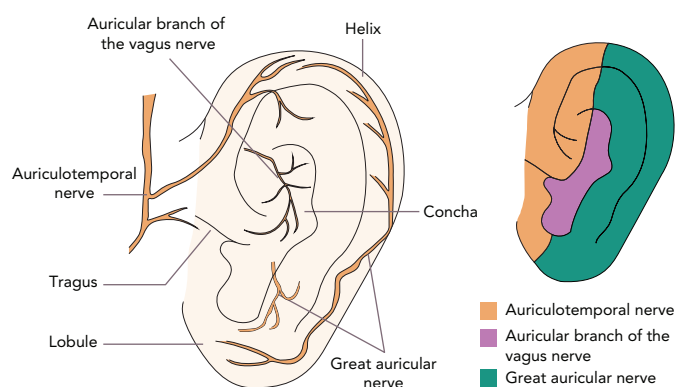


Electric impulses delivered to the tragus stimulate the auricular branch of the vagus nerve (afferent fibres). The excitation then enters the medulla oblongata at the brain stem, which excites the vagus efferent fibres to modulate cardiac function. Low-level tragus stimulation is reported to reduce AF burden, alleviate LV remodelling after MI and increase HRV. ABVN = auricular branch of the vagus nerve; HRV = heart rate variability; LV = left ventricular.

various complex communications before reaching the central nervous system. Nevertheless, ample evidence indicates that the ABVN remains the most important innervation of the external auricle and the cymba conchae.²²

Brain activation patterns, based on functional MRI (fMRI) during LLTS, were associated with greater activation of the vagal centres (dorsal vagal complex) throughout cortical, subcortical and cerebellar brain regions compared to sham stimulation.²³ In one of the most cited anatomical studies, 14 ears from seven cadavers were examined. A total of 45% of the ears were shown to be innervated by the great auricular nerve (GAN), 9% by the auriculotemporal nerve (ATN) and 46% were innervated by both the GAN and ATN. However, there has been some debate on the optimal site of transcutaneous VNS (tVNS). An fMRI study recently showed that stimulation at the cymba conchae had a greater effect on the vagal pathways and the dorsal vagal complex compared to three other locations: the inner surface of the tragus, the posterior-inferior wall of the external acoustic meatus and the earlobe.²³ A recent study used the triangular fossa innervated by the GAN as the stimulation site, because it allowed stimulation for a longer period of time without interfering with

Figure 2: Innervation of the Auricular Skin



The anterior auricular branches of the auriculotemporal nerve innervates the skin overlying the tragus, as well as the adjacent part of the helix. The auricular branch of the vagus nerve innervates the ear canal, tragus and part of the auricle. The great auricular nerve innervates the skin of the lateral auricle and the skin over both the parotid gland and mastoid process. Source: Roberts 2017.²⁸ Reproduced with permission from Elsevier.

patient comfort, daily hygiene requirements and sleep. Most importantly, it is located proximal to the antihelix and the concha,

Table 1: Summary of Preclinical Tragus Stimulation Studies

Publication	Subjects	n	Stimulation Parameters							Outcome
			Frequency (Hz)	Pulse Width (ms)	Amplitude	On and Off Cycle	Side	Duration	Chronic/ Acute	
Wang et al. 2014 ⁵⁹	MI dogs	30	20	1	80% below the heart rate slowing threshold	Yes, 5 s on and 5 s off	Bi	4 h	Daily, 90 days	Attenuated LV remodelling in dogs with healed MI
Wang et al. 2015 ²⁶	MI dogs	22	20	1	80% below the heart rate slowing threshold	Yes, 5 s on and 5 s off	Bi	4 h	Daily, 6 weeks	Improved cardiac function and attenuated cardiac remodelling in late stages after MI
Yu et al. 2016 ²⁷	MI dogs	22	20	1	80% below the heart rate slowing threshold	Yes, 5 s on and 5 s off	R	2 h	Daily, 2 months	Reduced ventricular arrhythmia inducibility, LSG neural activity and sympathetic neural remodelling
Nasi-Er et al. 2019 ⁴¹	MI dogs	12	20	1	50% below the heart rate slowing threshold	No	Bi	1 h	Every other day, 4 weeks	Reduced spontaneous ventricular arrhythmias, increased ventricular electrical stability and alleviated ventricular interstitial fibrosis
Yu et al. 2017 ³⁸	OSA dogs	18	20	1	80% below the heart rate slowing threshold	Yes, 5 s on and 5 s off	Left	1 h	Acute	LLTS suppressed shortening of atrial refractoriness and autonomic remodelling
Chen et al. 2015 ²⁸	AF dogs	32	20	1	80% below the heart rate slowing threshold	No	Left	9 h	Acute	Left-sided LLTS exerts anti-AF effects as effectively as right-sided LLTS
Yu et al. 2013 ³⁷	AF dogs	16	20	1	80% below the heart rate slowing threshold	No	Right	3 h	Acute	LLTS reversed RAP-induced atrial remodelling and inhibited AF inducibility
Zhou et al. 2019 ²⁵	HFpEF rats	48	20	0.2	2 mA	No	Bi	30 min	Daily, 4 weeks	Chronic intermittent LLTS ameliorated diastolic dysfunction, and attenuated cardiac inflammation and fibrosis
Zhou et al. 2016 ⁶⁰	IST dogs	16	20	2	80% below the heart rate slowing threshold	No	Right	3 h	Acute	LLTS suppressed RSG activity and inhibited sympathetically induced sinus node acceleration

