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Journal of Atrial Fibrillation
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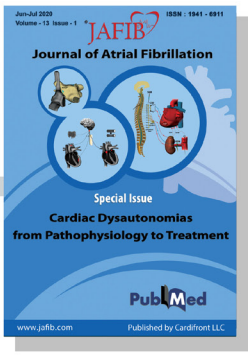

Vagal Stimulation and Arrhythmias

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Abstract

Imbalance of the sympathetic and parasympathetic nervous systems is probably the most prevalent autonomic mechanism underlying many arrhythmias. Recently, vagus nerve stimulation (VNS) has emerged as a novel therapeutic modality to treat arrhythmias through its anti-adrenergic and anti-inflammatory actions. Clinical trials applying VNS to the cervical vagus nerve in heart failure patients yielded conflicting results, possibly due to limited understanding of the optimal stimulation parameters for the targeted cardiovascular diseases. Transcutaneous VNS by stimulating the auricular branch of the vagus nerve, has attracted great attention due to its noninvasiveness. In this review, we summarize current knowledge about the complex relationship between VNS and cardiac arrhythmias and discuss recent advances in using VNS, particularly transcutaneous VNS, to treat arrhythmias.

Introduction

Neuromodulation of the cardiac autonomic nervous system (ANS) is evolving as a novel approach to treat arrhythmias. Excitation of the parasympathetic nervous system exerts negative chronotropic, dromotropic and inotropic effects on the heart [1,2]. Electrical stimulation of the vagus nerve (VNS) has emerged as a promising therapy for various conditions, including neural disorders and cardiac diseases [3-5]. VNS was approved by the US Food and Drug Administration to treat refractory epilepsy and depression [6,7] . Here, we focus on recent advances using VNS, particularly transcutaneous VNS, to treat arrhythmias.

1.1 Anatomy of the autonomic nervous system

Signal processing of the cardiac ANS occurs at several levels: i) central; ii) intrathoracic extracardiac; and iii) intrinsic cardiac level [8]. Neural trafficking is influenced by the brain, spinal cord, extrinsic and intrinsic cardiac ganglia (Figure 1). Autonomic neural signals from other organ systems (e.g. kidneys) can affect the cardiac ANS through complex interactions in the ANS [9-12].

Key Words

Vagus Nerve Stimulation; Autonomic Nervous System; Atrial Fibrillation; Ventricular Arrhythmia

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1.2 Sympathetic Efferent Neurotransmission

The cardiac sympathetic preganglionic fibers originate in the central nervous system primarily in the brainstem and are modulated by higher centers such as the subthalamic and periaqueductal grey as well as the rostral ventrolateral medulla [9-12]. Then, the sympathetic preganglionic fibers reach postganglionic neurons in the superior cervical, middle cervical, cervicothoracic (stellate) ganglia and mediastinal ganglia along the cervical and thoracic spinal cord (e.g. from C2 to T4 or T5) [9-12]. These postganglionic neurons project axons via multiple cardiopulmonary nerves to the atrial and ventricular myocardium as well as limited populations of intrinsic cardiac adrenergic neurons. The major post-ganglionic neurotransmitter of the sympathetic nervous system is norepinephrine. The most important mechanism underlying sympathetic-mediated arrhythmogenesis is the activation of the β-adrenergic receptors and stimulatory Gs proteins, which leads to stimulation of adenylyl cyclase followed by protein kinase A–mediated phosphorylation of the L-type calcium channels (increasing calcium influx) and ryanodine receptors [13]. Phosphorylation of the latter enhances the opening probability of the ryanodine receptors and increases calcium release from the sarcoplasmic reticulum (SR). Excessive calcium influx and SR calcium release are known to be arrhythmogenic

