STATE-OF-THE-ART REVIEW

Neuromodulation for the Treatment of Heart Rhythm Disorders

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CME/MOC/ECME Objective for This Article: Upon completion of this activity, the learner should be able to: 1) describe the neurohormonal pathways that affect cardiac arrhythmias; 2) identify therapeutic options for refractory ventricular tachycardia; and 3) discuss the potential mechanisms for neurohormonal modulation.

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HIGHLIGHTS

- Derangement of autonomic nervous signaling is an important contributor to cardiac arrhythmogenesis.
- Modulation of autonomic nervous signaling holds significant promise for the prevention and treatment of cardiac arrhythmias.
- Further clinical investigation is necessary to establish the efficacy and safety of autonomic modulatory therapies in reducing cardiac arrhythmias.

SUMMARY

There is an increasing recognition of the importance of interactions between the heart and the autonomic nervous system in the pathophysiology of arrhythmias. These interactions play a role in both the initiation and maintenance of arrhythmias and are important in both atrial and ventricular arrhythmia. Given the importance of the autonomic nervous system in the pathophysiology of arrhythmias, there has been notable effort in the field to improve existing therapies and pioneer additional interventions directed at cardiac-autonomic targets. The interventions are targeted to multiple and different anatomic targets across the neurocardiac axis. The purpose of this review is to provide an overview of the rationale for neuromodulation in the treatment of arrhythmias and to review the specific treatments under evaluation and development for the treatment of both atrial fibrillation and ventricular arrhythmias. (J Am Coll Cardiol Basic Trans Science 2019;4:546–62) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

ANATOMY OF THE NEUROCARDIAC AXIS

The neurocardiac axis is composed of multiple intricate areas that provide an interface between the nervous system and the cardiovascular system (Figure 1). This neurocardiac anatomy has been elegantly detailed in a recent review (1). A number of diverse brain structures contribute to efferent cardiac autonomic signaling, including the amygdala, insula, thalamus, and cerebellum (2). In general, second-to-second control of autonomic tone occurs at the level of the brainstem, whereas forebrain structures including the hypothalamus effect more prolonged or gradual shifts in autonomic tone (3). From these various brain areas, sympathetic signals are first transmitted via the cervical and thoracic spinal cord to the stellate (cervicothoracic) ganglion before synapsing with nerves of the intrinsic cardiac nervous system (4). In contrast, parasympathetic fibers originate in the brainstem and travel primarily via the vagus nerve into the pericardial sack (1). There, sympathetic and parasympathetic efferent fibers form a branching neural network clustering in autonomic ganglionic plexi (AGP) contained in fat pads on the posterior surface of the atria and the superior aspect of the ventricles (Figure 1) (5). AGP contain large populations of colocalized sympathetic and parasympathetic neurons (1), and may serve as

"integration centers" modulating cardiac responses to autonomic input (6). Emerging evidence indicates that these AGP contain an amalgam of afferent neurons, motor neurons, interconnecting local circuit neurons, and that some proportion of these neurons expresses both cholinergic as well as adrenergic immunoreactivity (1). The extensive interconnections as well as the colocalization of cholinergic and adrenergic neurons set the stage for interplay between the parasympathetic and sympathetic nervous system at the level of the AGPs. Beyond the direct communication between the autonomic nervous system (ANS) and the heart, the neurocardiac axis is under modulatory control from additional autonomic reflexes, including afferent nervous input from the baroreflex and the renal nerves, which may modulate the global and regional (cardiac) sympathetic tone.

ATRIAL FIBRILLATION

RATIONALE FOR AUTONOMIC MODULATION FOR ATRIAL FIBRILLATION. Atrial fibrillation (AF) is a common and significant medical problem that affects approximately 3% of the population (7). As the population ages, the in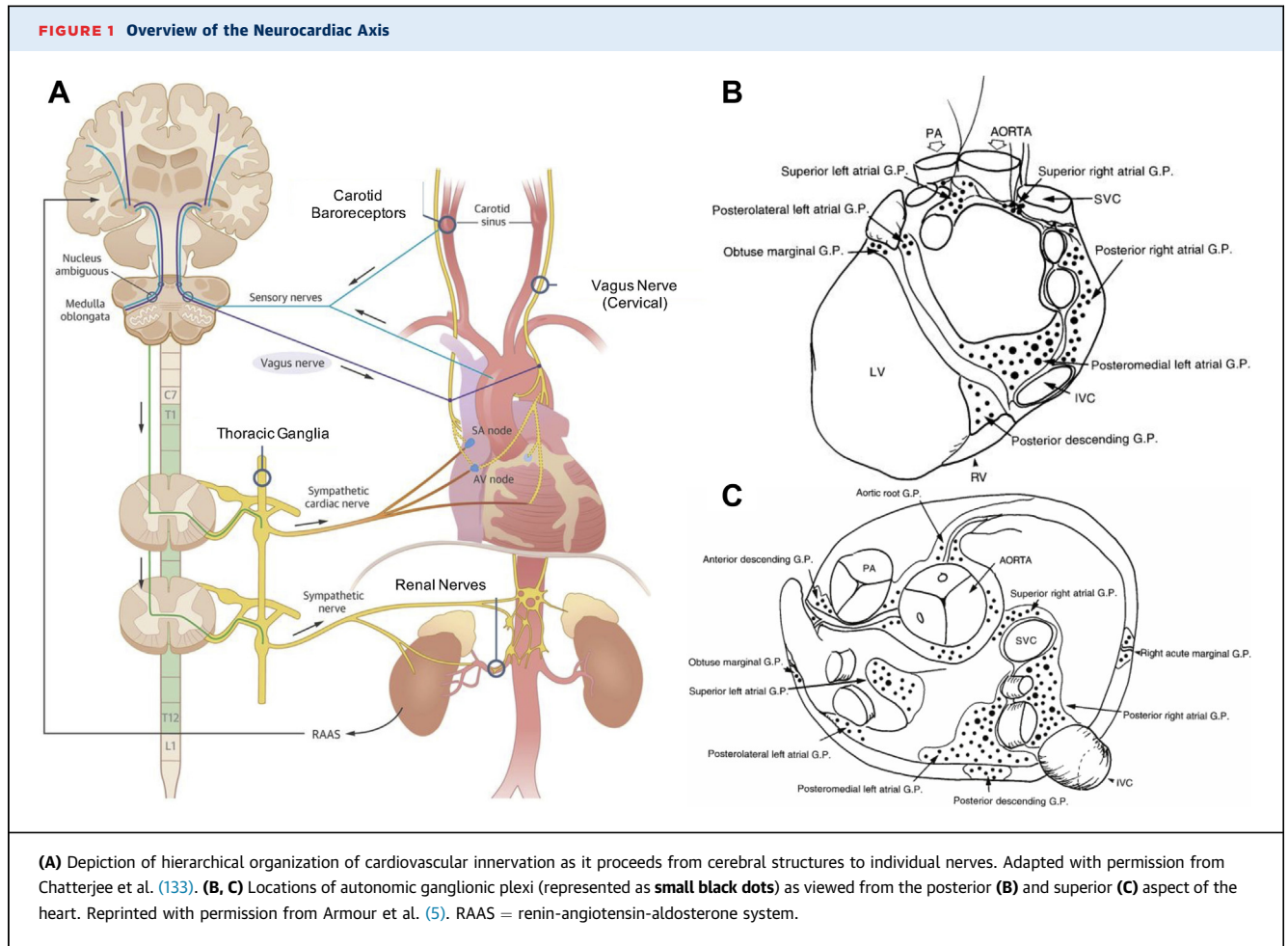cidence and prevalence of AF are projected to increase even further (8). In addition to being a leading cause of stroke, AF is associated with increased risks of heart failure (HF), myocardial infarction (MI), cognitive impairment, and death (9). The severity or persistence of AF has been associated with worse outcomes, including a higher risk of stroke (10); however, the role of AF burden (proportion of time spent in AF) in adverse outcomes remains incompletely understood (11). Given both its prevalence and impact, AF is a significant public health concern, and reduction of AF and its attendant complications remains a priority for the cardiovascular community.

