



# Development of neuromodulation for atrial fibrillation: a narrative review

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**Background and Objective:** Atrial fibrillation (AF) is a prevalent clinical arrhythmia with a high incidence of disability and mortality. Autonomic nervous system (ANS) plays a crucial role in the onset and persistence of AF, and can lead to electrophysiological changes and alterations in atrial structure. Both animal models and clinical findings suggest that parasympathetic and sympathetic activity within the cardiac ANS could induce atrial remodeling and AF. Remodeling of the cardiac autonomic nerves is a significant structural basis for promoting AF. Given the challenges faced by conventional pharmacological and atrial ablation techniques in the treatment of AF, increasing attention has been paid to autonomic intervention strategies for AF. Current research has demonstrated that the frequency and severity of AF episodes can be significantly reduced by modulating the activity of ANS. ANS neuromodulation is expected to lead more effective and personalized treatment options for patients with AF. The objective of this review is to provide a broader perspective for future related studies by reviewing preclinical and clinical studies of neuromodulation methods for the treatment of AF, searching for relevant approaches to treat AF, as well as identifying the strengths and weaknesses demonstrated by current relevant studies, and providing researchers with a broader overview of the latest neurological treatments for AF.

**Methods:** A narrative review was conducted on the literature on PubMed, WanFang data, and Google Scholar, including all relevant studies published until November 2023.

**Key Content and Findings:** In this review, we delve into the innervation of cardiac autonomic nerves, the role of the ANS in the development and maintenance of AF, and the current neuromodulation methods for AF treatment. These methods include stellate ganglion (SG) resection or ablation, vagus nerve stimulation (VNS), thoracic subcutaneous nerve stimulation (ScNS), renal denervation (RDN) therapy, ganglionated plexus (GP) ablation, and epicardial botulinum toxin or CaCl<sub>2</sub> injection. More and more research suggests that neuromodulation methods for the treatment of AF have broad prospects.

**Conclusions:** ANS plays a crucial role in AF development and maintenance through cardiac autonomic nerve remodeling. Modulating ANS activity can significantly reduce AF frequency and severity, offering more personalized treatment options. Current research on autonomic interventions for AF shows promise for more effective and personalized treatments.

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**Keywords:** Atrial fibrillation (AF); autonomic nervous system (ANS); neuromodulation; cardioneuroablation (CNA); development

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## Introduction

Atrial fibrillation (AF) is a prevalent clinical arrhythmia that can result in severe complications, including heart failure and stroke, and has a high incidence of disability and mortality. The cardiac autonomic nervous system (ANS) is crucial in maintaining the electrical activity and mechanical contraction of the heart (1-5). Remodeling of the cardiac autonomic nerves is a significant structural basis for promoting the development and maintenance of AF. Current approaches to autonomic intervention for AF include stellate ganglion (SG) resection or ablation, vagus nerve stimulation (VNS), thoracic subcutaneous nerve stimulation (ScNS), renal denervation (RDN) therapy, ganglionated plexus (GP) ablation, epicardial botulinum toxin or CaCl<sub>2</sub> injection, and others. This review explores the evidence supporting the role of the cardiac ANS in the development of AF and neuromodulation in the treatment of AF. We present this article in accordance with the Narrative Review reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-1981/rc>).

## Methods

We searched PubMed, WanFang data, and Google Scholar for references with the terms “cardiac innervation”, “atrial fibrillation”, “ANS”, “SG”, “RDN”, “GP ablation”, “epicardial injection” or their combination in the title or abstract and applied inclusion and exclusion criteria. We also found relevant articles by checking the reference lists of the selected articles. The search strategy is summarized in *Table 1*.

## Cardiac innervation

Cardiac ANS can be divided into three levels. The first level is central nervous system neurons (including the brainstem, hypothalamus spinal cord and spinal cord neurons regulated by higher centers). The second level is peripheral neurons, including the extracardiac intrathoracic ganglionic plexus,

such as SG. The third level is endogenous cardiac ANS. Besides, cardiac ANS can be divided into extrinsic and intrinsic nerves. Extrinsic nerves connect the fibers between the heart and the nervous system, while intrinsic nerves are located within the pericardium (1-3).