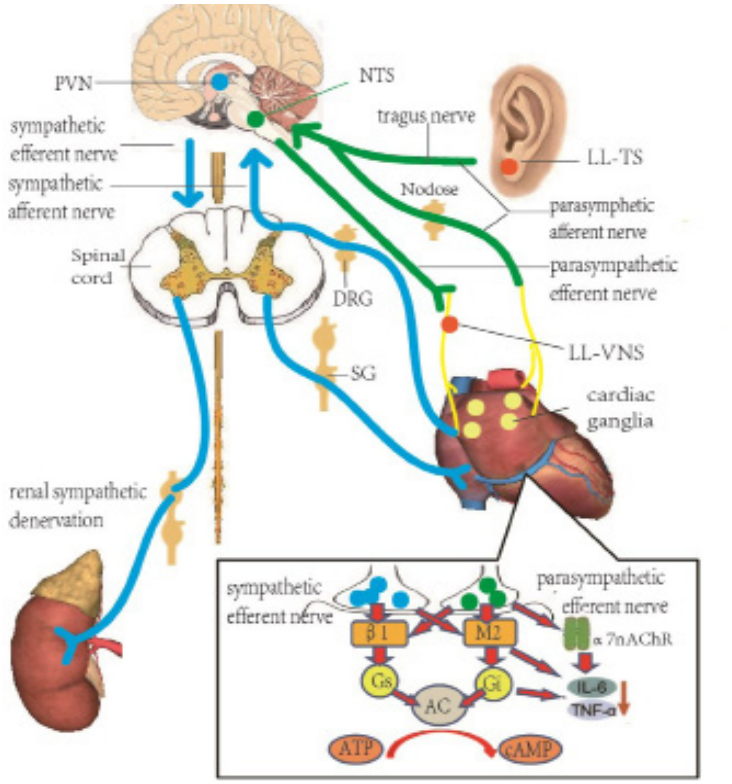


Figure 1: **Neurohumoral control and functional organization of cardiac autonomic innervation**

The autonomic nervous system related to arrhythmias consists of neurons and nerves in the brain, spinal cord, heart and kidneys and is similar to a closed-loop circuit that modulates the function of target organs. Activation of both the afferent and efferent vagal nerve fibers can increase the vagal tone in the cardiac closed-loop circuit and protect the heart. Blue lines represent sympathetic nerve fibers and green lines represent vagus nerve fibers. Inset: At the cellular level, sympathetic nervous system primarily releases norepinephrine, which stimulates the cardiac β-receptors. Parasympathetic nervous system primarily releases acetylcholine, stimulating cholinergic muscarinergic receptors on the myocytes and activating the α7nAChR pathway to reduce inflammation and fibrosis in the heart. SG, stellate ganglion; DRG, dorsal root ganglia; PVN, paraventricular nucleus; NTS, nucleus tractus solitaries; β1, β-adrenergic receptor; M2, muscarinic receptor; Gi, inhibitory G-protein; Gs, stimulatory G-protein; AC, adenylate cyclase; α7nAChR, α7 nicotinic acetyl-choline receptor.

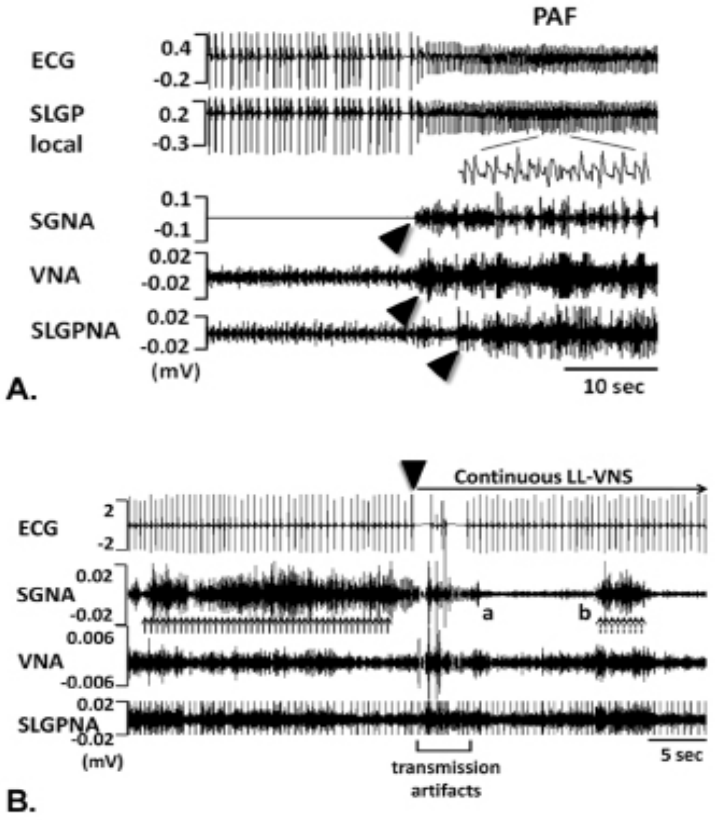


Figure 2: **Simultaneous recording of ECG, stellate ganglion nerve activity (SGNA), vagus nerve activity (VNA) and superior left GP nerve activity (SLGPNA) in ambulatory dogs**

A. Paroxysmal AF was preceded by nearly simultaneous activation of the SGNA, VNA and LSLGPNA. B. LL-VNS immediately suppressed SGNA, demonstrating its anti-adrenergic effect. Reproduced with permission from reference 53.