An increasing body of evidence suggests that activity of the ANS can contribute to the initiation and perpetuation of cardiac arrhythmias, including AF. In isolated atrial myocytes, parasympathetic input shortens the atrial effective refractory period (AERP) (12) and increases dispersion of refractoriness (13), whereas sympathetic input increases calcium transient currents and afterdepolarizations (4), synergistically promoting the onset of AF (14). Similar responses to sympathetic stimulation are observed in pulmonary veins, a common site of ectopy that

triggers AF (15). Although both parasympathetic and sympathetic stimulation may individually promote AF (16,17), data suggest that combined parasympathetic and sympathetic (sympathovagal) discharges are especially potent initiators of AF (15,18) due to the combined effects of shortened AERP and increased calcium transient currents, respectively. Changes in heart rate variability (HRV) before onset of AF (19,20) are consistent with combined sympathovagal discharges. There are also data to suggest that AGP may influence focal sources or drivers of AF. For example, a study of 97 patients undergoing catheter ablation of AF has shown that the majority of patients had a focal source or rotor that overlapped with the anatomic location of an AGP (21). Because AGPs play a crucial role in AF, several strategies to prevent or reduce AF have centered around modulating AGP activity directly or indirectly through the extrinsic cardiac nervous system.

PAST AND PRESENT. Current strategies in autonomic modulation for atrial arrhythmias. A number of strategies to reduce AF partially exert their effects through modulation of the cardiac ANS (**Table 1**). Beta blockers antagonize the effects of catecholamines on a variety of target tissues, such as cardiac and vascular adrenergic receptors (22). AF ablation may also exert some benefit through autonomic modulation. In addition to creating electrical isolation of the pulmonary veins from the left atrium (23), pulmonary vein isolation (PVI) also reduces AGP-induced firing of pulmonary vein potentials that initiate AF. A positive response to AGP stimulation after extensive PVI independently predicts recurrence of AF (24), suggesting that AGP modulation may contribute to the efficacy of AF ablation.

Aggressive risk factor reduction also reduces the risk of AF. Part of the benefit of weight loss may be explained by alteration of autonomic tone as the metabolic syndrome has been associated with increased sympathetic tone (25). Similarly, obstructive sleep apnea (OSA) results in sympathetic activation (26) and increased focal sources of AF (27) both contributing to an increased risk of AF. Management of these risk factors reduces ANS hyperactivity and may impact the success of AF ablation (28). Treatment of sleep apnea with continuous positive airway pressure decreases risk of AF progression (29), and reduces risk of recurrent AF after catheter ablation (30). Adaptive servo-ventilation, which may be used to treat obstructive, central, or mixed sleep apnea, was recently shown to decrease AF burden in patients with HF and sleep apnea (31). Risk factor reduction such as weight loss and treatment of sleep apnea has the
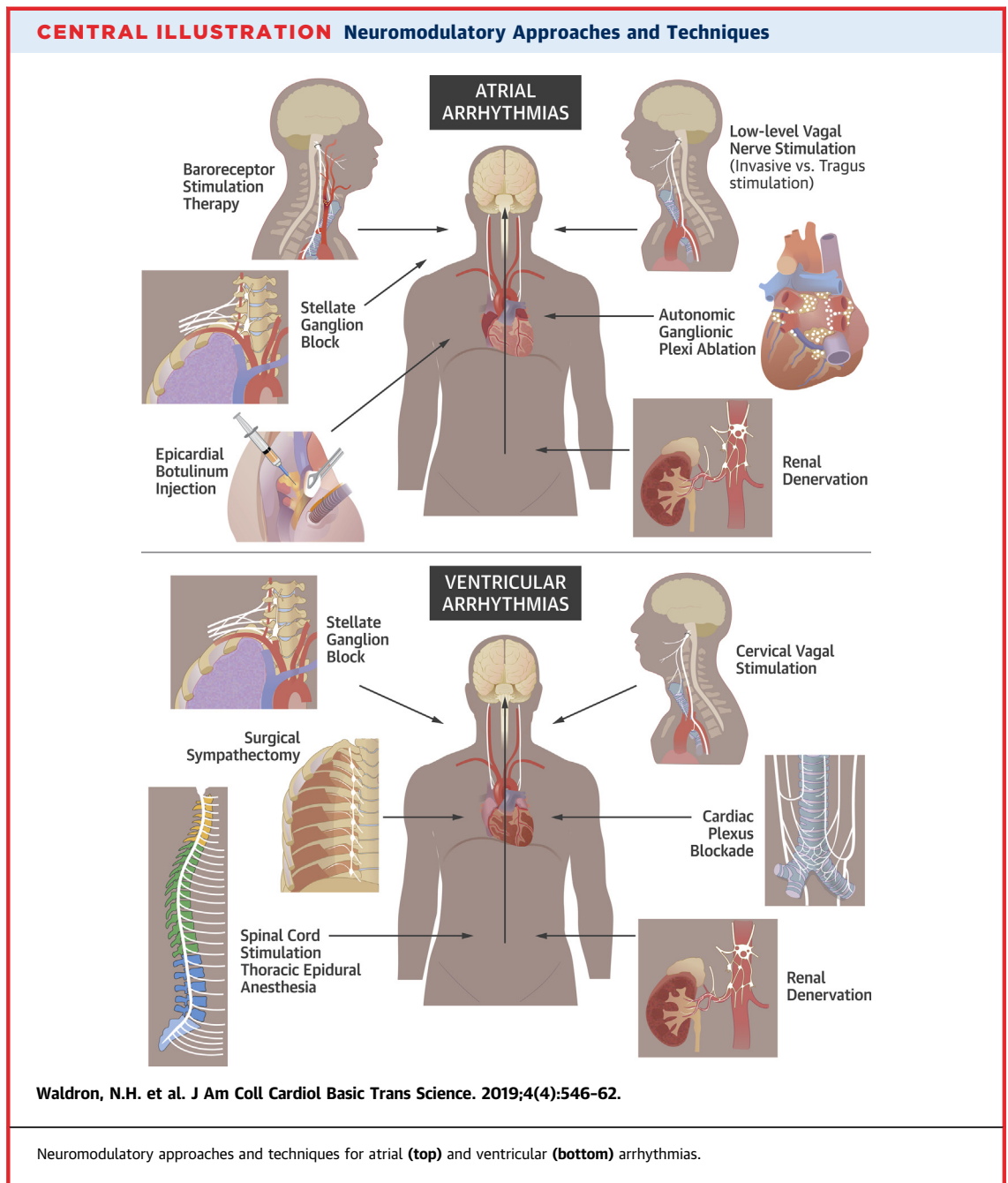
FIGURE 1 Overview of the Neurocardiac Axis

(A) Depiction of hierarchical organization of cardiovascular innervation as it proceeds from cerebral structures to individual nerves. Adapted with permission from Chatterjee et al. (133). **(B, C)** Locations of autonomic ganglionic plexi (represented as **small black dots**) as viewed from the posterior **(B)** and superior **(C)** aspect of the heart. Reprinted with permission from Armour et al. (5). RAAS = renin-angiotensin-aldosterone system.

potential to improve autonomic function and reduce AF through several different mechanisms.

