STATE-OF-THE-ART REVIEW

Neuromodulation for Ventricular Tachycardia and Atrial Fibrillation



A Clinical Scenario-Based Review

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ABSTRACT

Autonomic dysregulation in cardiovascular disease plays a major role in the pathogenesis of arrhythmias. Cardiac neural control relies on complex feedback loops consisting of efferent and afferent limbs, which carry sympathetic and parasympathetic signals from the brain to the heart and sensory signals from the heart to the brain. Cardiac disease leads to neural remodeling and sympathovagal imbalances with arrhythmogenic effects. Preclinical studies of modulation at central and peripheral levels of the cardiac autonomic nervous system have yielded promising results, leading to early stage clinical studies of these techniques in atrial fibrillation and refractory ventricular arrhythmias, particularly in patients with inherited primary arrhythmia syndromes and structural heart disease. However, significant knowledge gaps in basic cardiac neurophysiology limit the success of these neuromodulatory therapies. This review discusses the recent advances in neuromodulation for cardiac arrhythmia management, with a clinical scenario-based approach aimed at bringing neurocardiology closer to the realm of the clinical electrophysiologist. (J Am Coll Cardiol EP 2019;5:881–96) © 2019 by the American College of Cardiology Foundation.

OVERVIEW OF CARDIAC AUTONOMIC CONTROL

The autonomic nervous system provides beat-to-beat control of cardiac function over an individual's entire lifetime. The 2 canonical limbs, sympathetic and parasympathetic, of the nervous system exist in a fine balance in normal physiological states (1). Cardiac disease profoundly alters this balance, causing sympathoexcitation and concomitant reduction in parasympathetic drive that are adaptive in the short term but become maladaptive in the long term if left unchecked (2).

Cardiac responses to internal and external stimuli are controlled by autonomic neural structures that

can be divided into 3 main levels (Figure 1): 1) brainstem and spinal cord; 2) extracardiac-intrathoracic ganglia; and 3) intrinsic cardiac nervous system (ICNS) (1,2). Comprehensive details of the anatomy and functional interplay between these levels are provided in several recent reviews (2–5), and only a general description is provided here to establish a relevant framework for this clinical review.

The cardiac motor neurons, termed efferent neurons, are divided according to their roles in either sympathetic or parasympathetic signaling. Sympathetic efferent pre-ganglionic neurons have cell bodies in the intermediolateral column of the spinal cord and project axons onto post-ganglionic sympathetic neurons, which are organized into the

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BCSD = bilateral cardiac sympathetic denervation

CPVT = catecholaminergic polymorphic ventricular tachycardia

CSD = cardiac sympathetic denervation

EF = ejection fraction

ES = electrical storm

GP = ganglionated plexus

HF = heart failure

ICD = implantable cardioverter-defibrillator

ICNS = intrinsic cardiac nervous system

LCSD = left-sided cardiac sympathetic denervation

LL = low level

LLTS = low-level tragus stimulation

LOM = ligament of Marshall

LQTS = long QT syndrome

LSG = left stellate ganglia

MI = myocardial infarction

PV = pulmonary vein

PVI = pulmonary vein isolation

RDN = renal artery denervation

RSG = right stellate ganglia

SCS = spinal cord stimulation

SG = stellate ganglia

SGB = stellate ganglion block

SHD = structural heart disease

TEA = thoracic epidural anesthesia

TNS = tragus nerve stimulation

VF = ventricular fibrillation

VNS = vagal nerve stimulation

VOM = vein of Marshall

VT = ventricular tachycardia

extracardiac-intrathoracic ganglia, including the middle cervical ganglia, stellate ganglia ([SG], a fusion of the C8 and T1 ganglia), T2 to T4 of the paravertebral sympathetic chain ganglia, and mediastinal ganglia. These postganglionic neurons then project via cardiopulmonary nerves to atrial and ventricular myocardium and intrinsic cardiac neurons (6). Pre-ganglionic efferent neurons of the parasympathetic system are located within the brain stem and project axons, which travel via the vagus nerve and its branches to post-ganglionic neurons within the ICNS (1). Cardiac sensory neurons, or afferent neurons, have cell bodies in the nodose and dorsal root ganglia and carry information from the heart to the brain stem and spinal cord. This sensory information is processed at multiple levels in complex feedback loops, which control sympathetic and parasympathetic efferent signals to maintain rhythm and circulation in the face of acute and chronic stressors (7). Finally, the ICNS itself (often referred to as the "little brain on the heart") is organized into ganglionated plexi (GP) with efferent and afferent neurons, which not only relay central signals but also form local reflexive circuits to independently regulate regional cardiac electrical, mechanical, and metabolic responses (8). Importantly, these ICNS neurons remain intact even when the heart is excised, and thus a transplanted heart comes with its own "little

Autonomic reflexes are a major pathophysiological driver of cardiac arrhythmias. Reduced cardiac output in disease states triggers acute baroreceptor reflexes, inflammatory pathways, and neuronal remodeling, which increase sympathetic output and decrease parasympathetic signaling (9). At the level of the heart itself, the ICNS is also thought to process local sensory information

and increase sympathetic outflow in a cardio-cardiac reflex (10,11). The consequent electrophysiologic responses coincide with arrhythmic susceptibility (12,13).