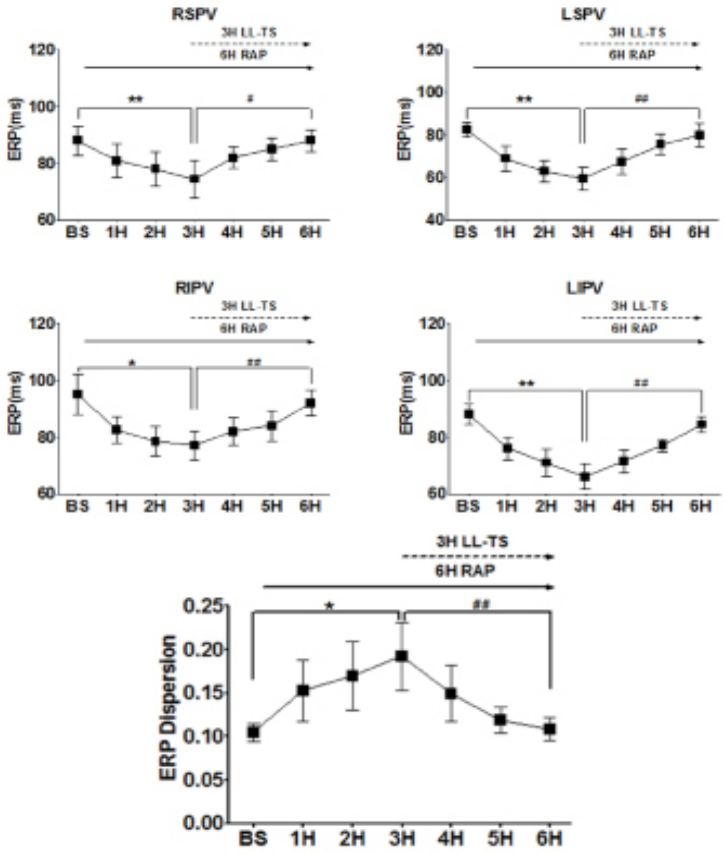
because calcium homeostasis is crucial in maintaining normal cardiomyocyte functions such as excitability and mitochondrial stability. Elevated intracellular calcium concentration can activate the sodium-calcium exchanger (NCX) to extrude intracellular calcium to the extracellular space. However, extruding one calcium ion occurs at the expense of importing 3 sodium ions, which is electrogenic and can lead to early or delayed after-depolarization [14]. Therefore, disturbed calcium homeostasis has been implicated as a leading mechanism underling high sympathetic outflow induced ventricular tachyarrhythmias (VAs) such as catecholaminergic polymorphic VT, long QT syndrome and heart failure.

1.3 Parasympathetic Efferent Neurotransmission

Preganglionic neurons of the parasympathetic nervous system are located in the nucleus ambiguous and dorsal motor nucleus of the medulla oblongata as well as scattered regions between these two structures [15,16]. Their axons project to the postganglionic parasympathetic neurons in the numerous intrinsic cardiac ganglia via bilateral vagosympathetic trunks and multiple intrathoracic cardiopulmonary nerves [17]. Postganglionic neurons, concentrated in epicardial fat pads, then provide direct innervation to the sinus node, atrioventricular node as well as both atria and ventricles [9,18,19]. Acetylcholine is the major parasympathetic neurotransmitter of the heart; stimulation of the cholinergic muscarinic receptors (mainly the M2 receptors) inhibits adenylyl cyclase and reduces cyclic adenosine monophosphate via pertussis toxin-sensitive inhibitory G-proteins (Gi), which inhibits the L-type calcium current and hyperpolarization-activated current I_f, as well as activates the Ach-gated potassium current (IKACh) [20]. Important co-transmitters released with vagus nerve stimulation include nitric oxide and vasoactive intestinal peptide [21].