### *Intrinsic cardiac nervous system (ICNS)*

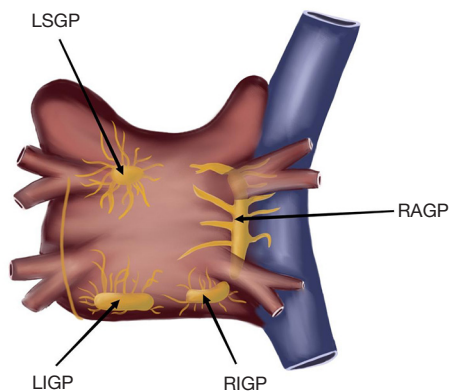
The main components of the intrinsic cardiac ANS are primarily ganglionic plexi. Anatomically, In the atria, ganglionic plexi are clustered in specific locations on the chamber walls. Another region that receives abundant ANS innervation and contains a high density of ganglionic plexi is the junction between the pulmonary vein (PV) and left atrium. The right superior GP (RSGP) is located on the anterosuperior surface of the right atrium, medial to the superior vena cava/right atrium junction and lateral to the aortic root. The left superior GP (LSGP) is located at the junction of the left superior PV with the posterior left atrium, in the left superolateral area; right inferior GP (RIGP) and left inferior GP (LIGP) are located at the inferior aspect of the posterior wall of the left atrium, below the right and left PVs; right anterior GP (RAGP) is located in the superoanterior area around the root of the right superior PV (*Figure 1*). The ligament of Marshall (LOM) which is located between the anterior aspect of the left PVs and the posterior left atrial appendage also contains autonomic neurons (4-7).

ICNS serves as a neural network crucially linked to the autonomic control of the heart and the pathophysiology of AF. When stimulated by afferent nerves, GPs function as network nodes. They initiate a cascade of signaling effects between themselves, fostering positive feedback to amplify activation effects. Consequently, this exposure prompts the atrial myocardium to release a significant amount of neurotransmitters rapidly, resulting in a profound remodeling of the atrial electrophysiological properties, ultimately culminating in AF induction (8). In addition, LOM has been implicated in the development and maintenance of AF. In animal study, researchers

**Table 1** The search strategy summary

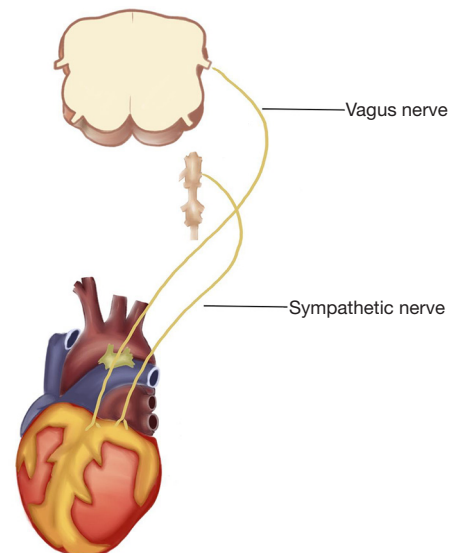
Items	Specification
Date of search	30/11/2023
Databases and other sources searched	PubMed, WanFang data, and Google Scholar
Search terms used	Search terms: “cardiac innervation” OR “atrial fibrillation” AND “ANS” OR “atrial fibrillation” AND “SG” OR “atrial fibrillation” AND “RDN” OR “atrial fibrillation” AND “GP ablation” OR “atrial fibrillation” AND “epicardial injection”
Timeframe	1975–2023
Inclusion and exclusion criteria	Inclusion: articles related to cardiac innervation and studies involving neuromodulation methods for the treatment of AF. All available studies, written in English or Chinese Exclusion: papers of which no full text was available
Selection process	N.Y. conducted the literature search and analysis. All authors reviewed the final list of studies included in the review
Any additional considerations, if applicable	Some papers were not obtained from PubMed but were rather referenced in papers from the original PubMed search

ANS, autonomic nervous system; SG, stellate ganglion; RDN, renal denervation; GP ablation, ganglionated plexus ablation; AF, atrial fibrillation.