Bi = bilateral; HFpEF = heart failure with preserved ejection fraction; IST = inappropriate sinus tachycardia; LLTS = low-level tragus stimulation; LSG = left satellite ganglion; LV = left ventricular; OSA = obstructive sleep apnoea; R = right; RAP = rapid atrial pacing; RSG = right stellate ganglion.

which are innervated by the ABVN in 73% and 100%, respectively.²⁴ Stimulating the effective triangular fossa was effective in suppressing postoperative AF in this study.

Parameters of Low-level Tragus Stimulation

Currently, optimal settings of LLTS remain undetermined. Parameters of LLTS for both preclinical and clinical studies have generally been empirical (Tables 1 and 2). In a rat model of heart failure with preserved ejection fraction (HFpEF), LLTS below the threshold of heart rate reduction was applied by placing two oppositely charged magnetic electrodes over the auricular concha region at 20 Hz frequency, 0.2 ms pulse duration and 2 mA amplitude.²⁵ In a rat MI model, LLTS at 20 Hz, 1 ms pulse wide and 80% below the threshold of slowing the sinus heart rate was used.²⁶ The same settings were extended to a canine model of post-infarction ventricular arrhythmia.²⁷ The majority of LLTS studies were right-sided, while one canine model study demonstrated that left-sided LLTS is also effective in suppressing AF.²⁸

In a clinical study in patients with ST-segment elevation MI (STEMI), LLTS was set at 20 Hz, 1 ms pulse wide and 50% below the heart rate-slowing threshold with a duty cycle of 5 seconds on and 5 seconds off.²⁹ The same parameters were used in an AF suppression study, but in a continuous manner without the on-and-off cycle.³⁰ To test if LLTS has a parameter-specific effect on heart rate, an exploratory study compared nine combinations of stimulating parameters (pulse width: 100 µs, 200 µs, 500 µs; frequency: 1 Hz, 10 Hz, 25 Hz) among 15 healthy volunteers.³¹ Essentially, the setting of 500 µs and 10 Hz had the strongest effect on heart rate reduction (-2.40 ± 0.275 BPM) during the 60 seconds of stimulation. Recently, a large clinical trial using VNS in patients with HFpEF failed to show a beneficial effect while another trial in patients with HFpEF using different stimulation parameters demonstrated efficacy, highlighting the importance of optimising stimulation parameters.^{13,32} Mechanistic studies have suggested that the optimal stimulation parameters for VNS are at the point at which the afferent and efferent fibres are activated in a well-balanced manner, i.e. the

Table 2: Summary of Human Tragus Stimulation Studies

Publication	Subjects	n	Stimulation Parameters						Follow-up period	Outcome	
			Frequency (Hz)	Pulse Width (ms)	Amplitude	On and Off Cycle	Side	Duration			Chronic/Acute
Stavarakis et al. 2015 ³⁰	Paroxysmal AF	40	20	1	50% below the heart rate slowing threshold	No	Right	1 h	Acute	None	Suppressed AF and decreased inflammatory cytokines in patients with paroxysmal AF
Tran et al. 2018 ⁴⁷	HFpEF	24	20	0.2	1 mA below uncomfortable threshold	No	Right	1 h	Acute	None	LLTS acutely ameliorated LV longitudinal mechanics and improved HRV
Dasari et al. 2018 ⁴⁸	HFREF	20	20	0.2	5–40mA	No	Right	1 h	Acute	None	Beneficial effect on micro-circulation and endothelial function
Yu et al. 2017 ²⁹	STEMI	95	20	1	50% below the heart rate slowing threshold	Yes, 5 s on and 5 s off	Right	2 h	Acute	7 days	Reduced myocardial ischaemia-reperfusion injury in patients with STEMI
Bretherton et al. 2019 ⁵⁰	Age ≥55 years	Study 1: 14	30	0.2	Just below the threshold of causing discomfort	No	NS	15 min	Acute	None	TS increased vagal tone and was associated with greater increases in baroreflex sensitivity
		Study 2: 51							Acute	None	
		Study 3: 29							Chronic, daily for 2 weeks	2 weeks	

HFpEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction; HRV = heart rate variability; LLTS = low-level tragus stimulation; LV = left ventricular; NS = not specified; STEMI = ST-segment elevation MI.

afferent-driven decreases in central parasympathetic drive are counteracted by direct activation of the cardiac parasympathetic efferent projections to the intrinsic cardiac autonomic nervous system, resulting in a relatively neutral heart rate response.³³ Consistent with this notion, a recent study of LLTS (30 Hz, 10–50 mA, 200 ms, which was slightly below the sensory threshold) in healthy volunteers showed a significant decrease in muscle sympathetic nerve activity (MSNA) without a change in heart rate.³⁴ Recently, the works by Sclocco et al. suggested that tVNS is headed toward a more refined and sophisticated direction.^{35,36} Through respiratory gating and EEG-informed fMRI, the efficacy and accuracy of this therapy can be further improved.