DEVELOPING NEUROMODULATORY APPROACHES.
Ablation-based approaches. ***AGP ablation.*** Ablation of AGP by either catheter-based or surgical approaches has shown some promise in improving the success of AF ablation (**Central Illustration**). Percutaneous anatomically guided AGP ablation as a stand-alone technique has limited efficacy (32) and is inferior to circumferential PVI (33). However, randomized data have shown that the addition of AGP ablation to PVI may increase freedom from AF compared to either technique in isolation (34). Additionally, AGP ablation combined with PVI may result in increased long-term freedom from AF and lower rates of atrial flutter than PVI + linear ablation (35). Not all studies have supported the efficacy of AGP ablation. A recent comparison of video-assisted thoracoscopic surgery for AF with or without AGP ablation showed no difference in freedom from AF; additionally, patients undergoing epicardial AGP ablation had

higher rates of procedural complications and pacemaker implantation (36). Further studies are needed to clarify optimal methods of AGP localization and ablation, and the potential benefits of AGP ablation.

TABLE 1 Current Therapeutic Strategies for Rhythm Control of AF

Current Therapeutic Strategies for AF	Examples
Antiarrhythmic drug therapy	Class I: flecainide, propafenone Class III: amiodarone, dronedarone, sotalol, dofetilide
Catheter ablation	Pulmonary vein isolation Substrate modification Ablation of nonpulmonary vein triggers
Surgical ablation	Cox-Maze procedure Thoracoscopic ablation ("mini-maze")
Risk-factor modification	Positive airway pressure for obstructive sleep apnea Blood pressure reduction Weight Loss
AF = atrial fibrillation.	

CENTRAL ILLUSTRATION   Neuromodulatory Approaches and Techniques

Waldron, N.H. et al. J Am Coll Cardiol Basic Trans Science. 2019;4(4):546–62.

Neuromodulatory approaches and techniques for atrial **(top)** and ventricular **(bottom)** arrhythmias.

Renal denervation. Renal denervation (RDN) is a method of modulating central afferent input. Renal afferent and efferent nerves function in a reflex loop where afferent input from the kidney to the central nervous system (CNS) regulates the efferent sympathetic nerve output to the heart and back to the kidney. Renal afferent nerves are diverse and represent a heterogeneous population of fibers including myelinated and nonmyelinated fibers (37,38). Two main types of renal afferents are responsible for relaying information to the CNS, mechanosensitive (hydrostatic pressure from renal vasculature), and chemosensitive receptors (sensitive to ischemia, osmolar changes, and ionic composition) (39). Functionally, the renal afferent fibers can be divided into: 1) pressor; 2) reno-renal; and 3) depressor types (40,41). In other words, some fibers when activated contribute to the elevation of the sympathetic tone (sympatho-stimulant), whereas others reduce the sympathetic tone (sympatholytic). This is supported

TABLE 2 Current Status of Developing Neuromodulatory Strategies for Arrhythmias

Intervention	Anatomical Target	Current Status	Diseases of Interest	Number of Patients	Ongoing Clinical Trials
AGP ablation	Autonomic Ganglionic Plexi	Clinical trials	AF	60	NCT03535818: Adjunctive Ganglionated Plexus Ablation in Redo-Pulmonary Vein Isolation (ADD-GP); Randomized trial testing the efficacy of AGP ablation in patients with ongoing paroxysmal arrhythmias after PVI
			AF	14	NCT03636100: Release of Acetylcholine From the Ganglionated Plexus During the Thaw Phase of Cryoballoon Pulmonary Vein Ablation (GP RESPONSE Study); Observational study designed to study the role of systemic acetylcholine release in response to cryoballoon ablation.
			POAF	62	NCT02035163: Atrial Fibrillation Prevention in Post Coronary Artery Bypass Graft Surgery with Cryoablation for Ganglionic Plexi; A randomized study to test the ability of AGP cryoablation during cardiac surgery to prevent POAF.
Epicardial botulinum toxin injection	Autonomic ganglionic plexi	Clinical trials	POAF	170	NCT02617069: Botulinum Toxin Injection Into Epicardial Fat Pads to Prevent Atrial Fibrillation in Patients Undergoing Cardiac Surgery; Randomized trial of epicardial botulinum toxin for the prevention of POAF after cardiac surgery in patients with paroxysmal AF.
			POAF	330	NCT03779841: A Phase II, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of Botulinum Toxin Type A (AGN-151607) Injections Into the Epicardial Fat Pads to Prevent Post-Operative Atrial Fibrillation in Patients Undergoing Open-Chest Cardiac Surgery; Randomized double-blind, placebo-controlled, dose-ranging trial evaluating the efficacy and safety of epicardial botulinum toxin type injections to prevent POAF in patients undergoing cardiac surgery.
BRS therapy	Carotid and aortic baroreceptors	Preclinical	POAF	95	NCT03243279: BRS and Outcomes in Cardiothoracic Surgery; Observational study to determine if perioperative baroreceptor sensitivity (BRS) correlates with POAF and outcomes after cardiothoracic surgery
TVNS	Auricular branch of the Vagus Nerve (Afferent)	Clinical trials	POAF	42	NCT03533140: Postoperative Atrial Fibrillation Suppression By Nerve Stimulation; Randomized trial testing TVNS to prevent POAF and reduce inflammation
			POAF	200	NCT02783157: Transcutaneous Autonomic Modulation In Thoracic Surgery (TON-POINTS); Trial evaluating TVNS to reduce POAF after cardiothoracic surgery.
			AF	52	NCT02548754: Transcutaneous Electrical Vagus Nerve Stimulation to Suppress Atrial Fibrillation (TREAT-AF); A small study to evaluate the ability of TVNS to reduce atrial fibrillation burden and inflammation in patients with paroxysmal AF.
RDN	Sympathetic nerves around the renal arteries (afferent)	Clinical trials	AF	300	NCT01635998: Adjunctive Renal Denervation in the Treatment of Atrial Fibrillation (H-FIB); Phase II trial to evaluate the ability of combined RND and PVI versus PVI only to reduce recurrent AF.
			AF	100	NCT01990911: Renal Sympathetic Denervation Prevents Atrial Fibrillation in Patients with Hypertensive Heart Disease: a Pilot Study (RDPAF); Phase II trial testing efficacy of RDN to reduce subclinical AF and restore autonomic imbalance.
			AF	138	NCT02115100: Treatment of Atrial Fibrillation in Patients by Pulmonary Vein Isolation in Combination With Renal Denervation or Pulmonary Vein Isolation Only (ASAF); Open-label trial testing the ability of combined RDN and PVI to reduce recurrent AF after PVI.
			AF	61	NCT01907828: A Feasibility Study to Evaluate the Effect of Concomitant Renal Denervation and Cardiac Ablation on AF Recurrence (RDN+AF); Phase II trial evaluating the feasibility of RDN combined with AF ablation in reducing recurrent AF in patients with AF and uncontrolled hypertension.
			AF	40	NCT03246568: Renal Nerve Denervation After Pulmonary Vein Isolation for Persistent Atrial Fibrillation; Phase II study to evaluate the efficacy of RDN added to PVI in reducing recurrent AF in patients with persistent AF.
			AF	100	NCT01686542: CPVI Plus Renal Sympathetic Modification Versus CPVI Alone for AF (Atrial Fibrillation) Ablation; Open-label trial evaluating the ability of RDN combined with PVI to reduce recurrent AF compared with PVI alone.
			AF	245	NCT02064764: Renal Nerve Denervation in Patients with Hypertension and Paroxysmal and Persistent Atrial Fibrillation (Symplicity AF); Phase II trial to assess the feasibility of concurrent RDN and PVI, and the rate of chronic treatment success in patients receiving RDN and PVI vs. PVI only
			AF	40	NCT01952925: Combined Afib Ablation and RA Denervation for the Maintenance of Sinus Rhythm and Management of Resistant Hypertension; Non-randomized prospective study to evaluate the ability of concurrent AF ablation and RDN to reduce ambulatory blood pressure.
			VT/VF	60	NCT02856373: Renal Nerve Stimulation and Renal Denervation in Patients With Sympathetic Ventricular Arrhythmias (Redress VT); Will assess impact of renal nerve stimulation before and after percutaneous transluminal RDN on cardiac excitable properties including induction of ventricular tachyarrhythmias before and after RDN
			VT/VF	38	NCT01858194: REnal Sympathetic dEnervaTion as an Adjunct to Catheter-based VT Ablation (RESET-VT); Prospective, multicenter, randomized control trial testing the impact of catheter-based renal sympathetic denervation (RSDN) as an adjunctive treatment for patients with cardiomyopathy undergoing catheter ablation of ventricular tachycardia (VT).