1.4 The intrinsic cardiac autonomic nervous system

Sympathetic and parasympathetic nerves and neurons as well as interconnecting nerves and neurons form a complex cardiac neural network. These neural elements converge at several ganglionated plexi (GP) embedded within epicardial fat pads [22,23]. In the atria, the great majority of GP are concentrated at the pulmonary vein-atrial junctions. In contrast, the ventricular GP are primarily located at the origins of major coronary arteries or aortic root [24]. These GP act as integration centers that modulate the interactions between the extrinsic cardiac ANS and the heart [25] and contain both afferent and efferent sympathetic as well as parasympathetic nerves and neurons.



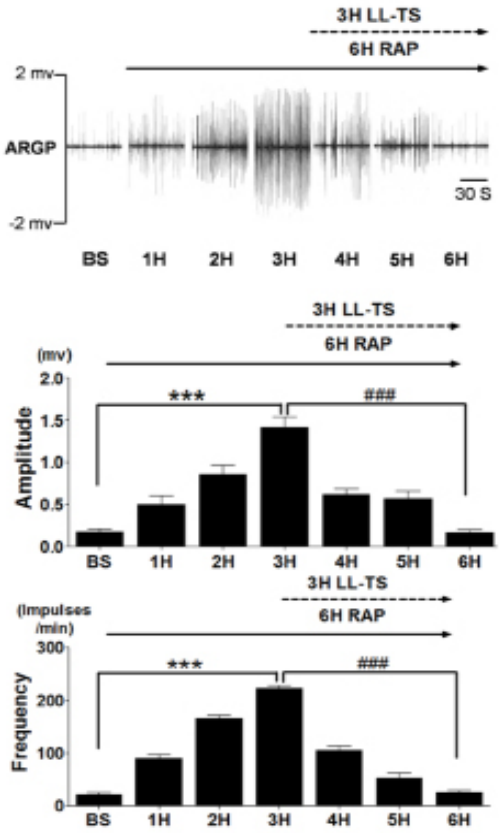


Figure 3A:

Figure 3B:

Figure 3: **Effects of transcutaneous low-level vagus nerve stimulation on effective refractory period of atria, pulmonary veins and on neural activity of ganglionated plexi.**

A. Parameters were measured during 6 hours of rapid atrial pacing (RAP) simulating paroxysmal AF. In the last 3 hours, LL-TS, 80% below threshold, was applied with RAP. At all sites, mean ERP decreased significantly after 3 hours of RAP (*:p<0.05; **:p<0.01; compared to baseline). After 3 hours of RAP+LL-TS, mean ERP at all sites showed a significant reversal toward baseline values (#:p<0.05 , ##:p<0.01; compared with the end of 3rd hour of RAP). Increased ERP dispersion by RAP was also reversed by LL-TS. B. Top. A typical example of neural recordings from the anterior right ganglionated plexi (ARGP) taken each hour (during sinus rhythm) when RAP was temporarily stopped. The middle and bottom panels showed the average amplitude and frequency of neural recordings. During the first 3 hours of RAP, there was a progressive increase in both the amplitude as well as the frequency of neural firing in the ARGP. With the addition of LL-TS, at 80% below threshold, the amplitude and frequency returned toward initial levels. RSPV, LSPV, RIPV and LIPV: right superior, left superior, right inferior and left inferior pulmonary vein, respectively. Reproduced from reference 65 with permission.

For example, the bradycardic response elicited by cervical VNS was mediated by the anterior right GP adjacent to the sinus node; ablation of that GP greatly attenuated the bradycardic response [25].

1.5 Afferent Neurotransmission

Afferent nerve fibers from the mechanosensory and chemosensory receptors provide critical feedback from the cardiovascular system [26]. Trafficking from these nerve fibers are processed in the intrinsic cardiac ganglia, intrathoracic ganglia, dorsal root ganglia of the spinal cord, nodose ganglia (the inferior ganglia of the vagosympathetic trunk) and brainstem [27]. Afferent cardiac sympathetic neural trafficking is transmitted to the nucleus tractus solitaries (NTS) and the paraventricular nucleus (PVN) [28-31]. In addition to projections from the PVN to the neurohypophysis, anatomic and electrophysiological studies revealed that axons from the PVN also project directly to the autonomic centers in the medulla and spinal cord, indicating that the PVN is a key integrative center for the sympathetic neural trafficking in the brain and is involved in cardiovascular regulation [32,33]. Parasympathetic afferent fibers carry peripheral information to the NTS first; axons from the NTS project to the autonomic and cardiovascular centers in the brainstem as well to the hypothalamus and cerebrum. It is important to note that the afferent parasympathetic neural trafficking from peripheral organs back to the brain allows the brain to modulate the ANS and maintain autonomic homeostasis.