Results in Animal Models

AF

It has been established that the abnormal regulation of the cardiac autonomic nervous system contributes to the initiation and perpetuation of AF. High sympathetic/vagal tone contribute to the substrate of AF while sudden changes in autonomic balance lead to AF episodes. Theoretically, suppressing either the sympathetic or parasympathetic tone could have a moderating effect on AF. There have been at least two animal models testing the acute effect of LLTS. For example, in a canine AF model, right sided LLTS reduced AF inducibility and reversed acute atrial electrical remodelling. Its anti-remodelling effect was indicated by a prolonged effective refractory period and a narrowed window of vulnerability (to measure the difficulty of AF induction).³⁷ In a canine model of obstructive sleep apnoea, LLTS suppressed shortening of atrial refractoriness and autonomic

remodelling caused by obstructive sleep apnoea, thus reducing the vulnerability to AF.³⁸

Post MI

The close relationship between ventricular arrhythmias after MI and sympathetic activation is well recognised.^{39,40} Suppressing the sympathetic tone and increasing the parasympathetic tone protected against post-MI ventricular arrhythmias.

In a canine MI model, right-sided LLTS performed 2 hours a day for 2 months reduced left stellate ganglion activity in both frequency and amplitude.²⁷ Both of these parameters of neural activity were significantly lower in the MI plus LLTS group than the MI group alone. Ventricular arrhythmias inducibility evaluated by ventricular programmed stimulation was also suppressed by LLTS. Besides electrical remodelling, in a canine model intermittent bilateral LLTS for 4 weeks alleviated left ventricular remodelling by reducing ventricular interstitial fibrosis post MI.⁴¹ In another post-MI canine model, 6 weeks of bilateral LLTS (20 Hz, 1 ms pulse wide, 80% below the sinus slowing threshold) for 4 hours per day reduced left ventricle dilation and infarct size, improved both left ventricular contractility and diastolic function and alleviated myocardial fibrosis.²⁶

Heart Failure with Preserved Ejection Fraction

HFpEF, another clinical syndrome associated with dysregulation of the autonomic nervous system and inflammation, comprises approximately 50% of all patients with heart failure.⁴² Patients with

HFpEF have been shown to have increases in plasma renin activity and arginine vasopressin compared with healthy controls.⁴³ In a rat model of HFpEF (Dahl salt-sensitive rats), LLTS (20 Hz, 2 mA, 0.2 ms) attenuated the elevation of both systolic and diastolic blood pressure. Echocardiography revealed that LLTS improved left ventricular hypertrophy, circumferential strain and diastolic function as measured by E/A ratio and E/e' ratio.²⁵ Histological studies showed that LLTS attenuated ventricular inflammatory cell infiltration and fibrosis. Downregulation of the pro-inflammatory and pro-fibrotic genes (interleukin [IL]-11, IL18, IL23-A and osteopontin) was seen in the LLTS group as well.²⁵

Mechanisms of Low-level Tragus Stimulation

Tragus stimulation exerts its modulating effects through an integrated nervous reflex system. The ABVN is the afferent nerve fibre while the medulla oblongata (nuclei including NTS, nucleus of the solitary tract; NSNT, nucleus spinalis of the trigeminal nerve; NA, nucleus ambiguus; DMN, dorsal motor nucleus) function as the reflex centre.⁴⁴ The efferent vagus nerve then arrives at the ganglionated plexi within the epicardial fat pads to achieve the related physiological effects. Though the neuropathway of tVNS is grossly understood, the exact mechanisms underlying the various beneficial effects of LLTS are still poorly understood. The inherent sympathovagal imbalance is different in various cardiovascular states. Modulation of this tone may have variable beneficial effects and is likely directly related to the underlying pathophysiology. For example, even in heart failure, acute and chronic states exhibit a wide spectrum of sympathovagal imbalance and there are likely differential effects of non-invasive vagal modulation. In common cardiovascular disease states, vagal stimulation probably suppress arrhythmias, ischaemia and heart failure through different mechanisms. Up-regulation of c-fos (a proto-oncogene expressed within some neurons following depolarisation) and nerve growth factor (NGF) expression in left superior ganglionated plexus and the left stellate ganglion is found to contribute to autonomic remodelling of AF. LLTS suppressed AF by down-regulating both c-fos and NGF.³⁸ Connexins (Cx) are an essential component of gap junctions and a key player in the formation of AF substrate. LLTS has been shown to suppress AF by preventing the loss of atrial Cxs (Cx40 and Cx43).²⁸

At the cardiac remodelling and fibrosis level, downregulation of matrix metalloproteinase 9 and transforming growth factor-beta 1 was observed in LLTS treated post-MI dogs.²⁶ Small conductance calcium-activated potassium channel type 2 (SK2) is an ion channel molecule responsible for after-hyperpolarisation that suppresses nerve discharges that are crucial to regulating neuronal excitability. In a canine MI model, LLTS down-regulated the NGF protein and up-regulated the SK2 protein.²⁷ These studies indicate that LLTS affects the pathophysiological progress on multiple levels – from neural remodelling to myocardial remodelling.