TABLE 2 Continued

Intervention	Anatomical Target	Current Status	Diseases of Interest	Number of Patients	Ongoing Clinical Trials
			VT/VF	462	NCT01747837: REnal SympathetiC Denervation to sUpprEss Tachyarrhythmias in ICD Recipients (RESCUE); Randomized, blinded trial to assess the efficacy of RDN in preventing ventricular arrhythmias and ICD shocks.
SCS	Efferent sympathetic fibers in the spinal cord	Clinical trials	POAF	60	NCT03539354: Temporary Spinal CoRd StiMulatIon to PreveNt Atrial FibrillaTION After Cardiac Surgery (TerminationAF); Phase II trial to assess the ability of temporary spinal cord stimulation in preventing POAF
TEA	Efferent sympathetic fibers in the spinal cord	Preclinical	AF or VT/VF		None, though TEA infrequently used in some centers to reduce pain and prevent POAF after cardiac surgery
SGB	Stellate ganglion (efferent fibers)	Clinical trials	POAF	707	NCT03269383: Study to Evaluate the Effectiveness of SGB in Preventing Post-Op Atrial Fibrillation; Phase II trial to evaluate the efficacy of safety of temporary SGB with bupivacaine to prevent POAF.
			VT/VF	20	NCT02646501: Prospective Randomized Clinical Trial for Effect of Stellate Ganglion Block in Medically Refractory Ventricular Tachycardia; Study evaluates the effect of SGB in patients with recurrent VT/VF despite optimal medical management
			VT/VF or AF	40	NCT03450226: Effects of Stellate Ganglion Block on Hemodynamics Instability During Beating Heart Surgery; A randomized controlled, blinded trial evaluating the effect of pre-operative SGB on perioperative arrhythmias and myocardial infarction after off-pump CABG.
Invasive VNS	Vagus nerve (efferent fibers)	Preclinical	VT/VF or AF		None, although animal studies have demonstrated the ability of low-level invasive VNS to reduce sympathetic outflow as well as AF inducibility
Surgical sympathectomy	Thoracic sympathetic ganglia (efferent fibers)	Clinical trials	Heart failure - VT/VF prevention	30	NCT03071653: Left Cardiac Sympathetic Denervation for Cardiomyopathy Feasibility Pilot Study (LCSD); A randomized controlled trial to test the potential safety and efficacy of LCSD in patients with heart failure due to non-ischemic and ischemic cardiomyopathy
Transtracheal cardiac plexus blockade	Cardiac plexus (efferent fibers)	Preclinical	VT/VF		None

AF= atrial fibrillation; AGP = autonomic ganglionic plexus; BRS = baroreceptor stimulation; ICD = implantable cardioverter-defibrillator; POAF= postoperative atrial fibrillation; PVI = pulmonary vein isolation; RDN = renal denervation; SCS = spinal cord stimulation; SGB = stellate ganglion block; TEA = thoracic epidural anesthesia; TVNS = transcutaneous vagal nerve stimulation; VF = ventricular fibrillation; VNS = vagal nerve stimulation; VT = ventricular tachycardia.
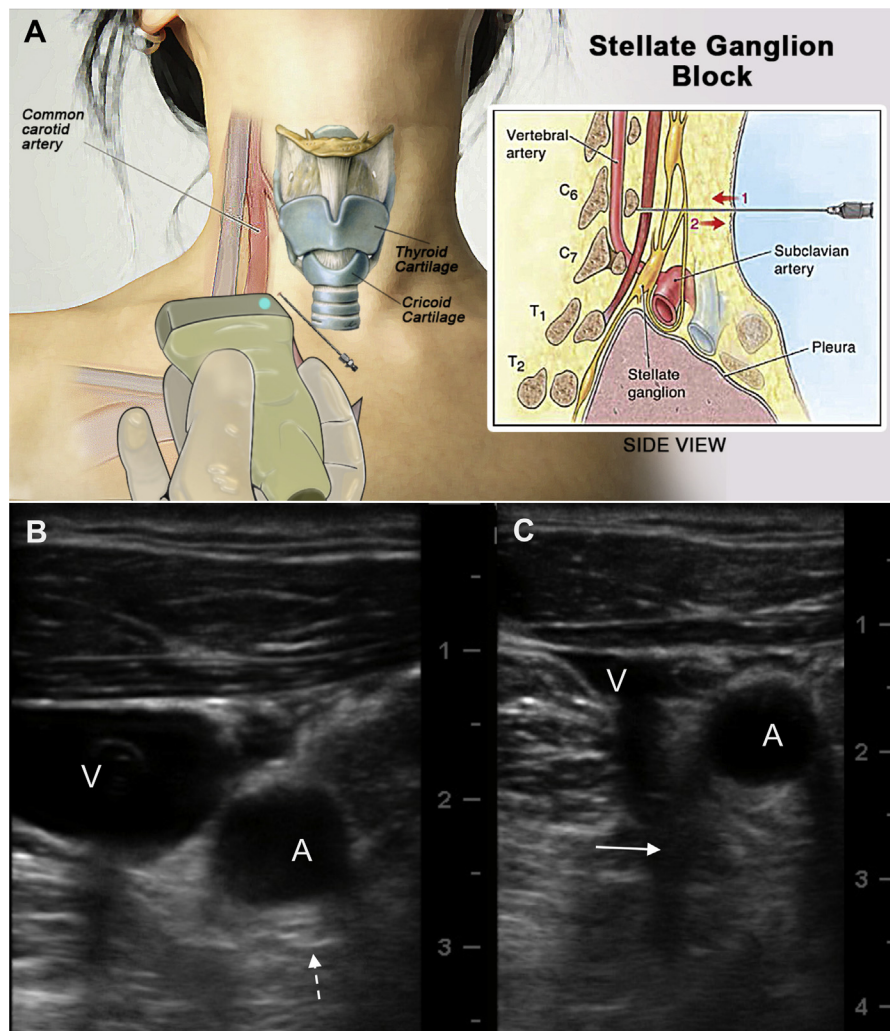
by increasing preclinical and clinical evidence suggesting that endovascular electrical mapping with stimulation of the renal arteries can result in a differential response including an elevation in blood pressure (42-46).