**Figure 1** Left atrial autonomic GP: LSGP; LIGP; RAGP; RIGP. GP, ganglionated plexus; LSGP, left superior ganglionated plexus; LIGP, left inferior ganglionated plexus; RAGP, right anterior ganglionated plexus; RIGP, right inferior ganglionated plexus.

found that LOM ablation prolonged the atrial effective refractory period (AERP), inhibited the induction of AF and reduced sympathetic indicators of heart rate variability and serum norepinephrine concentrations (9). Chugh *et al.* (10) mapped and ablated the LOM in 56 patients undergoing AF catheter ablation or post-ablation atrial tachycardia (AT), and the experimental results also confirmed involvement of LOM in the initiation and maintenance of AF or AT.



**Figure 2** Extrinsic cardiac nervous system.

### *External cardiac nervous system*

The extrinsic cardiac nervous system (ECNS) can be further divided into sympathetic and parasympathetic branches (*Figure 2*). The sympathetic nerves innervating the heart originate from the posterior lateral nuclei of the hypothalamus, with preganglionic sympathetic fibers entering the lateral horn of the thoracolumbar spinal cord, mainly at T1–T5 level, and emanating from the spinal cord

into SG, which sends out postganglionic fibres to innervate the heart. SG is located on the surface of longissimus cervicis muscle anterior to C7 and T1 transverse processes, anteromedial to vertebral arteries, posteromedial to common carotid artery and jugular vein, and lateral to trachea and esophagus. Sympathetic innervation of sinoatrial node (SAN) is mainly from right SG (RSG), and sympathetic innervation of atrioventricular node (AVN) is mainly from left SG (LSG). Cardiac vagal fibres are derived mainly from dorsal and ambiguous nuclei of vagus nerve located in medulla oblongata, and the ganglion is located in the junctional area of PV, inferior vena cava (IVC), lower left atrium, and in the fat pad of atrioventricular groove. SAN is mainly innervated by right vagus nerve, while left vagus nerve mainly innervates AVN (11-14).

### Role of ANS in AF

ANS is correlated with electrical remodelling, which is an important feature of AF initiation and maintenance. The structural basis for this theory originates from the discovery of rich autonomic innervation and GPs associated with the PVs and sites in the atria from which AF triggers often originated. The mechanism of AF is related to the ANS and local innervation of the heart. Several studies from basic science laboratories and clinical investigations have provided compelling evidence implicating abnormal autonomic reactivity in the genesis and propagation of AF (15). In animal models, parasympathetic stimulation has been found to increase susceptibility to AF. Vagal nerve stimulation (VNS) not only shortens the AERP and action potential duration (APD), but also increases AERP dispersion, providing substrate for AF. Additionally, VNS causes slowing of the heart rate, premature depolarisation, and the onset and persistence of AF (16). It should be noted that while medium to high levels of VNS promote AF, low levels of VNS (LLVNS) reduce AF induction and autonomic remodelling (17).

The sympathetic nervous system plays a crucial role in the development and maintenance of AF. Sympathetic activation facilitates ectopic activity by causing both early afterdepolarization (EAD) and delayed afterdepolarization (DAD). Direct recordings of the SG, and the IVC-inferior atrial GP also suggest that sympathetic activation increases ventricular rate (VR) in ambulatory dogs with AF (18). Moreover, sympathetic discharges were found to always precede the onset of paroxysmal atrial fibrillation (PxAf) in animal studies (8). Furthermore, a clinical study found

that skin sympathetic nerve activity (SKNA) shows a positive correlation with VR during both paroxysmal and persistent AF, and bursts of this activity are linked to an acceleration of VR (19). Sympathetic neuromodulation has been shown to exert antiarrhythmic effects in humans with AF. One study shown that changes in sympathetic tone modulate immunoinflammation and activate myocardial inflammatory infiltrates, and that sympathetically released norepinephrine (NE) significantly increases P53 expression in endothelial cells and macrophages. Sympathetic tone was increased by rapid stimulation of the atria, and an increase in atrial macrophage infiltration was observed, as well as elevated levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6), and interleukin-1 (IL-1) (20). Increased or prolonged  $Ca^{2+}$  transient during an abbreviated action potential can give rise to EADs and triggered AF by enhanced forward sodium-calcium (Na-Ca) exchange (21). Sympathetic nerves release excessive amounts of NE during overactivation, causing a large inward flow of  $Ca^{2+}$ , resulting in intracellular  $Ca^{2+}$  overload and triggering early posterior depolarization or delayed posterior depolarization, which is an important mechanism by which increased sympathetic nerve activity triggers AF (22).