Human Studies

AF

Reports of tragus stimulation on human subjects are still limited. LLTS for 1 hour during ablation procedures reduced the duration of induced AF, while levels of inflammatory markers (circulatory tumour necrosis factor [TNF] alpha and C-reactive protein) were reduced.³⁰ In patients with paroxysmal AF who received chronic LLTS for 1 h/day for 6 months, there was a 85% decrease in AF burden in the active stimulation group compared to the sham group (stimulating the earlobe).⁴⁵

MI and Angina

In patients with STEMI undergoing primary percutaneous coronary intervention, 2 hours of right LLTS after reperfusion attenuated reperfusion-related ventricular arrhythmias during the first 24 hours, with smaller area under the curve of creatine kinase myocardial band, which theoretically indicated reduced infarct size.²⁹ In addition to reduced ventricular arrhythmias and cardiac biomarkers, significant improvement in left ventricular ejection fraction and N-terminal pro-B-type natriuretic peptide was observed in the LLTS group. The wall motion index, calculated using the 16-segment model, was used to evaluate the extent of left ventricular dysfunction. The percentage of left ventricular akinetic and dyskinetic segments was significantly lower in the LLTS group than the sham group. The level of inflammatory cytokines including IL-6, IL1-beta, TNF-alpha and HMGB1 were significantly reduced. However, MRI was not conducted to accurately evaluate the infarct size and their differences between groups. It remains to be proven if chronic LLTS would improve morbidity and mortality in patients with STEMI.

Alongside STEMI, the application of vagal neural stimulation for the treatment of coronary artery disease is also worth mentioning. Though conducted in a small population of patients, the clinical and histological messages in the article by Zamotrinsky et al. were impressive.⁴⁶ Vagal stimulation via trans-auricular electroacupuncture showed antianginal effect that could last for 2–3 weeks after the completion of the treatments. The effects of LLTS in refractory angina deserves further study.

Heart Failure

Human studies of LLTS on heart failure patients are also limited. In a prospective, randomised, double-blind, 2x2 cross-over study, 1 hour of LLTS acutely ameliorated left ventricular longitudinal mechanics and favourably altered heart rate variability (HRV) frequency domain components in patients with HFREF.⁴⁷ In a pilot, sham controlled, randomised study in patients with HFREF, 1 hour of LLTS (20 Hz frequency and 200 μ s pulse width) led to improvements in microcirculation (as assessed by flow mediated vasodilatation) and nail bed microcirculation (assessed by laser speckle contrast imaging).⁴⁸

Ageing

As people age, the contribution of the parasympathetic activity to the heart declines, whereas sympathetic tone increases, resulting in a less balanced autonomic function. Tragus stimulation was found to be beneficial in healthy young subjects as demonstrated by an increase in HRV.⁴⁹ After preliminary LLTS studies showed its safety and efficacy as an alternative to invasive stimulation of cervical vagus nerve, Bretherton et al. applied daily LLTS at a level just below the threshold of causing discomfort (usually 2–4 mA) to people \geq 55 years of age.⁵⁰ Higher baroreflex sensitivity and HRV were observed by LLTS. Furthermore, it was reported in the same article that in 26 healthy adults with an average age of 64 years, daily sessions of LLTS for 14 days resulted in improvements in HRV parameters, higher quality of life questionnaire score (SF-36), better moods (measured by profile of mood states questionnaire) and better sleep quality (measured by sleep questionnaire), thus showing potential against aging.

Safety of Low-level Tragus Stimulation

The non-invasive nature of tVNS granted it an impressive safety record. Drop in blood pressure and/or heart rate during stimulation is rarely observed. Some mild skin lesions were observed in the study by

Stavrakis et al. and they did not recur after adjusting the tension of the medial clips delivering the stimulation.³⁰

A systematic review published by Redgrave et al. summarised all available literature on tVNS, not limited to cardiovascular diseases and found that local irritation (tingling/pain/redness/itching) is the most common discomfort (16.7%) that is attributable to stimulation, with headache being the second (3.3%) and nasopharyngitis (1.6%) the third.⁵¹ Dizziness and syncope was found in 20 patients across eight studies, with a prevalence of 1.4%. However, only three severe adverse events were considered tVNS-related.

Conventional wisdom suggests that stimulation of the right vagus nerve exerts more prominent cardiovascular effects than stimulation of the left vagus nerve. Left vagal stimulation is therefore the preferred approach to treat epilepsy.⁵² This conventional wisdom has been challenged by reported side effects of left VNS studies.^{53,54} For non-invasive VNS, whether left and right tragus stimulation will affect the sinus node and atrioventricular node is still unknown.