RDN has received a lot of interest for the treatment of hypertension but may also have utility in reducing arrhythmias through autonomic mechanisms. As mentioned above, the renal vasculature is richly innervated by both afferent and efferent sympathetic nerves which contribute to systemic autonomic signaling. Ablating these nerves may reduce both systemic and cardiac catecholamine levels, as well as reduce atrial fibrosis through modulation of the renin-angiotensin-aldosterone system (47). In a rabbit model of ischemic cardiomyopathy, RDN reduced deleterious atrial structural and electrical remodeling and AF inducibility (48). Additionally, percutaneous RDN reduces atrial nerve sprouting, catecholamine levels, atrial fibrosis, and complexity of AF in a goat model of pacing-induced AF (49). Finally, RDN has been shown to attenuate the electrical and structural remodeling of the left atrium induced by long-term intermittent atrial pacing in a canine model (50).

There are few clinical trials evaluating RDN as an adjunct to PVI for the treatment of recurrent AF. A pilot study of 69 patients with chronic kidney disease and paroxysmal AF showed improved freedom from AF and reduction of AF burden at 1 year in patients randomized to PVI and RDN compared with PVI and spironolactone (51). A study of 86 patients with moderate or severe treatment-resistant hypertension randomized to either PVI alone or PVI with RDN showed improved freedom from AF with the addition of RDN; however, the benefit was most apparent in patients with severe hypertension (52). A follow-up analysis from this cohort has shown a reduction in AF recurrences and burden of AF in patients receiving RDN and PVI (53).

As a stand-alone therapy, RDN may also promote reverse-remodeling and improve atrial substrate. A pilot trial of 20 patients with paroxysmal or persistent AF and hypertension showed that RDN reduced AF burden and improved quality of life (54). Moreover, RDN reduced atrial conduction time, complex fractionated atrial activity, and ventricular mass in 14 patients with treatment-resistant hypertension (55). Multiple upcoming trials will help elucidate the role of

FIGURE 2 Stellate Ganglion Block

(A) Illustration of an ultrasound-guided percutaneous stellate ganglion block. **(B, C)** Ultrasound images of the percutaneous approach on the right side. **(B)** Image obtained before needle insertion. **Dashed arrow** indicates the sympathetic ganglion. **(C)** Image obtained during needle insertion (**arrow**) and anesthetic infusion. **A** marks the carotid artery. **V** marks the jugular vein. Adopted with permission from Armour et al. (104).
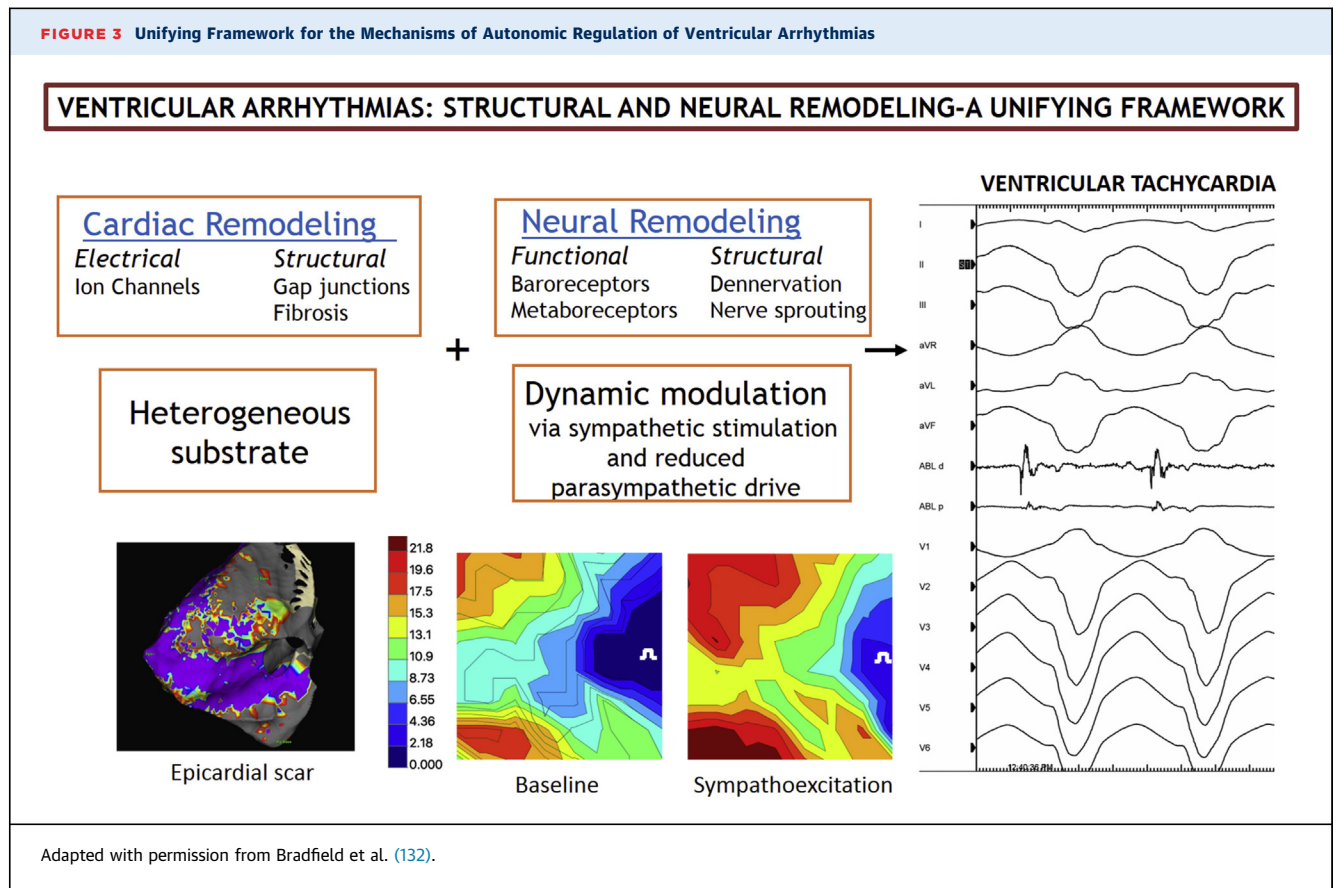
RDN as a stand-alone technique or in addition to PVI to reduce sympathetically mediated AF (**Table 2**).

Pharmacologic approaches. *Epicardial botulinum toxin injection.* Given the role of the AGP in the initiation and perpetuation of AF, additional nonablative strategies to modulate AGP signaling are currently under active investigation (**Table 2**). Injection of botulinum toxin into AGP reduces vagal influences on the AERP as well as vulnerability to AF in both canine (12,56) and ovine models (57). Given the temporary nature of this strategy, autonomic modulation using botulinum toxin injected into AGP has recently

gained attention as a potential strategy to reduce post-operative AF (POAF), a common and impactful complication after cardiac surgery (58,59).

