

Neural Mechanisms and Therapeutic Opportunities for Atrial Fibrillation

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ABSTRACT: Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with an increased risk of all-cause mortality and complications. The autonomic nervous system (ANS) plays a central role in AF, with the heart regulated by both extrinsic and intrinsic properties. In the extrinsic ANS, the sympathetic fibers are derived from the major paravertebral ganglia, especially the stellate ganglion (SG), which is a source of cardiac sympathetic innervation since it connects with multiple intrathoracic nerves and structures. The major intrinsic ANS is a network of axons and ganglionated plexi that contains a variety of sympathetic and parasympathetic neurons, which communicate with the extrinsic ANS. Simultaneous sympathovagal activation contributes to the development of AF because it increases calcium entry and shortens the atrial action potential duration. In animal and human studies, neuromodulation methods such as electrical stimulation and renal denervation have indicated potential benefits in controlling AF in patients as they cause SG remodeling and reduce sympathetic outflow. This review focuses on the neural mechanisms relevant to AF and the recent developments of neuromodulation methods for AF control.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with an increased risk of all-cause mortality and complications.¹ The autonomic nervous system (ANS) is one of the important mechanisms in atrial arrhythmogenesis.² While pulmonary vein isolation is widely used for AF ablation, it is an invasive procedure with potentially significant complications. Neuromodulation techniques that reduce ANS activity have been developed using animal models and studied in humans to control atrial arrhythmias, including AF. In this review, we summarize the neural mechanisms related to AF and the recent developments of neuromodulation procedures for AF control.

CARDIAC AUTONOMIC NERVOUS SYSTEM

The heart has both extrinsic and intrinsic ANS regulation.³ The extrinsic cardiac ANS includes both sympathetic and parasympathetic components. The sympathetic cardiac fibers are largely derived from major paravertebral ganglia, including the superior cervical ganglia, the stellate ganglion (SG), or cervicothoracic ganglion, and the thoracic ganglion.⁴ Among them, the SG is a major source of cardiac sympathetic innervation, connecting with multiple intrathoracic nerves and structures as well as skin. The ganglion cells and SG nerve fibers mostly stain positive for tyrosine-hydroxylase (TH), which indicates a sympathetic phenotype. However, a small percentage (roughly 5%) of ganglion cells are negative for TH and positive for choline acetyltransferase (ChAT), indicating that these cells may produce acetylcholine.⁵ Many ganglion cells express both TH and ChAT, and that phenotypic switch may occur in disease states or after neuromodulation procedures.^{5,6} The extrinsic parasympathetic

fibers, which come from nuclei in the medulla, are carried almost entirely within the vagal nerve. Most of the cardiac parasympathetic nerve fibers converge at a distinct fat pad between the superior vena cava and the aorta⁷ en route to the sinus and atrioventricular nodes. While the vagal nerve carries the parasympathetic nerve fibers, it also contains significant sympathetic nerve structures.⁸ The sympathetic nerve fibers occupy between 1% and 5% of the cross section of the vagal nerves in dogs and in humans.⁹

The intrinsic cardiac ANS is a complex network composed of ganglionated plexi (GP) on the atrial surface and ventricles within epicardial fat pads that contain large populations of colocalized sympathetic and parasympathetic neurons.^{3,10} As the integration center, the GP modulate the intricate autonomic interactions between the extrinsic and intrinsic ANS.¹¹ In the atria, GP are concentrated in distinct locations on the chamber walls.^{3,10} Specifically, there is a high density of GP in the pulmonary vein–left atrium junction.¹²

ATRIAL ELECTROPHYSIOLOGY AND ARRHYTHMOGENESIS NEURAL ACTIVITIES

As a normal reaction, sympathetic activation of the heart enhances cardiac output by increasing Ca^{2+} entry into myocyte via the L-type Ca^{2+} channel and spontaneous Ca^{2+} release and uptake on the sarcoplasmic reticulum.¹³ Parasympathetic activation of the heart can activate the G-protein-gated K^+ channel (IKACH), shortening the atrial action potential duration (APD) and in turn the atrial effective refractory period (ERP).¹⁴