Next Steps

There are some limitations associated with previous studies. These include lack of a well controlled sham group, absence of longitudinal data and small sample sizes. Optimal parameters for stimulation are yet to be determined. Furthermore, the lack of a uniform stimulation parameter makes results less generalisable. Some studies used active stimulation at another site while others used sham stimulation at the same site. All of the current clinical studies are acute or short-term studies except one recent study by Stavrakis et al. reporting that chronic LLTS suppressed paroxysmal AF.⁴⁵ Longitudinal data are warranted to evaluate the long-term benefit of LLTS.

Lastly, there is a lack of a reliable biomarker to indicate the effectiveness of LLTS. MSNA may serve as an attractive method to determine changes in sympathetic tone with LLTS. However, this technique is time-consuming and lack of widespread availability limits its usage. Serum/

plasma markers of neuroendocrine activity (such as vasostatin and catestatin) could also potentially be used to gauge change in neuroendocrine function, pending future data. Stimulus-driven event-related potentials and vagus-sensory evoked potentials in electroencephalogram, fMRI and HRV are potential biomarkers as well.^{34,55–57} In some clinical studies, a simple reduction in heart rate is considered a marker of parasympathetic activation.²⁹ Individual disease states may have respective biomarkers that would predict adequate response to LLTS. While HRV may sound attractive as a biomarker of response, it would be premature to state that this alone could direct this field forward. Searching for a reliable biomarker for effective LLTS should be a continued focus of future research. The aforementioned limitations show clear paths for future research studies.

Conclusion

Non-invasive autonomic modulation using LLTS appears promising in its early stages. The ability to stimulate the central vagal complexes at a level below the heart-rate-lowering threshold seems very attractive. LLTS has promising data in animal models of AF, post-acute MI and heart failure. Accumulating data in humans with paroxysmal AF, post-acute MI and both systolic and diastolic heart failure may pave the way for larger clinical trials focused on demonstrating improvement in morbidity and mortality associated with such disease states. Larger trials are needed to prove the safety and efficacy of tragus stimulation. ■

Clinical Perspective

- Tragus stimulation is an emerging therapy for non-invasive modulation of the autonomic nervous system.
- Pre-clinical and clinical studies proved the potential of tragus stimulation in AF, MI and heart failure.
- Though the number of clinical trials is still limited, available data point to safety and efficacy of tragus stimulation. Large-scale trials are critically warranted.