### Neuromodulation methods for AF

#### SG resection or ablation

SG plays a key role in atrial sympathetic remodeling and is related to the development and maintenance of AF (23). Electrical stimulation of the SG can induce sympathetic hyperinnervation leading to more atrial nerve sprouting, and a higher incidence of PxAf (24). In an animal study, researchers successfully eliminated PxAf in dogs with atrial rapid pacing-induced heart failure by cryoablation of bilateral SG and T2 to T4 thoracic ganglia (25). Zhou *et al.* (26) found that unilateral SG excision reduced the rate of AF induction in AF model of dogs. In another animal experiment, twelve dogs were randomly assigned to two groups (experimental group: establishment of AF model + LSG resection; Control group: establishment of AF model only) and manipulated to observe. Finally, it was found that 1 month after LSG resection, the mean VR was approximately  $139.2 \pm 5.6$  beats/min in control dogs and  $106.5 \pm 4.9$  beats/min in experimental dogs ( $P < 0.001$ ), and AVN anterograde effective refractory period (ERP) was significantly prolonged in experimental dogs compared with that in control dogs ( $265.6 \pm 7.8$  vs.  $251.1 \pm 4.6$  ms,  $P = 0.003$ ),

the results suggest that resection of lower part of left SG may be effective in slowing down the fast VR in AF dogs by prolonging the AVN forward ERP (27). Other researchers have found that VR can be effectively reduced by removing the lower portion of SG in dogs with persistent AF (28). All of the above studies have effectively demonstrated that resection or ablation of SG reduces the sympathetic innervation of heart and can effectively inhibit the onset and maintenance of AF. Therefore, the treatment of AF by SG resection or ablation deserves to be thoroughly investigated.

### **SG block (SGB)**

SG is an important source of major sympathetic inputs to heart, and SGB has been shown to be beneficial in the treatment of recalcitrant ventricular arrhythmias by inhibiting cardiac neuromembrane signaling, but SGB is less studied in the treatment of AF (29). In a prospective study, 36 patients with PxAF were randomly assigned to treatment with percutaneous SGB or placebo prior to pulmonary vein isolation (PVI), and the trial found a significant reduction in the rate of AF induction after SGB compared with before SGB (54% vs. 100%,  $P < 0.01$ ) (30). In another pilot study, the rate of postoperative AF (POAF) in patients who successfully underwent SGB was significantly lower than the institution's rate of POAF in coronary artery bypass graft (CABG) surgery patients (18.2% vs. 27%) (31). In a randomized controlled trial, 200 patients scheduled to undergo lobectomy were randomized to receive SGB and not to receive SGB, and final experiment found that the incidence of AF was 3% and 10% in the group that received SGB and the group that didn't receive SGB, respectively ( $P = 0.045$ ), and the results of the study showed that preoperative SGB can effectively reduce the incidence of intraoperative and postoperative AF (32). In addition, although image guidance has improved visualisation of targets, anatomical variants of relevant structures may lead to block failure (33). However, based on the previous studies, we can still see that SGB shows promise in reducing POAF. At present, SGB is still in initial stage of research on the treatment of AF, further research is needed to determine its exact efficacy and safety.

### **VNS**

VNS was first used to treat refractory epilepsy (34) and refractory depression (35). VNS could increase parasympathetic tone (36), which may counteract the effects

induced by sympathetic activation and its associated NE release (37). VNS may also limit apoptosis and remodeling of cardiomyocytes (38,39). VNS reduces the release of inflammatory factors through the "cholinergic anti-inflammatory pathway" to attenuate myocardial injury (40), and protects cardiomyocytes against ischemia and hypoxia by releasing acetylcholine (41). In addition, VNS limit apoptosis through inducing the phosphorylation of Akt and Bad and inhibiting the release of mitochondrial cytochrome c into the cytosol and the activation of caspase-3 (42). The LLVNS group had significantly lower levels of TNF- $\alpha$  and IL-6 compared to the control group (43). Li *et al.* (44) found that subthreshold cervical VNS could significantly prolong ERP, inhibit AF induction, and shorten the duration of AF. Jiang *et al.* (45) found that LLVNS increased IVC-inferior atrial ganglionated plexus nerve activity (IAGPNA) and impaired bilateral SG structure, resulting in VR control during persistent AF. In a clinical study, POAF was found to occur in 3 patients (12%) in the LLVNS group, which was significantly lower than that in the group did not receive LLVNS (36%) ( $P = 0.03$ ) (43).