Abnormal neural activities induce arrhythmias in both the atria and ventricles. In the atria, excessive sympathetic activation

promotes focal ectopic activity through enhanced automaticity, early after depolarization (EAD), or delayed after depolarization. Parasympathetic activity produces spatial electrophysiological heterogeneity of the atria.¹⁵ Mechanistically, both simultaneous sympathetic and parasympathetic activations cause short atrial APD and large and long Ca^{2+} transience, creating a condition for late-phase 3 EAD that can induce AF.¹⁶ Short APD also promotes the maintenance of reentrant activity. As pulmonary veins naturally have short APDs, they are particularly prone to develop these Ca^{2+} transient-triggered arrhythmias.¹⁷ Electrical stimulation to the GPs around the pulmonary veins can stimulate both adrenergic and cholinergic nerves and may trigger atrial arrhythmias.

NEUROMODULATION FOR ATRIAL FIBRILLATION

While pulmonary vein isolation (PVI) has been the most widely used ablation approach to treat AF, its long-term results remain unsatisfactory, particularly for persistent AF.¹⁸ As a result, several neuromodulation techniques have been attempted to manage patients with AF. The following introduces our strategy using subcutaneous nerve stimulation (ScNS) for AF and reviews the recent progress of other methods.

Subcutaneous Nerve Stimulation

The skin is an easily accessible place to perform mechanical neuromodulation. Because the postganglionic sympathetic nerve fibers of the upper extremities and thorax come primarily from the SG, thoracic ScNS may activate the sympathetic axons in the skin to cause calcium accumulation and remodeling of the SG, including neuronal cell death.^{19,20} We showed in canine models that long-term intermittent ScNS in the thorax led to stimulus strength-dependent changes of SG nerve activity (SGNA), frequency and duration of spontaneous atrial tachyarrhythmias (Figure 1A, B), and the plasma norepinephrine concentration (Figure 1C).^{21,22} In ambulatory dogs with persistent AF, thoracic ScNS reduced SGNA and controlled the ventricular rate via SG remodeling (Figure 1D-F), additionally showing neural remodeling in the brain stem and preservation of the left ventricular ejection fraction (Figure 1D-F).²³ The brain stem remodeling in ScNS dogs consists of increased ^{18}F -FDG uptake but no neuronal cell death. These findings indicate that thoracic ScNS at appropriate stimulus strength may remodel the SG and brain stem and reduce atrial tachyarrhythmias. Because of both central (brain stem) and peripheral (SG) remodeling, ScNS may be a new method for long-term atrial arrhythmia control. More recently, we showed that ScNS with blindly inserted electrodes can be used to achieve rate control in persistent AF.²⁴ This simplified method may facilitate future clinical trials of neuromodulation. However, Yuan et al. showed that prolonged (.3-second) pauses were observed with increased frequency in the ScNS group but not in the sham control group of dogs with persistent AF.²³ Therefore, bradycardia is a potential side effect for ScNS in AF.

Ganglionated Plexi Ablation

As described above, the GPs surrounding the pulmonary veins may play a role in triggering atrial arrhythmias and therefore can serve as targets of neuromodulation. A randomized multicenter trial by Katritsis et al. showed that addition of GP ablation to PVI conferred a significantly higher success rate compared with either PVI or GP ablation alone in patients with paroxysmal AF.²⁵ Furthermore, anatomic ablation of the main left atrial GP alone, without complete PVI, prevented AF recurrence in 48% of the patients. Compared with PVI with linear ablation, GP ablation in addition to PVI indicated lower AF recurrence and lower rates of ablation-related atrial flutter after 3 years of follow-up.²⁶ Further studies need to explore optimal GP locations and appropriate strategy to determine therapeutic effect.

Renal Sympathetic Denervation

Renal sympathetic denervation (RDN) with catheter ablation is a method of modulating both afferent and efferent sympathetic nerves and has been studied as a treatment for drug-resistant hypertension.²⁷ One possible mechanism is that ablating the afferent nerves decreased feedback activation to the central nervous system and thereby decreased sympathetic input to the heart or other structures.²⁸ In a porcine model of obstructive sleep apnea, RDN inhibited the shortening of atrial ERP and lowered AF inducibility.²⁹ RDN also reduced atrial nerve sprouting, atrial fibrosis, and complexity of AF in a goat model with persistent AF.³⁰ In a canine study, we found that RDN can result in significant remodeling of the SG, reduction of SGNA, and brain stem remodeling as evidenced by neuronal cell death and reduced ^{18}F -FDG uptake.³¹ These changes, in turn, were associated with a significant reduction of paroxysmal atrial tachyarrhythmia episodes.