This approach has been studied in 2 small clinical trials. In the first study, 60 patients with paroxysmal AF undergoing coronary artery bypass grafting (CABG) received botulinum toxin or placebo injected into the 4 major left atrial fat pads. With this approach, patients receiving epicardial botulinum toxin had reduced incidence of POAF in the first month after surgery (60), as well as reduced recurrent AF and AF burden at 1 and 3 years after surgery,

FIGURE 3 Unifying Framework for the Mechanisms of Autonomic Regulation of Ventricular Arrhythmias

Adapted with permission from Bradfield et al. (132).

respectively (61,62). In the second study, 130 patients undergoing CABG and/or valve surgery were randomized to receive epicardial botulinum toxin or placebo injected into the 4 left atrial fat pads as well as the anterior fat pad. Using this technique, there

was no difference between groups in the occurrence of in-hospital POAF; however, initial POAF episodes were shorter and there were no discernible adverse effects of botulinum toxin injections (63). Further large-scale clinical trials are necessary to determine the utility of this strategy in preventing POAF after cardiac surgery. Additionally, future work is necessary to determine whether botulinum toxin could be delivered to AGP in a less invasive fashion.

Stellate ganglion block. Percutaneous stellate ganglion block (SGB) is a minimally invasive interruption of autonomic innervation from the cervical sympathetic ganglia to the heart (**Figure 2**). As a key relay station for sympathetic nerve signaling, the stellate ganglion is a prime target for autonomic modulation to reduce AF. Ablation of bilateral stellate ganglia eliminates atrial tachycardia episodes in a canine model of pacing-induced HF (64). A promising minimally invasive strategy to temporarily modulate autonomic signaling is SGB with percutaneous injection of local anesthetic—a procedure frequently used to treat pain syndromes in ambulatory clinics. A pilot study of 36 patients undergoing PVI as well as short duration SGB (unilateral, left or right) has shown that

TABLE 3 Current Therapeutic and Adjunctive Strategies for VT/VF

Current Therapeutic Strategies for VT/VF	Examples

Pharmacotherapy	Beta-adrenergic blockade
	  Nonselective (ß-1, ß-2): carvedilol, nadolol, propranolol
	  Selective (ß-1): metoprolol, esmolol
	Membrane active antiarrhythmic drugs
	  Class I: lidocaine, mexiletine, procainamide
	  Class III: sotalol, amiodarone, dofetilide

Ablation	Catheter ablation of focal VT, triggers, and substrate modification (endocardial and epicardial)
Mechanical circulatory support	Temporary: Intra-aortic balloon pump, Impella (ABIOMED, Danvers, Massachusetts) extracorporeal membrane oxygenation, et cetera Permanent: Left ventricular assist device, et cetera
Surgery	Surgical ablation Ventricular aneurysm resection Transplantation

Abbreviations as in **Table 2**.

SGB lengthened the AERP while reducing inducibility and duration of AF (65). Similarly, a pilot study of 25 patients undergoing CABG and/or aortic valve surgery showed the feasibility and potential efficacy of left-sided SGB for the prevention of POAF (66). A larger study of SGB to prevent POAF is forthcoming and will provide important insight regarding the potential effectiveness of this technique (NCT03269383).

Bioelectronic approaches. *Low-level vagal nerve stimulation.* High-frequency vagal nerve stimulation (VNS) shortens the AERP (67) and action potential duration in the pulmonary veins (68), facilitating the initiation of AF. However, the intensity of VNS appears to modulate its arrhythmogenicity, with low-level VNS (LLVNS) (below the bradycardia threshold) generally showing a protective or antiarrhythmic effect. Left-sided LLVNS causes upregulation of inhibitory small-conductance calcium-activated potassium channels in the stellate ganglia (69). Similarly, intermittent left cervical VNS is able to slow the ventricular rate in a canine model of pacing-induced AF by damaging the ganglion (70) and increasing activity of the AGP (71). Together, these studies suggest that the antiarrhythmic effect of LLVNS may be mediated through decreased stellate ganglia activity as well as alteration of AGP signaling.

The vagus nerve can be stimulated directly with electrodes; however, given the risks of cervical VNS implantation, recent attention has focused on alternative and less-invasive methods of delivering VNS. Stavrakis et al. (72) recently explored the role of LLVNS in preventing POAF. In their study, 54 patients undergoing cardiac surgery who had a temporary bipolar pacing wire placed in vagal preganglionic fibers near the superior vena cava were randomized to LLVNS or sham stimulation for the duration of postoperative intensive care unit stay. They found that LLVNS reduced the occurrence of POAF. They also found that LLVNS ameliorated the post-operative cytokine elevation associated with cardiac surgery, raising the hypothesis that LLVNS has an anti-inflammatory effect (72).

Because vagal nerve projections exist in the ear, LLVNS may be delivered through stimulation of the tragus. In canine models of pacing-induced AF, LLVNS delivered by tragus stimulation reduced the electrical and structural remodeling induced by rapid atrial pacing (73). Transcutaneous LLVNS increases HRV and decreases muscle sympathetic nerve activity in healthy volunteers, reflecting an anti-adrenergic effect (74). In a pilot study of 40 patients undergoing AF ablation, 1 hour of transcutaneous LLVNS via tragus stimulation decreased pacing-induced AF duration as well as systemic cytokine levels (75). Two trials are currently underway to evaluate the effectiveness of transcutaneous LLVNS in reducing ambulatory (NCT02548754) as well as postoperative AF (NCT02783157).

Baroreceptor stimulation. Mechanoreceptors in the carotid sinus and aortic arch (baroreceptors) generate dynamic feedback to brainstem centers responsible for autonomic tone, thereby exerting beat-to-beat control of blood pressure and heart rate (76). Electric stimulation of carotid baroreceptors reduces sympathetic tone (77) while augmenting vagal tone (78). Thus, baroreceptor stimulation (BRS) has the capacity to generate both pro-arrhythmic and antiarrhythmic influences relative to AF. In a canine model of low-level BRS at a voltage below the threshold to lower systemic blood pressure, 2 h of BRS was associated with increased AERP, increased AF threshold, and decreased cardiac AGP activity (79). This effect was further confirmed in porcine model of high- versus low-level BRS in simulated OSA, where low-level BRS prolonged AERP and reduced AF inducibility, whereas high-level baroreceptor stimulation shortened AERP and did not meaningfully impact AF inducibility. Whether low-level BRS can reduce the occurrence of AF remains to be seen. However, investigation into this potential avenue of neuromodulation for treatment of AF continues.

FUTURE OUTLOOK. Given the increasing prevalence as well as the morbidity associated with AF, new strategies to prevent or reduce AF remain an important unmet need. There has been great progress with current therapeutic strategies to reduce the morbidity of AF, including ablation-based as well as pharmacologic techniques. However, current therapies incompletely use the developing mechanistic understanding of the pathogenesis of AF. Because the ANS is an important contributor in the development of AF, strategies to modulate autonomic signaling hold significant promise in reducing both the incidence and consequences of AF. As outlined above, a number of early-stage clinical trials are ongoing to directly translate promising basic science findings into safe, efficacious strategies to reduce AF (**Table 2**). As the evidence base surrounding autonomic modulation to reduce AF continues to develop, one can anticipate a growing number of effective strategies using autonomic modulation to reduce AF.