Generally, VNS was performed in the cervical vagal nerve by implanting a programmable pulse generator to stimulate vagal efferent fibers and increase the activity of vagal nerve (29). Cervical VNS has some adverse side effects, which limit its clinical application. Cervical VNS requires surgical implantation of hardware, which can increase the risk of postoperative complications such as infection (46). Other acute side effects of VNS include neck pain, coughing, difficulty swallowing, voice alteration and nausea. In the longer term, a failure of the hardware may require revision surgery, leaving the patient at risk of experiencing a relapse of their symptoms until the VNS can be restored (47). In recent years, noninvasive transcutaneous vagal nerve stimulation (tVNS) was applied to suppress AF (48). In AF canine model, tVNS was found to suppress AF by reversing atrial remodeling and shortening AERP with rapid atrial pacing (49). Yu *et al.* (50) found that tVNS can inhibit the shortening of atrial refractoriness reduce the activity of cardiac ANS, and slow down autonomic remodeling in obstructive sleep apnea-induced AF. In a randomized clinical trial investigating the impact of chronic low level tragus stimulation (LLTS) on patients with PxAF, it was discovered that chronic, intermittent LLTS led to a reduced AF burden compared to sham control stimulation. This supports the use of LLTS as a treatment for PxAF in certain patients [Transcutaneous Electrical Vagus Nerve Stimulation to Suppress Atrial Fibrillation (TREAT-AF);

NCT02548754] (20). As a noninvasive neuromodulation method, tVNS would have great advantages to be used in the clinical treatment of AF. However, there are many parameters that need to be considered in the real-life application, such as the stimulation frequency, stimulation site, interval period, current intensity, etc. Therefore, more studies are still necessary to understand the mechanism of action and effect of tVNS.

### **Thoracic ScNS**

Thoracic subcutaneous nerve originates primarily from the SG (51). Stimulating the subcutaneous sympathetic nerves in the area or the sympathetic component within the vagal nerve may also be effective in treating AF (52). Some studies suggest that low-intensity (0.25 mA) ScNS results in increased cardiac sympathetic sprouting, elevated plasma NE concentrations, and prolonged AT duration leading to arrhythmias, whereas the opposite effect is observed with high-intensity (2.5 and 3.5 mA) stimulation (53). In an experimental animal study, Yuan *et al.* (54) found that ScNS in the thorax could lead to SG cell death, reduced SG nerve activity, and suppress paroxysmal AT in ambulatory dogs. In another study conducted by this team, 13 dogs with persistent AF were randomly assigned to the ScNS (n=6) and sham control (n=7) groups, and postoperative results showed that mean SG nerve activity decreased from  $4.00 \pm 1.68 \mu\text{V}$  after induction of persistent AF to  $1.72 \pm 0.42 \mu\text{V}$  after ScNS (P=0.03), and demonstrated that thoracic ScNS induces neural remodeling in the brain stem and SG, regulates the VR, and maintains the left ventricular ejection fraction in ambulatory dogs with persistent AF (55). There is also a prospective randomized clinical trial (NCT04529941) underway. However, more study is needed on ScNS to confirm its safety and effectiveness.