- Andersson U, Tracey KJ. Neural reflexes in inflammation and immunity. *J Exp Med* 2012;209:1057–68. <https://doi.org/10.1084/jem.20120571>; PMID: 22665702.
- Chavan SS, Tracey KJ. Essential neuroscience in immunology. *J Immunol* 2017;198:3389–97. <https://doi.org/10.4049/jimmunol.1601613>; PMID: 28416717.
- Bonaz B, Sinniger V, Pellissier S. The vagus nerve in the neuro-immune axis: Implications in the pathology of the gastrointestinal tract. *Front Immunol* 2017;8:1452. <https://doi.org/10.3389/fimmu.2017.01452>; PMID: 29163522.
- Chatterjee NA, Singh JP. Novel interventional therapies to modulate the autonomic tone in heart failure. *JACC Heart Fail* 2015;3:786–802. <https://doi.org/10.1016/j.jchf.2015.05.008>; PMID: 26364257.
- Giordano F, Zicca A, Barba C, et al. Vagus nerve stimulation: Surgical technique of implantation and revision and related morbidity. *Epilepsia* 2017;58 (Suppl 1):85–90. <https://doi.org/10.1111/epi.13678>; PMID: 28386925.
- Carreno FR, Frazer A. Vagal nerve stimulation for treatment-resistant depression. *Neurotherapeutics* 2017;14:716–27. <https://doi.org/10.1007/s13311-017-0537-8>; PMID: 28585221.
- Lendvai IS, Maier A, Scheele D, et al. Spotlight on cervical vagus nerve stimulation for the treatment of primary headache disorders: a review. *J Pain Res* 2018;11:1613–25. <https://doi.org/10.2147/JPR.S129202>; PMID: 30214271.
- Braunwald E, Epstein SE, Glick G, et al. Relief of angina pectoris by electrical stimulation of the carotid-sinus nerves. *N Engl J Med* 1967;277:1278–83. <https://doi.org/10.1056/NEJM196712142772402>; PMID: 5299662.
- Annoni EM, Xie X, Lee SW, et al. Intermittent electrical stimulation of the right cervical vagus nerve in salt-sensitive hypertensive rats: effects on blood pressure, arrhythmias, and ventricular electrophysiology. *Physiol Rep* 2015;3:e12476. <https://doi.org/10.14814/phy2.12476>; PMID: 26265746.
- Meyers EC, Solorzano BR, James J, et al. Vagus nerve stimulation enhances stable plasticity and generalization of stroke recovery. *Stroke* 2018;49:710–7. <https://doi.org/10.1161/STROKEAHA.117.019202>; PMID: 29371435.
- Kimberley TJ, Pierce D, Prudente CN, et al. Vagus nerve stimulation paired with upper limb rehabilitation after chronic stroke. *Stroke* 2018;49:2789–92. <https://doi.org/10.1161/STROKEAHA.118.022279>; PMID: 30355189.
- Dicarlo L, Libbus I, Amurthur B, et al. Autonomic regulation therapy for the improvement of left ventricular function and heart failure symptoms: the ANTHEM-HF study. *J Card Fail* 2013;19:655–60. <https://doi.org/10.1016/j.cardfail.2013.07.002>; PMID: 24054343.
- Gold MR, Van Veldhuisen DJ, Hauptman PJ, et al. Vagus nerve stimulation for the treatment of heart failure: the INOVATE-HF trial. *J Am Coll Cardiol* 2016;68:149–58. <https://doi.org/10.1016/j.jacc.2016.03.525>; PMID: 27058909.
- De Ferrari GM, Stolen C, Tuinenburg AE, et al. Long-term vagal stimulation for heart failure: eighteen month results from the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) trial. *Int J Cardiol* 2017;244:229–34. <https://doi.org/10.1016/j.ijcard.2017.06.036>; PMID: 28663046.
- Akdemir B, Benditt DG. Vagus nerve stimulation: An evolving adjunctive treatment for cardiac disease. *Anatol J Cardiol* 2016;16:804–10. <https://doi.org/10.14744/AnatolJCardiol.2016.7129>; PMID: 27723668.
- Deuchars SA, Lall VK, Clancy J, et al. Mechanisms underpinning sympathetic nervous activity and its modulation using transcutaneous vagus nerve stimulation. *Exp Physiol* 2018;103:326–31. <https://doi.org/10.1113/EP086433>; PMID: 29205954.
- Clancy JA, Deuchars SA, Deuchars J. The wonders of the wanderer. *Exp Physiol* 2013;98:38–45. <https://doi.org/10.1113/expphysiol.2012.064543>; PMID: 22848084.
- Schwaber JS, Cohen DH. Electrophysiological and electron microscopic analysis of the vagus nerve of the pigeon, with particular reference to the cardiac innervation. *Brain Res* 1978;147:65–78. [https://doi.org/10.1016/0006-8993\(78\)90772-2](https://doi.org/10.1016/0006-8993(78)90772-2); PMID: 656917.
- Jones JF, Wang Y, Jordan D. Heart rate responses to selective stimulation of cardiac vagal C fibres in anaesthetized cats, rats and rabbits. *J Physiol* 1995;489:203–14. <https://doi.org/10.1113/jphysiol.1995.sp021042>; PMID: 8583404.
- Peuker ET, Filler TJ. The nerve supply of the human auricle. *Clin Anat* 2002;15:35–7. <https://doi.org/10.1002/ca.1089>; PMID: 11835542.
- Eshraghi AA, Buchman CA, Telischi FF. Sensory auricular branch of the facial nerve. *Otol Neurotol* 2002;23:393–6. <https://doi.org/10.1097/00129492-200205000-00028>; PMID: 11981401.
- Frangos E, Ellrich J, Komisaruk BR. Non-invasive access to the vagus nerve central projections via electrical stimulation of the external ear: fMRI evidence in humans. *Brain Stimul* 2015;8:624–36. <https://doi.org/10.1016/j.brs.2014.11.018>; PMID: 25573069.
- Badran BW, Dowdle LT, Mithoefer OJ, et al. Neurophysiological effects of transcutaneous auricular vagus nerve stimulation (taVNS) via electrical stimulation of the tragus: a concurrent taVNS/fMRI study and review. *Brain Stimul* 2018;11:492–500. <https://doi.org/10.1016/j.brs.2017.12.009>; PMID: 29361441.
- Andreas M, Arzl P, Mitterbauer A, et al. Electrical stimulation of the greater auricular nerve to reduce postoperative atrial fibrillation. *Circ Arrhythm Electrophysiol* 2019;12:e007711. <https://doi.org/10.1161/CIRCEP.119.007711>; PMID: 31597476.
- Zhou L, Filiberti A, Humphrey MB, Po SS, et al. Low-level transcutaneous vagus nerve stimulation attenuates cardiac remodeling in a rat model of heart failure with preserved ejection fraction. *Exp Physiol* 2019;104:28–38. <https://doi.org/10.1113/EP087351>; PMID: 30398289.
- Wang Z, Yu L, Huang B, Wang S, et al. Low-level transcutaneous electrical stimulation of the auricular branch of vagus nerve ameliorates left ventricular remodeling and dysfunction by downregulation of matrix metalloproteinase 9 and transforming growth factor beta1. *J Cardiovasc Pharmacol*