2. Vagus nerve stimulation to treat atrial fibrillation

2.1 Rationale for vagus nerve stimulation to treat atrial fibrillation

Simultaneous recordings of the canine left stellate ganglion (LSG) and left vagus nerve over several weeks revealed that co-activation of the sympathetic and parasympathetic nervous systems may precede paroxysmal AF (Figure 2) [34,35]. That is, sympathetic and parasympathetic activity act synergistically to facilitate AF initiation[38,39]. In isolated atrial myocytes, parasympathetic stimulation shortened the atrial effective refractory period (ERP), whereas sympathetic stimulation increases calcium influx and SR calcium release which activates NCX, depolarizes the myocytes and elicit and

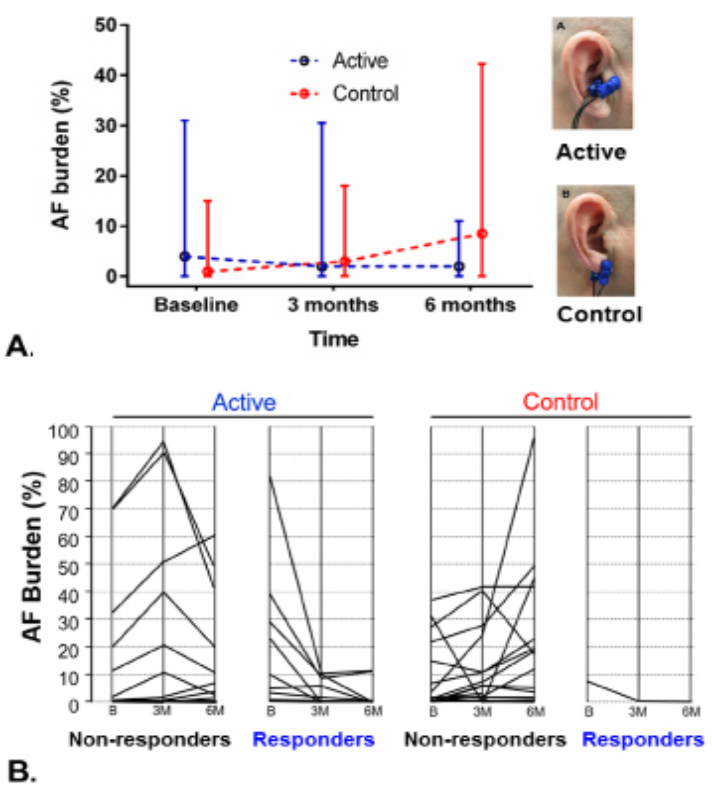


Figure 4: **Effects of chronic transcutaneous low-level vagus nerve stimulation in atrial fibrillation burden**

A. Comparison of AF burden between the 2 groups (median values and interquartile range). The p-value is based on a comparison of median AF burden levels at the 6-month time point after adjusting for baseline measures. In the control group, stimulation was delivered to the ear lobule where no vagal innervation exits. B. Patient-level data on AF burden change in the 2 groups. Patients whose AF burden decreased by >75% at follow up were categorized as responders. The proportion of responders was significantly larger in the active compared to the sham control group (47% vs. 5%, respectively, p=0.003). B = baseline; 3M = 3 months; 6M = 6 months. Reproduced from reference 68 with permission.

early after-depolarization [36,37]. Parasympathetic stimulation activates acetylcholine dependent potassium currents (IKACh), leading to shortening the atrial ERP and action potential duration (APD) [20,40,41] as well as a reduction in the atrial reentrant wavelength (the product of ERP and conduction velocity) to increase the probability that multiple reentrant circuits coexist in the atrial myocardium and facilitate AF maintenance [42].

Direct VNS produces atrial ERP heterogeneity due to the heterogeneous distribution of vagal innervation and varying density of the M2 receptors in the atria [43]. In past decades, VNS, at the strength to slow the sinus rate or atrioventricular (AV) conduction, was used as an experimental tool to induce and maintain AF [44,45]. In contrast, mild activation of vagal tone through the baroreflex has been shown to suppress firing of pulmonary veins [46]. This paradox illustrates the complexity of the cardiac ANS and arrhythmogenicity. That is, VNS can either enhance or suppress AF, depending on the strength of stimulation [47].