### **RDN**

RDN is an interesting neuromodulation strategy for the treatment of AF. RDN was originally developed technique for the treatment of hypertension by disrupting renal sympathetic afferent and efferent nerves in order to attenuate renal and systemic sympathetic nerve activity. In recent years, RDN is gradually beginning to be used in therapeutic strategies for AF. Many experimental studies have investigated the mechanisms underlying the potential antiarrhythmic effects of RDN and have found that RDN could reduce atrial sympathetic sprouting (56), modulate

atrial substrate (57), reverse atrial electrical and structural remodeling, and inhibit AF-induced changes (58). In a clinical study, 9 out of 13 patients (69%) who received PVI with RDN were free of AF, compared to 4 out of 14 patients (29%) in the PVI-only group, showing a statistically significant difference with a P value of 0.03. The result found that RDN reduced systolic and diastolic blood pressure in patients with drug-resistant hypertension and reduced AF recurrences when combined with PVI (59). In a pilot study of 20 patients followed for 1 year, RDN decreased the AF burden in min/day from a median (interquartile range) of 1.39 (0–11) pre-RDN to 0.67 (0–31.6) at 6 months (P=0.64) and to 0.94 (0–6.0) at 12 months (pre-RDN *vs.* 12 months; P=0.03), with a significant improvement in quality of life (60). In the randomized controlled trial (NCT01873352), Steinberg *et al.* compared RDN combined with PVI to PVI alone for the treatment of AF, and found that RDN added to PVI significantly increased the likelihood of freedom from AF at 12 months compared with PVI alone (61). Recent studies have indicated that achieving complete RDN with RF energy may be challenging due to inconsistent circumferential denervation and insufficient depth to induce irreversible nerve injury. As a result, alternative catheter-based RDN approaches such as ultrasound, cryogenic, or chemical methods have been explored (62–64). There is limited data regarding the efficacy and safety of these methods. However, there are also some studies indicate that RND by ultrasound could ensure consistent and complete energy delivery all around and a more reliable procedure compared to RF energy, and feasibility trials have demonstrated its effectiveness and safety (65). Therefore, RND by ultrasound have a promising future. With the development of basic and clinical research and approaches on RDN, RDN may be a candidate method to treat AF in patients with refractory hypertension in the future.

### **GP ablation**

Epicardial GP has an important role in the pathogenesis of AF. The GP function as the “integration centers” modulating the autonomic interactions between the extrinsic and intrinsic cardiac ANS. Scherlag *et al.* (66) suggested that the activation of cholinergic neurotransmitters from atrial ganglionic plexus results in the shortening of atrial and PV sleeve refractoriness. At the same time, the release of adrenergic neurotransmitters triggers an excessive intracellular calcium mobilization, leading to EADs and triggered firing, especially in PV cells. The heightened

activity of these local atrial ganglionic plexus nodes played a crucial role in initiating drug-resistant PxAF and resisting cardioversion. Numerous studies have shown that stimulation of the GP adjacent to the orifice of the right or left superior PVs in normal dogs greatly facilitates the induction and maintenance of AF by rapid pacing at the left atrium-PV junction (67,68).

Over the past decade, the ablation of GPs has been assessed as an additional procedure for treating patients with AF. GP ablation plays a crucial role in reducing and minimizing AF recurrence (69,70). A recent study by Hu *et al.* (71) suggests that endocardial ablation of the right anterior GPs resulted in a notable heart rate increase in 93% of patients. Furthermore, the right anterior GP seems to play a crucial role in suppressing positive vagal responses and elevating heart rate during PVI (72). These findings demonstrate the importance of GP ablation of specific sites between the PVs and interatrial groove when targeting AF. Kondo *et al.* (73) reported that ablation of active GPs on the right side of the PVs resulted in 92% sinus rhythm maintenance in patients at 3 months' follow-up.

### Traditional GP ablation

The main methods of GP ablation include radiofrequency (RF) catheter ablation and surgical ablation. Cardioneuroablation (CNA) was the first technique proposing vagal denervation by endocardial RF ablation, and AF is one of the CNA's first indications (74). In a long-term evaluation of vagal denervation by CNA, researchers found that there was an important and significant vagal and sympathetic denervation after 2 years of CNA, with a significant reduction in bradyarrhythmia and tachyarrhythmia in the whole group, and there were no complications (75). In addition, previous study showed that targeting GP with catheter ablation improves the outcomes of PxAF ablation in addition to PVI. GP ablation alone without PVI is also useful in controlling PxAF in some patients. A systematic meta-analysis demonstrates that the addition of GP ablation is associated with increased rates of freedom from AT/AF in patients with paroxysmal AF (76). And another meta-analysis also shows a significant reduction in AF recurrence when GP ablation is added to PVI compared with PVI alone (77). However, few study showed that GP ablation did not result in additional benefits in patients with a large left atrium, persistent AF and/or a history of prior catheter ablation (78). These different outcomes suggest that GP ablation is effective in managing patients with PxAF, but its effects in patients with persistent AF and advanced atrial diseases might be limited. There