- 2015;65:342–8. <https://doi.org/10.1097/FJC.0000000000000201>; PMID: 25502306.
27. Yu L, Wang S, Zhou X, et al. Chronic intermittent low-level stimulation of tragus reduces cardiac autonomic remodeling and ventricular arrhythmia inducibility in a post-infarction canine model. *JACC Clin Electrophysiol* 2016;2:330–9. <https://doi.org/10.1016/j.jacep.2015.11.006>; PMID: 29766893.
 28. Chen M, Zhou X, Liu Q, Sheng X, Yu L, Wang Z, et al. Left-sided noninvasive vagus nerve stimulation suppresses atrial fibrillation by upregulating atrial gap junctions in canines. *J Cardiovasc Pharmacol* 2015;66:593–9. <https://doi.org/10.1097/FJC.0000000000000309>; PMID: 26317165.
 29. Yu L, Huang B, Po SS, et al. Low-level tragus stimulation for the treatment of ischemia and reperfusion injury in patients with st-segment elevation myocardial infarction: A proof-of-concept study. *JACC Cardiovasc Interv* 2017;10:1511–20. <https://doi.org/10.1016/j.jcin.2017.04.036>; PMID: 28797427.
 30. Stavrakis S, Humphrey MB, Scherlag BJ, et al. Low-level transcutaneous electrical vagus nerve stimulation suppresses atrial fibrillation. *J Am Coll Cardiol* 2015;65:867–75. <https://doi.org/10.1016/j.jacc.2014.12.026>; PMID: 25744003.
 31. Badran BW, Mithoefer OJ, Summer CE, et al. Short trains of transcutaneous auricular vagus nerve stimulation (taVNS) have parameter-specific effects on heart rate. *Brain Stimul* 2018;11:699–708. <https://doi.org/10.1016/j.brs.2018.04.004>; PMID: 29716843.
 32. Premchand RK, Sharma K, Mittal S, et al. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial. *J Card Fail* 2014;20:808–16. <https://doi.org/10.1016/j.cardfail.2014.08.009>; PMID: 25187002.
 33. Ardell JL, Nier H, Hammer M, et al. Defining the neural fulcrum for chronic vagus nerve stimulation: implications for integrated cardiac control. *J Physiol* 2017;595:6887–903. <https://doi.org/10.1113/JP274678>; PMID: 28862330.
 34. Clancy JA, Mary DA, Witte KK, et al. Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity. *Brain Stimul* 2014;7:871–7. <https://doi.org/10.1016/j.brs.2014.07.031>; PMID: 25164906.
 35. Sclocco R, Garcia RG, Kettner NW, et al. The influence of respiration on brainstem and cardiovagal response to auricular vagus nerve stimulation: a multimodal ultrahigh-field (7T) fMRI study. *Brain Stimul* 2019;12:911–21. <https://doi.org/10.1016/j.brs.2019.02.003>; PMID: 30803865.
 36. Sclocco R, Tana MG, Visani E, et al. EEG-informed fMRI analysis during a hand grip task: estimating the relationship between EEG rhythms and the BOLD signal. *Front Hum Neurosci* 2014;8:186. <https://doi.org/10.3389/fnhum.2014.00186>; PMID: 24744720.
 37. Yu L, Scherlag BJ, Li S, et al. Low-level transcutaneous electrical stimulation of the auricular branch of the vagus nerve: a noninvasive approach to treat the initial phase of atrial fibrillation. *Heart Rhythm* 2013;10:428–35. <https://doi.org/10.1016/j.hrthm.2012.11.019>; PMID: 23183191.
 38. Yu L, Li X, Huang B, et al. Atrial fibrillation in acute obstructive sleep apnea: autonomic nervous mechanism and modulation. *J Am Heart Assoc* 2017;6:e006264. <https://doi.org/10.1161/JAHA.117.006264>; PMID: 28903938.
 39. Cao JM, Chen LS, KenKnight BH, et al. Nerve sprouting and sudden cardiac death. *Circ Res* 2000;86:816–21. <https://doi.org/10.1161/01.res.86.7.816>; PMID: 10764417.
 40. Swissa M, Zhou S, Gonzalez-Gomez I, et al. Long-term subthreshold electrical stimulation of the left stellate ganglion and a canine model of sudden cardiac death. *J Am Coll Cardiol* 2004;43:858–64. <https://doi.org/10.1016/j.jacc.2003.07.053>; PMID: 14998630.
 41. Nasi-Er BG, Wenhui Z, HuaXin S, et al. Vagus nerve stimulation reduces ventricular arrhythmias and increases ventricular electrical stability. *Pacing Clin Electrophysiol* 2019;42:247–56. <https://doi.org/10.1111/pace.13585>; PMID: 30552763.
 42. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2017;14:591–602. <https://doi.org/10.1038/nrcardio.2017.65>; PMID: 28492288.
 43. Benedict CR, Weiner DH, Johnstone DE, et al. Comparative neurohormonal responses in patients with preserved and impaired left ventricular ejection fraction: results of the Studies of Left Ventricular Dysfunction (SOLVD) Registry. *J Am Coll Cardiol* 1993;22(4 Suppl A):146A–53A. [https://doi.org/10.1016/0735-1097\(93\)90480-o](https://doi.org/10.1016/0735-1097(93)90480-o); PMID: 8376686.