2.2 Cervical low-level vagus nerve stimulation

The Oklahoma group first reported the antiarrhythmic effect of applying low-level VNS (LL-VNS) to canine cervical vagus nerve [48]. LL-VNS, without slowing the sinus rate or AV conduction, increased the ERP in the atrium and pulmonary veins, suppressed AF inducibility, and shortened the duration of acetylcholine-induced AF [48,49]. Since the atrial autonomic neural network is dominated by parasympathetic neural elements, inhibiting the GP by LL-VNS leads to anti-cholinergic effects on GP and prolonged the ERP. Other mechanisms that LL-VNS suppresses AF have been proposed, including suppression of the LSG activity [50], release of the neurotransmitter vasostatin-1 [51] and nitric oxide [52]. Direct neural recordings of the canine atrial GPs showed that LL-VNS could inhibit the neural activity of GPs, thereby suppressing AF [49]. Studies on ambulatory dogs demonstrated that paroxysmal AF was often initiated by simultaneous or sequential firing of the stellate ganglion, vagus nerve and GP (Figure 2). LL-VNS inhibited the LSG activity and sympathetic nerve density in the LSG, thereby suppressing paroxysmal atrial tachyarrhythmias [53]. These findings indicated that LL-VNS was both anticholinergic and antiadrenergic, which may account for its antiarrhythmic effects.

High sympathetic outflow enhances inflammation; inflammation leads to fibrosis through activation of pro-inflammatory cells (e.g. T-lymphocytes, monocytes/macrophages) and the cytokines they release. Inflammation, therefore, plays an important role in the pathogenesis of AF as well as neural, electrical and structural remodeling [54]. Since the discovery of the $\propto -7$ nicotinic acetylcholine receptor ($\propto -7$nAChR)-mediated cholinergic anti-inflammatory pathway, the anti-inflammatory effects of the parasympathetic nervous system on cardiovascular diseases have attracted substantial attention [55]. Some studies suggested that activation of $\propto -7$nAChR significantly reduces inflammation and fibrosis in the heart, in which the expression levels of high-mobility group box 1 (HMGB1), chemokine receptors and pro-inflammatory factors such as interleukin-6 and TNF-$\propto$ were decreased[56]. In an ischemia/reperfusion model, VNS increased STAT3 phosphorylation

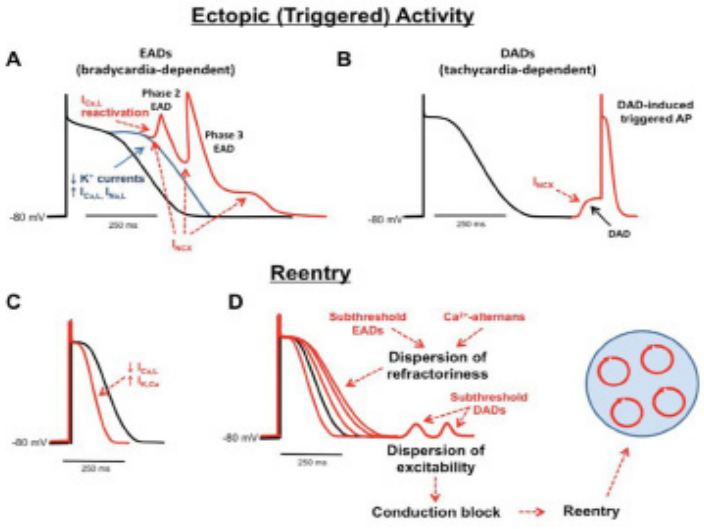


Figure 5: **Arrhythmogenesis related to high sympathetic outflow.**

Both early afterdepolarization (EAD), A) and delayed afterdepolarization (DAD, B) can be elicited by the inward current generated by sodium-calcium exchanger (NCX). Reentry can be facilitated by shortened refractory period or action potential duration (C) as well as increased dispersion of the refractory period (D). Reproduced with permission from reference 14.

and inhibited NF-kB activation. The cholinergic anti-inflammatory pathway was involved in these effects [57].

Pre-clinical evidence indicates that LL-VNS is anti-arrhythmic and anti-inflammatory. Because of the invasive nature of cervical LL-VNS, it has only been tested acutely in post-operative AF in patients undergoing open heart surgery. The incidence of postoperative AF was reduced by 66% by LL-VNS (20 Hz) for 72 hours after cardiac surgery [58].