are still many questions regarding how to achieve complete GP ablation without partial denervation, the best targets and methods for catheter-based GP ablation or surgical GP ablation, and how to prevent reinnervation after GP ablation. Further research in this field and the development of new technologies and strategies are necessary before GP ablation can be effectively utilized in the management of patients with AF.

### Epicardial botulinum toxin or CaCl<sub>2</sub> injection

Direct epicardial injection of botulinum toxin or CaCl<sub>2</sub> into the major GP induces neurotoxicity and inhibits cardiac ANS hyperactivity (12). Botulinum toxin is a neurotoxin that has been shown to reduce vagal nerve-induced AERP shortening and prevent ANS remodeling in animal models (79,80). In a clinical pilot study, 60 patients with PxAF undergoing CABG received either botulinum toxin or placebo injections in four major GPs (RAGP, IVCI-IAGP, LSGP, and LIGP). The results showed that epicardial botulinum toxin injection reduced incidence of POAF in the month and up to 3 years following CABG (81). CaCl<sub>2</sub> injections have also been shown to induce apoptosis within the cardiac GPs and prevent POAF in animal studies (82). CaCl<sub>2</sub> is thought to lead to intracellular calcium overload, causing neurotoxicity. A recently published randomized sham-controlled trial of 200 patients demonstrated that injection of CaCl<sub>2</sub> into the four major atrial GPs reduced the risk of POAF by 63% (83).

### Pulsed field ablation (PFA) techniques

Modern PFA derived from direct current (DC) ablation which is initially investigated for the treatment of arrhythmias. However, due to technological limitations at the time, DC ablation has some complications, such as coronary sinus injury (84). With the development of the technology, PFA has been successful in the field of oncology (85) and has attracted interest in its application in the cardiac field. PFA achieves ablation by inducing apoptosis through the non-thermal process of irreversible electroporation (86,87). Preclinical studies have demonstrated focused ablation of targeted tissues using specific energy parameters while sparing non-target tissues such as the PVs, the esophagus, coronary arteries, and the phrenic nerves (88-91). An animal study shows that targeting GPs-rich areas of the heart with PFA is feasible and effective in altering markers of cardiac autonomic tone (92). Another study also demonstrates the safety and feasibility of PFA to modulate the ANS during cardiac

surgery (93). These data support the excellent safety profile of the treatment. The reported freedom from atrial arrhythmia at 1 year is 81% for paroxysmal AF patients and 71% for those with persistent AF, showing an improvement compared to outcomes observed with RF and cryoballoon ablation technologies (94). To date, scientific and clinical evidence indicates that this epicardial selective GP ablation approach holds significant promise for treating AF.

## Conclusions

ANS plays a crucial role in the development and maintenance of AF. Remodeling of the cardiac autonomic nerves is a significant structural basis for promoting AF. Current research has demonstrated that the frequency and severity of AF episodes can be significantly reduced by modulating the activity of ANS. This provides more personalized and effective treatment options for AF patients. Before treatment, neuroscience therapies are selected according to the patient's different conditions and needs. For example, GP ablation can reduce recurrence rates, particularly after circumferential PVI in AF patients, and epicardial botulinum toxin or CaCl<sub>2</sub> injection aims to harness the neural regulation of myocardial tissue rather than using a destructive approach such as GP ablation. In addition, RDN has been shown to reduce implantable cardioverter-defibrillator (ICD) therapy in cardiomyopathy patients with recurrent ventricular tachycardia following catheter ablation and cardiac sympathetic denervation procedures (95). LLVNS represents a promising non-invasive method of autonomic modulation. But the sample sizes of many studies are small, more study is needed to confirm its safety and effectiveness. Overall, the current state of research on autonomic interventions for the treatment of AF shows good promise and is expected to lead more effective and personalized treatment options for patients with AF.

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