VENTRICULAR TACHYCARDIA

RATIONALE FOR AUTONOMIC MODULATION FOR VENTRICULAR TACHYCARDIA. Despite improvements in our therapies for cardiovascular disease,

ventricular tachycardia (VT) and ventricular fibrillation (VF) remain significant challenges in cardiovascular practice. These life-threatening dysrhythmias are particularly common in cardiac and surgical intensive care units, and are responsible for more than 450,000 deaths every year in the United States alone (80). The sympathetic nervous system (SNS) plays a significant role in the genesis of ventricular arrhythmias, and thus represents an important therapeutic target (Central Illustration).

The interaction between the SNS and the heart can be reduced to efferent signals to the heart and afferent signaling from the heart. Sympathetic efferent signaling induces maladaptive changes in ventricular electrophysiology. Sympathetic activation has been shown to be able to either activate or maintain ventricular arrhythmias via the following mechanisms: 1) shortened refractory periods (81,82); 2) abbreviated action potential duration (83,84); 3) increased dispersion of refractoriness (85); 4) increased heterogeneity of repolarization (86), and; 5) induced early afterdepolarizations (87). In sum, sympathetically mediated changes in electrophysiology decrease the ventricular threshold and can induce ventricular arrhythmias. Furthermore, the underlying cardiomyopathy often results in autonomic imbalance and dysregulation as a result of underlying structural changes (scar/fibrosis) or persistent/recurrent states of HF (Figure 3).

It is now increasingly well understood that the afferent inputs from the heart and peripheral organs (such as the kidney to the ANS) contribute to maladaptive remodeling of the ANS in the presence of myocardial injury. For example, investigations in a canine model of MI have shown that myocardial injury induces morphologic and neurochemical changes in the bilateral stellate ganglia approximately 5 weeks after the initial insult (88,89). Beyond an increase in neuronal size, MI results in a persistent increase in the synaptic density of bilateral stellate ganglia and is associated with increased stellate ganglion nerve activity for up to 8 weeks.

Furthermore, there is evidence of circadian variation in the stellate ganglion nerve activity. Changes in gene expression and neuronal structure are not restricted to the stellate ganglia but can also be found in the dorsal root ganglia of the spinal cord (90,91). Finally, even without an apparent neuroanatomical link between renal nerves and the cardiac sympathetic tone, direct or indirect (myocardial ischemia) renal nerve activation leads to central nervous remodeling (stellate ganglia) with direct impact on cardiac sympathetic tone (92). These results suggest a potential mechanistic link between neural remodeling and ventricular arrhythmias.

PAST AND PRESENT. Current strategies in autonomic modulation for ventricular arrhythmias. *Clinical management.* At present, clinical management of VT/VF is often restricted to pharmacological therapy and catheter ablation (Table 3). In the setting of VT/VF storm, the underlying sympathetic hyperactivation is further exacerbated by ventricular arrhythmias, internal or external defibrillations, pain, anxiety, and progressive HF (93). Initial medical management that targets the ANS includes beta blockade.

Use of beta blockade is commonly the first and most important pharmacologic intervention for preventing VT/VF given its effectiveness in reducing sympathetic tone. However, beta blockade in the acute setting of electrical storm ($\geq$ 3 VT/VF episodes in 24 h) is often underused due to concerns for potential beta blockade-induced cardiac decompensation. The recently presented clinical study evaluating a non-selective beta blocker propranolol versus a selective beta blocker metoprolol in the setting of electrical storm has shown the safety and effectiveness of nonselective beta blockers in patients with high morbidity and mortality (94). In these patients, propranolol led to less ventricular arrhythmia compared with metoprolol. However, VT and VF are often refractory to medical management including beta blockade, antiarrhythmic drug therapy, and even mechanical hemodynamic support. Although monomorphic VT and premature ventricular contraction - triggered polymorphic VT may be amenable to successful radiofrequency ablation, this approach is not always immediately feasible, especially in critically ill or hemodynamically unstable patients.

Surgical approach. The concept of physically interrupting cardiac sympathetic innervation to treat ventricular arrhythmias was first introduced by Schwartz et al. (95), who studied the interaction of the ANS with ventricular arrhythmias and showed that surgical cardiac denervation increases the ventricular arrhythmia threshold in healthy dogs (n = 11), preventing induction of VT/VF with external stimulation. In the 1990s, unilateral (predominantly left-sided) surgical sympathectomy was applied in patients (n = 40) at high risk for ventricular arrhythmias after an MI and was found to reduce risk of sudden death significantly compared to controls without pharmacologic or surgical sympathetic inhibition (96). Given the success with SGB in patients with MI, surgical sympathectomy has been used to

treat patients with long-QT syndrome and catecholaminergic polymorphic VT (97).

Because unilateral sympathetic denervation may be insufficient in some cases, bilateral surgical sympathetic denervation has been proposed as an alternative and more effective therapy (98). Bilateral sympathetic denervation may be more effective due to bilateral stellate ganglion remodeling with cardiac injury (89) and anatomical variation in cardiac innervation (99). Ajijola et al. (98) have shown that bilateral surgical cardiac sympathetic denervation can be useful for the treatment of medically refractory electrical storm due to a number of causes and may result in improved outcomes compared to unilateral surgical denervation (100). With the exception of a single prospective study (96) that compared surgical sympathectomy to placebo, contemporary studies have been limited to retrospective observational studies. The largest published experience now encompasses 121 cases, and shows an association with decreased sustained VT and implantable cardioverter-defibrillator (ICD) shocks in patients with refractory VT (101).

Interventional approaches. Today, the modulation of the autonomic tone via operative sympathetic denervation (i.e., sympathectomy) is considered a useful intervention only when all other therapeutic options have been exhausted. However, not infrequently, patients presenting with electrical storm (≥3 VT/VF episodes in 24 h) have either failed traditional therapeutic approaches or are deemed too unstable to undergo surgical sympathectomy. These situations have led some investigators to use minimally invasive approaches to achieve temporary blockade cardiac sympathetic innervation. As a result, minimally invasive approaches to cardiac sympathetic blockade have emerged as therapeutic options and diagnostic tools to help gauge whether a given patient would benefit from the permanent surgical sympathectomy (**Figure 2**). Notably, interventional approaches to modulate the ANS in patients with VT are not widely adopted and often limited to select institutions across the world.

SGB. Similar to the limited evidence base for the use of SGB in the treatment of AF, the utility of SGB for the treatment of ventricular arrhythmias has been chronicled in individual case reports (102,103). Moreover, SGB has never been investigated in a prospective, controlled clinical study for the treatment of VT/VF. A systematic review of the literature yielded 35 published cases using mostly unilateral SGB (86% of cases) (104). SGB resulted in a significant reduction of ventricular arrhythmia episodes from 24-h pre- to 24-h post-SGB (mean, 16.5; 95% confidence interval [CI]: 9.7 to 23.1 events vs. mean, 1.4; 95% CI: 0.85 to 2.01 events; p = 0.0002) (104). The need for defibrillation decreased comparably (pre-SGB mean, 14.2; 95% CI: 6.8 to 21.6 events vs. post-SGB mean, 0.6; 95% CI: 0.3 to 0.9 events; p = 0.0026). Importantly, SGB was associated with a reduction of ventricular arrhythmia burden regardless of the etiology of cardiomyopathy (nonischemic vs. ischemic), type of ventricular arrhythmia (monomorphic vs. polymorphic), and degree of contractile dysfunction (preserved vs. reduced ejection fraction). In this series of uncontrolled observations, SGB was followed by surgical sympathectomy in 21% of cases.