2.3 Transcutaneous low-level vagus nerve stimulation

A major drawback of cervical LL-VNS is its invasiveness, requiring surgical implantation of a neurostimulator and a cuff electrode around the cervical vagus nerve. Adverse effects include infection, Horner syndrome, discomfort and pain at implant site [59-62]. These adverse effects led to the investigation of transcutaneous LL-VNS. Tragus, a small pointed eminence of the external ear, is innervated by the auricular branch of the vagus nerve. The tragus is easily accessible to transcutaneous LL-VNS. Prior research using horseradish peroxidase to trace the cranial projection of the auricular branch of the vagus nerve found that the vagal afferent nerve fibers of the auricular branch terminate mainly in the NTS [63]. It is important to note that VNS through the tragus only activates the afferent vagal neural trafficking because there is no efferent vagus nerves in the tragus that innervates the heart.

Preclinical studies showed that low-level tragus stimulation (LL-TS), at the strength not slowing the sinus rate or AV conduction, exerted similar electrophysiological effects to cervical LL-VNS in terms of lengthening the ERP, suppressing pulmonary vein firing and AF as well as inhibiting the neural activity of major atrial GPs (Figure 3) [64,65]. Notably, the anti-arrhythmic effects of LL-TS were still profound at the stimulation strength 80% below the threshold that slowed the sinus rate or AV conduction, suggesting that this level of stimulation might be tolerable in ambulatory patients with arrhythmias.

Electrical stimulation of the tragus was tested in 48 healthy participants showing that tragus VNS significantly decreased the low-frequency/high-frequency ratio (LF/HF) measurement of heart rate variability, indicating a tendency toward parasympathetic tone [66]. In 2015, the Oklahoma group [67] reported a randomized clinical study applying transcutaneous LL-TS to patients with refractory paroxysmal AF referred for catheter ablation. Only one hour of transcutaneous LL-TS was enough to suppress ERP shortening and AF inducibility, shorten the AF duration, and decrease pro-inflammatory markers such as tumor necrosis factor-$\propto$ (TNF-$\propto$) and C-reactive protein. A recent sham-controlled randomized clinical trial published by same group indicated that in ambulatory patients with paroxysmal AF, daily transcutaneous LL-TS (one hour, 20 Hz, 1 mA below the perception threshold) reduced the AF burden by 83% at 6 months (Figure 4). Plasma level of the TNF-$\propto$ was reduced by 23% as well. These results suggest that transcutaneous LL-TS may serve as a novel, non-invasive therapy for patients in early stage of AF [68]. However, as a major limitation of transcutaneous LL-TS, the response to transcutaneous LL-TS was variable among individual patients due to the lack of an acute biomarker of response to therapy that can predict the response to chronic transcutaneous LL-TS therapy (Figure 4B). Although transcutaneous LL-TS has been shown to be able to affect heart rate variability and inflammatory markers within an hour [67], if these biomarkers predict long-term success remains unknown. Future large scale randomized clinical trials will be needed to optimize patient selection for transcutaneous LL-TS based on biomarkers as well as to determine if patients with more advanced stage of AF (e.g. persistent AF) still respond to transcutaneous LL-TS.

3. Vagus nerve stimulation to treat ventricular tachyarrhythmias

3.1 Rationale for VNS to treat ventricular tachyarrhythmias (VAs)

VAs are often triggered by high sympathetic tone or reduced vagal tone [69]. Sympathetic activation can facilitate the initiation of VAs through the following mechanisms: 1) shortening of the ventricular ERP [70] and increasing the steepness of the slope of the action potential duration restitution curve to facilitate ventricular fibrillation initiation [71]; 2) increasing dispersion of refractoriness [72]; 3) enhancing of ventricular repolarization heterogeneity [73]; and 4) triggering of early and delayed after-depolarization (Figure 5) [14,74,75]. Furthermore, underlying cardiomyopathy can enhance the sympathetic activity and further promote the occurrence of VAs, forming a vicious cycle between the sympathetic activity and VAs. For instance, in a canine model of myocardial infarction, LSG synapses and nerve density were increased due to ischemia, which in turn caused more instability in the electrophysiological properties and increase the propensity for VAs [76].