These findings indicate that modulation of the ANS by RDN might be effective in reducing atrial arrhythmogenesis and preventing the generation of atrial substrate to sustain arrhythmias. A recent prospective clinical trial randomized patients with paroxysmal AF and hypertension to receive either RDN with catheter ablation or catheter ablation alone.³² The results showed that RDN with ablation significantly increased the likelihood of freedom from AF at 12 months. This and other studies suggest that RDN may be helpful in controlling AF.³³

Low-Level Vagal Nerve Stimulation

Vagal nerve stimulation (VNS) shortens atrial ERP and APD in the pulmonary vein and is a reliable technique used for the experimental induction of AF.³⁴ Low-level cervical VNS (LL-VNS) at a stimulus strength of 1 V below the threshold necessary to reduce heart rate can lower intrinsic cardiac nerve activity and, paradoxically, suppress electrically induced AF in open-chest, anesthetized dogs.³⁵ The antiarrhythmic effects are still present even when the

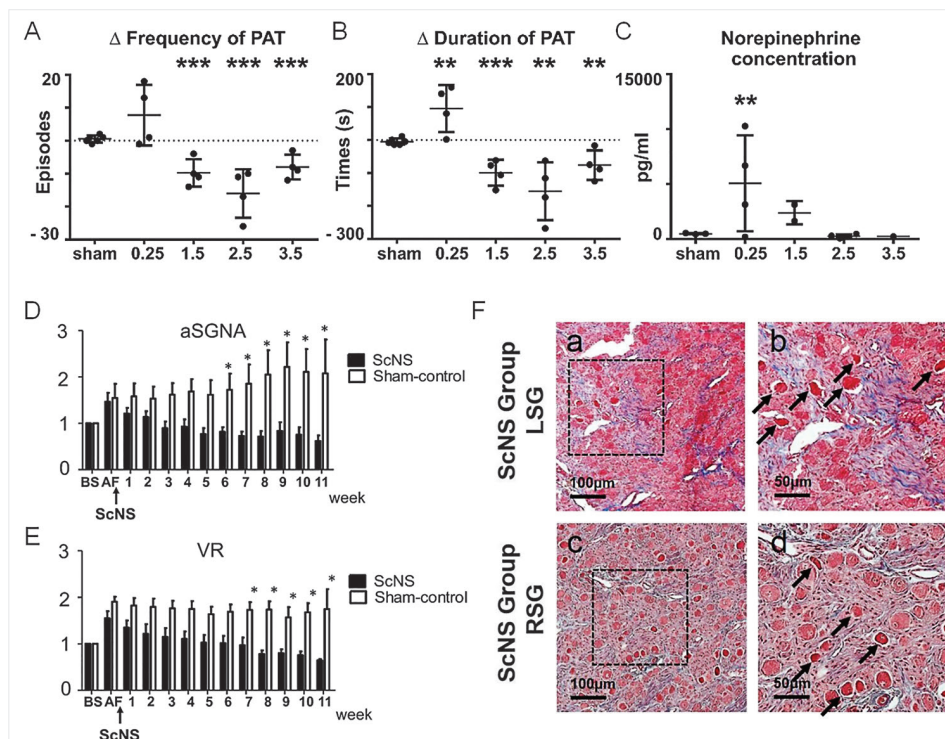


Figure 1.