An observational study of several different methods of autonomic blockade for the treatment of electrical storm has shown a substantial difference in mortality (~60% absolute risk reduction compared with standard care) in 49 patients (only 6 received unilateral percutaneous SGB) (105). Finally, the repeated observation that SGB is associated with a prolonged duration of arrhythmia suppression (3 to 4 days) well beyond what is expected from the duration of a pharmacological bock (~1 day) (102,103,106) suggests the presence of an afferent mechanism with potential effects on neural remodeling. The safety profile of this intervention appears to be favorable given the ability to deliver the nerve block under ultrasound guidance.

Thoracic epidural anesthesia. An alternative pathway to block the central sympathetic output and input to/from the heart is thoracic epidural anesthesia (TEA). Using an established anesthetic approach, TEA blocks afferent and efferent innervation between the heart and CNS. Anti-arrhythmic properties of TEA have been shown in several preclinical models (107,108). The safety and efficacy of thoracic epidural anesthesia was explored as part of several small case series (109,110). Successful reduction of ventricular arrhythmia burden was achieved in the majority of patients with refractory arrhythmias (6 of 11 patients, 55%). Notably, the use of thoracic epidural anesthesia is limited in the setting of antiplatelet or oral anticoagulation therapy due to concerns for high-risk bleeding.

Developing neuromodulatory approaches. *Alternative approaches to cardiac sympathetic modulation.* Beyond the direct surgical or minimally invasive approaches to modulate the autonomic innervation of the heart, there are series of novel interventional approaches to alter the sympathetic nervous tone. Spinal cord stimulation (SCS) at the level of T1 to T5 can modulate autonomic output, likely via inhibition of the stellate

ganglia, and possibly increased vagal activity (111,112). In animal models, SCS reduces HRV, decreases the incidence of ventricular arrhythmias, and reduces left stellate ganglion activity in acute MI (111). There are limited preliminary clinical data regarding the use of SCS. In 2 patients with ischemic and nonischemic cardiomyopathy, SCS reduced the VT and VF burden up to 75% to 100% (113). A prospective, multicenter randomized clinical study (N = 81 patients) that investigated the effects of SCS therapy for the treatment of systolic HF failed to show improved outcomes (114). Nevertheless, the exact mechanism of SCS on ventricular arrhythmias remains to be determined, and the clinical safety and efficacy of SCS for the prevention of recurrent ventricular arrhythmia remains unknown.

Transtracheal cardiac plexus blockade is a most recent novel attempt to interrupt cardiac sympathetic innervation. Sympathetic nerves converge from both stellate ganglia to form the cardiac plexus. Given the anatomical location of the cardiac plexus between pulmonary artery, aortic arch, and anterior wall of the trachea (115), the cardiac plexus is amendable to a transtracheal access. In a recent study, investigators provided initial evidence that temporary interruption of nerve traffic via lidocaine injection can counteract the effects of stellate ganglion stimulation and thus serve as a new avenue for temporary or permanent minimally invasive cardiac denervation (116).

RDN. As previously mentioned, RDN was initially developed for the treatment of hypertension and has been shown to reduce global and regional sympathetic nerve activity (117). In a porcine ischemia model, RDN reduced the number of spontaneous ventricular extrasystoles and VF in a similar manner to beta blocker therapy (118). The effects of RDN on ventricular electrophysiology appear to be independent of its effects on blood pressure as shown in initial preclinical and clinical studies. The early clinical experience with RDN and ventricular arrhythmias has also been encouraging (119). The largest multicenter case series has shown that bilateral RDN in 13 patients with refractory VT was associated with an 85% freedom from VT at 3 months and no periprocedural complications (120). In a second study including 10 patients, RDN led to a significant decrease in VT/VF burden and ICD shocks at 6 months (121). Despite recent advances for RDN as an antihypertensive strategy (122) and our improved understanding of the best procedural approach (46), definitive evidence to support its use as supplementary strategy for ventricular arrhythmias is needed.

VNS. VNS to augment cardiac parasympathetic tone and oppose sympathetic hyperactivation is also being evaluated for the prevention of ventricular arrhythmias. Preclinical studies support a favorable sympatholytic effect of direct efferent via the cervical vagus nerve or indirect afferent VNS via its auricular branches (123). Post-MI models provide additional evidence for the protective myocardial effects of VNS that are heart rate independent. In canine model of MI, high-intensity vagal stimulation led to a 71% VF-free survival versus 40% with low intensity and 10% in the control group (124). In parallel, prophylactic VNS in the setting of MI minimized the risk of VF onset (125).

FUTURE OUTLOOK. The growing burden of ventricular arrhythmias and their significant morbidity and mortality demands new effective therapeutic approaches. While there are several effective pharmacologic and catheter-based therapies for ventricular arrhythmias, these therapies frequently meet their limits in an increasingly complex medical environment (e.g., use of mechanical circulatory devices). The ANS is a new frontier in the management of ventricular arrhythmias. Before novel therapeutic strategies can be widely adopted in clinical practice, randomized clinical trials are needed to establish evidence of safety and efficacy (**Table 2**).

Given the myriad of new strategies to modulate the autonomic tone, there is a need to develop methods for individualizing treatment based on a given patient's triggers, comorbidities, and underlying pathology. Future therapies do not have to restrict themselves to secondary prevention nor a device-based approach to neuromodulation.

Recently published work has pioneered the use of optogenetic modulation of cardiac sympathetic nerve activity to prevent ventricular arrhythmias (126). Optogenetics is a relatively novel technology applied in neuroscience to silence or enhance neural activity via targeted genetic modification. Viral vectors are used to introduce an inhibitory light sensitive opsin into stellate ganglion neurons to silence them (127). When ArchT (inhibitory light-sensitive opsin) is genetically expressed in targeted cells, it can be activated via illumination using characteristic wavelength. Activation leads to cell hyperpolarization via activation of ionic channels and as a result silences target cells (128,129).

In a canine model, optogenetic (and reversible) stellate ganglia inhibition was protective against myocardial ischemia-induced ventricular arrhythmias (126). This work builds on prior attempts to modulate norepinephrine release from cardiac neurons via optogenetic modification (130). Targeted

genetic modulation resulted in a desired increase in norepinephrine release with consequent stimulation in cardiac function. Arguably, if this technology can be applied in man (cardiac plexus, stellate ganglia, thoracic sympathetic ganglia, and vagus nerve) it could be used as a preventative tool for high-risk patients with ventricular arrhythmias and as a therapeutic tool for patients with recurrent ventricular arrhythmias. The unique on/off property of the optogenetic modification is the central strength of this technology. A major limitation is the current need for direct application to the target nerve structure via injection for example.

The use of autonomic modulation for primary prevention is currently under investigation and if successful could have potentially far-reaching implications. An ongoing prospective randomized clinical trial is exploring the use of surgical sympathetic denervation for primary prevention of sudden cardiac death in patients with heart failure (131).

CONCLUSIONS

Over the past several decades, there has been increasing recognition of the importance of interactions between the heart and the ANS in the pathophysiology of arrhythmias. There are now a multiplicity of potential therapies under development to target several different neurologic targets and structures for both atrial and ventricular arrhythmias. Moving forward, randomized clinical trials will be essential to establish the safety, efficacy, and comparative effectiveness of these new and promising interventions.

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