The beneficial effects of VNS on VAs are mediated directly by reducing the sympathetic activity and indirectly by inhibiting myocardial remodeling and inflammation [61-62,77]. Activation of the IKACh current through the muscarinic receptors and augmentation of neuronal nitric oxide production also contributes to the beneficial effects of VNS [78-81]. In addition, inflammatory pathways have an important role in fibrosis [82], scar formation and hypertrophy [83]; inflammatory mediators such as interleukin-1 can be directly arrhythmogenic [84]. In a rat model of ischemia/reperfusion, VNS reduced the infarct size, inflammatory cell infiltration and the levels of circulating inflammatory cytokines [85]. Chronic VNS in a dog model of heart failure also normalized the levels of interleukin-6 and TNF-$\propto$ [86]and reduced plasma levels of angiotensin-II [87], a potent profibrotic mediator. Moreover, chronic VNS preserved the connexin 43 proteins and reduced the prevalence of spontaneous ventricular tachycardia after myocardial infarction [88].

At present, clinical management of ventricular tachycardia/ventricular fibrillation is often restricted to pharmacological therapy and catheter ablation. Lately, invasive procedures such as thoracic epidural anesthesia (TEA), stellate ganglion blockade and cardiac sympathetic denervation (CSD), aiming at decreasing sympathetic outflow to the heart, have been shown to reduce the incidence of VTs in various conditions [89,91]. The use of TEA is limited by antiplatelet or anticoagulation therapy due to concerns about bleeding. The effect of stellate ganglion blockade as well as left CSD or bilateral CSD often depends on the operator; collateral damage to sympathetic

innervation to the head, neck, and eyes can cause significant adverse effects [91-94].

3.2 Cervical low-level vagus nerve stimulation

Increased sympathetic tone is typical in patients with myocardial infarction or heart failure and is an important contributing factor to VAs. Preclinical studies demonstrated that VNS can increase ventricular electrical stability and protect against VAs during acute ischemia and reperfusion in animal models 95-99. Vanoli et al [100] showed that VNS effectively prevents ventricular fibrillation in conscious animals with myocardial infarction. During the repeated exercise stress tests, VNS decreased the incidence of ventricular fibrillation from 92% to 10%. Furthermore, VNS may stabilize the infarct border zones and reduce the incidence of VAs [101]. Chen et al [102] found that LL-VNS with a stimulation voltage below the 80% voltage threshold required to slow the heart rate significantly decreased the incidence of VAs and exerts protective effects on myocardial ischemia/reperfusion injury, presumably by preserving the acetylcholine levels and intact parasympathetic neuronal pathways. At present, several clinical trials of VNS for the treatment of advanced heart failure have yielded conflicting results, probably caused by the combination of heterogeneous study population and lack of the knowledge of the optimal stimulation parameters [47,61,62].

3.3 Transcutaneous low-level vagus nerve stimulation

Due to the invasiveness of cervical LL-VNS, transcutaneous LL-VNS has been investigated as a novel noninvasive method to treat VTs. Yu et al [103] found that in a canine post-myocardial infarction model, chronic transcutaneous LL-VNS (2h/day) for 2 months reduced inducibility of VTs, LSG neuronal activity, left ventricular remodeling and ANS remodeling at the infarct border zone. Recently, this group provided the first clinical evidence that when transcutaneous LL-VNS, 50% below the threshold slowing the sinus rate or AV conduction, was delivered at the time of ST elevation myocardial infarction, transcutaneous LL-VNS reduced the infarct size, myocardial ischemia/reperfusion related ventricular premature contraction and ventricular tachycardia as well as pro-inflammatory markers such as interleukin-1β, interleukin-6 and TNF-∝ in patients presenting with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention [104]. This first-in-man trial suggests that transcutaneous LL-VNS may be applied to patients in early stage of myocardial infarction to reduce myocardial injury and VAs.

While preclinical cervical VNS showed promising results in suppressing VAs, long-term beneficial outcomes have not been verified in clinical trials [61,62]. For its noninvasiveness, transcutaneous LL-VNS is an attractive alternative to cervical VNS to treat VAs related to high sympathetic outflow such as ventricular tachycardia in patients with structural heart diseases and premature ventricular contraction. Future preclinical and clinical studies should focus on identifying the optimal stimulation parameters (e.g. frequency, pulse width, duty cycles) as well as acute biomarkers that can predict long-term efficacy.

Conclusion

Transcutaneous LL-VNS may offer a non-invasive and an inexpensive alternative to treat a variety of cardiovascular or inflammatory diseases related to high sympathetic outflow. The optimal stimulus parameters of VNS for individual disease are yet to be determined. Future pre-clinical and clinical studies are needed to clarify mechanisms responsible for its therapeutic effects and optimize the stimulation parameters fortargeted disease.

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