 44. Kaniasus E, Kampusch S, Tittgemeyer M, et al. Current directions in the auricular vagus nerve stimulation ii - An engineering perspective. *Front Neurosci* 2019;13:772. <https://doi.org/10.3389/fnins.2019.00772>; PMID: 31396044.
 45. Stavrakis S, Stoner JA, Humphrey MB, et al. TREAT AF (Transcutaneous Electrical Vagus Nerve Stimulation to Suppress Atrial Fibrillation): a randomized clinical trial. *JACC Clin Electrophysiol* 2020;6:282–91. <https://doi.org/10.1016/j.jacep.2019.11.008>; PMID: 32192678.
 46. Zamotirinsky A, Afanasiev S, Karpov RS, Cherniavsky A. Effects of electrostimulation of the vagus afferent endings in patients with coronary artery disease. *Coron Artery Dis* 1997;8:551–7. PMID: 9431484.
 47. Tran N, Asad Z, Elkholey K, et al. Autonomic neuromodulation acutely ameliorates left ventricular strain in humans. *J Cardiovasc Transl Res* 2019;12:221–30. <https://doi.org/10.1007/s12265-018-9853-6>; PMID: 30560316.
 48. Dasari TW, Gabor F, Csipo T, et al. Non-invasive neuromodulation of vagus activity improves endothelial function in patients with heart failure with reduced ejection fraction: a randomized study. *J Card Fail* 2018;24:Suppl S59–60. <https://doi.org/10.1016/j.cardfail.2018.07.266>.
 49. Antonino D, Teixeira AL, Maia-Lopes PM, et al. Non-invasive vagus nerve stimulation acutely improves spontaneous cardiac baroreflex sensitivity in healthy young men: a randomized placebo-controlled trial. *Brain Stimul* 2017;10:875–81. <https://doi.org/10.1016/j.brs.2017.05.006>; PMID: 28566194.
 50. Bretherton B, Atkinson L, Murray A, et al. Effects of transcutaneous vagus nerve stimulation in individuals aged 55 years or above: potential benefits of daily stimulation. *Aging* 2019;11:4836–57. <https://doi.org/10.18632/aging.102074>; PMID: 31358702.
 51. Redgrave J, Day D, Leung H, et al. Safety and tolerability of transcutaneous vagus nerve stimulation in humans; a systematic review. *Brain Stimul* 2018;11:1225–38. <https://doi.org/10.1016/j.brs.2018.08.010>; PMID: 30217648.
 52. McGregor A, Wheless J, Baumgartner J, Bettis D. Right-sided vagus nerve stimulation as a treatment for refractory epilepsy in humans. *Epilepsia* 2005;46:91–6. <https://doi.org/10.1111/j.0013-9580.2005.16404.x>; PMID: 15660773.
 53. Tatum WO 4th, Moore DB, Stecker MM, et al. Ventricular asystole during vagus nerve stimulation for epilepsy in humans. *Neurology* 1999;52:1267–9. <https://doi.org/10.1212/wnl.52.6.1267>; PMID: 10214755.
 54. Matheny RG, Shaar CJ. Vagus nerve stimulation as a method to temporarily slow or arrest the heart. *Ann Thorac Surg* 1997;63(6 Suppl):S28–9. [https://doi.org/10.1016/s0003-4975\(97\)00423-2](https://doi.org/10.1016/s0003-4975(97)00423-2); PMID: 9203592.
 55. Lewine JD, Paulson K, Bangera N, Simon BJ. Exploration of the impact of brief noninvasive vagal nerve stimulation on EEG and event-related potentials. *Neuromodulation* 2019;22:564–72. <https://doi.org/10.1111/ner.12864>; PMID: 30288866.
 56. Hagen K, Ehlis AC, Schneider S, et al. Influence of different stimulation parameters on the somatosensory evoked potentials of the nervus vagus—how varied stimulation parameters affect VSEP. *J Clin Neurophysiol* 2014;31:143–8. <https://doi.org/10.1097/WNP.0000000000000038>; PMID: 24691232.
 57. Fang J, Egorova N, Rong P, et al. Early cortical biomarkers of longitudinal transcutaneous vagus nerve stimulation treatment success in depression. *Neuroimage Clin* 2017;14:105–11. <https://doi.org/10.1016/j.nicl.2016.12.016>; PMID: 28180068.
 58. Roberts J. Chapter 63. Otolaryngologic procedures. In: *Roberts and Hedges' Clinical Procedures in Emergency Medicine and Acute Care*. Philadelphia, PA: Elsevier, 2017;1338–83.e2.
 59. Wang Z, Yu L, Wang S, et al. Chronic intermittent low-level transcutaneous electrical stimulation of auricular branch of vagus nerve improves left ventricular remodeling in conscious dogs with healed myocardial infarction. *Circ Heart Fail* 2014;7:1014–21. <https://doi.org/10.1161/CIRCHEARTFAILURE.114.001564>; PMID: 25332149.
 60. Zhou X, Zhou L, Wang S, et al. The use of noninvasive vagal nerve stimulation to inhibit sympathetically induced sinus node acceleration: a potential therapeutic approach for inappropriate sinus tachycardia. *J Cardiovasc Electrophysiol* 2016;27(2):217–23. <https://doi.org/10.1111/jce.12859>; PMID: 26467778.