Effects of subcutaneous nerve stimulation in an ambulatory canine model. (A) The delta PAT frequency per 48 hours and (B) PAT durations between baseline and after ScNS protocol among the 5 groups: sham, 0.25 mA, 1.5 mA, 2.5 mA, and 3.5 mA output of ScNS. (C) The plasma norepinephrine concentrations among the 5 groups. Asterisks indicate significantly ($P < .009$) higher concentrations in the 0.25 mA group ($n = 4$) than in all other dogs ($n = 10$). (D, E) Temporal changes of the aSGNA and VR, respectively, at different times after persistent AF in the ScNS group (filled columns) and in the sham stimulation group (unfilled columns). Compared with baseline (BS), there are significant decreases in aSGNA after 6 weeks and in VR after 7 weeks of ScNS. (F) Examples of Masson's trichrome staining in stellate ganglion (SG) after ScNS, indicating damaged region with increased fibrosis in both the left SG (LSG in a and b) and right SG (RSG in c and d). High-power views in the dotted square (b and d), indicate abnormal morphology of damaged neurons with eosinophilic staining (arrows). * $P < .05$, ** $P < .01$, *** $P < .001$. A-C modified from Wan et al., *Heart Rhythm*, with permission.²¹ D-F modified from Yuan et al. *Heart Rhythm*, with permission.²³ PAT: paroxysmal atrial tachycardia; ScNS: subcutaneous nerve stimulation; aSGNA: average stellate ganglion nerve activity; VR: ventricular rate; AF: atrial fibrillation

stimulus strength is 50% below the threshold. In addition, LL-VNS reverses the electrical remodeling caused by rapid atrial pacing.³⁶ Shen et al. used direct nerve recordings to demonstrate that continuous LL-VNS suppressed paroxysmal atrial tachyarrhythmias in ambulatory dogs by suppressing SGNA.³⁷ The mechanisms of LL-VNS in AF suppression are not fully understood. Histologically, LL-VNS causes structural remodeling in the

left SG, characterized by a significant reduction of ganglion cells stained by TH. Subsequent studies have shown that in the left SG, LL-VNS also resulted in the upregulation of the small-conductance Ca^{2+} -activated K^+ channel type 2 and increased its expression in the cell membrane.⁵ These changes may facilitate afterhyperpolarization of the ganglion cells and reduce the frequency of neuronal discharges.³⁸

Thus, LL-VNS can functionally and structurally remodel the left SG and reduce sympathetic outflow to the heart, hence its anti-AF property.³⁹ The effect of VNS is therefore not limited to its interaction with the parasympathetic nervous system.

In a clinical trial, 54 patients undergoing cardiac surgery were randomized into LL-VNS and sham groups, and a temporary bipolar pacing wire was sutured to vagal nerve preganglionic fibers near the superior vena cava.⁴⁰ LL-VNS was found to reduce the occurrence of postoperative AF. Considering the invasiveness of VNS, which can directly connect the electrodes with vagal nerves, less-invasive methods are needed to facilitate its clinical application. For example, the auricular branch of the vagal nerve is accessible through stimulation of Tragus, the anterior protuberance of the ear. In canine models, tragus stimulation reduced the electrical and structural remodeling induced by rapid atrial pacing.⁴¹ In a pilot study of 40 patients who presented for AF ablation, tragus stimulation decreased pacing-induced AF duration and systemic cytokine levels compared with earlobe stimulation.⁴² Larger randomized trials are necessary to determine the clinical efficacy of tragus stimulation in managing AF.

CONCLUSION

The neural mechanisms of AF have been studied, and the cardiac ANS is believed to play an important role. Simultaneous sympathovagal activation via both the extrinsic and intrinsic cardiac ANS increases calcium entry and simultaneously shortens the APD, which induces AF through late-phase 3 EAD and triggered firing in the pulmonary veins. Neuromodulation methods such as electrical stimulation and renal denervation cause SG remodeling and reduce sympathetic outflow and may be more effective for managing patients with AF. Further clinical trials testing neuromodulation methods are needed to determine their role in managing AF.

KEY POINTS

- Large sympathetic nerve discharges precede the onset of paroxysmal cardiac arrhythmias, including atrial fibrillation.
- Sympathetic nerve activity activates calcium and potassium channels to initiate cardiac arrhythmias.
- Electrical stimulation of sympathetic nerves and renal denervation both cause stellate ganglion remodeling, which reduces sympathetic nerve activity and controls cardiac arrhythmias.

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Conflict of Interest Disclosure:

Dr. Chen noted that Indiana University has received a patent for the neuECG technology.

Keywords:

autonomic nervous system, atrial fibrillation, neuromodulation, skin sympathetic nerve activity

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