All 3 levels of the cardiac neuraxis undergo significant adverse remodeling in cardiac disease. In myocardial infarction (MI), for example, the ICNS undergoes denervation followed by nerve sprouting (attempted regeneration) at the peri-infarct zone, which is thought to contribute to regional heterogeneity in sympathetic response and repolarization

HIGHLIGHTS

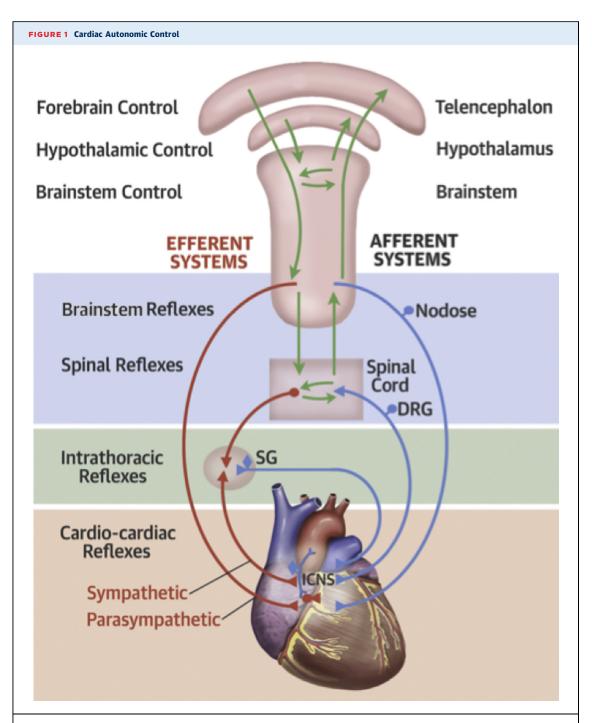
- Autonomic imbalance is inextricably linked with cardiac arrhythmias and has become an important therapeutic target.
- Recent advances in neuromodulatory techniques have shown promise in treating VT and AF.
- Further investigation into basic mechanisms of cardiac neural control is needed to improve antiarrhythmic therapies.

dispersion leading to ventricular tachycardia or ventricular fibrillation (VT/VF) (14-16). At the extracardiac-intrathoracic level, SG from humans with ischemic and nonischemic cardiomyopathy have shown neuronal inflammatory changes and glial activation (17,18). Additionally, neuronal injury has been reported in the brain stem and spinal cord in human and animal models of heart failure (HF) (19-21).

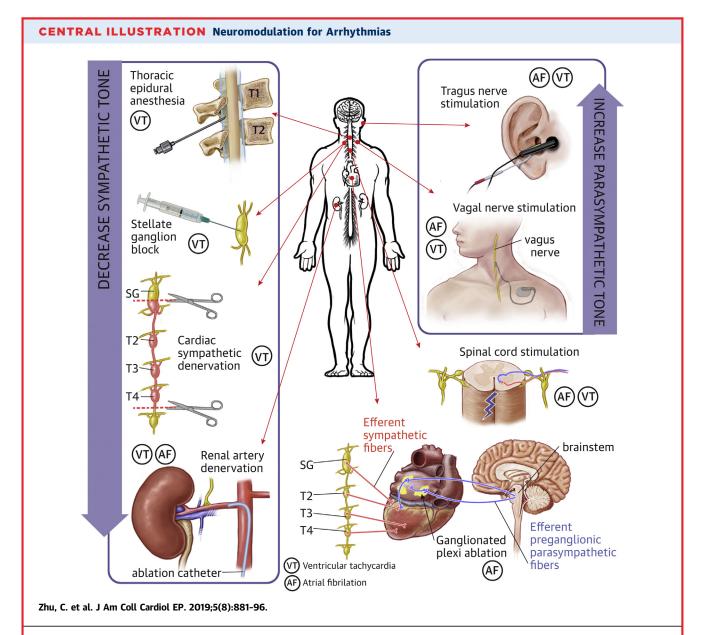
Over the last few decades, substantial evidence has accumulated that supports the association between autonomic imbalance and cardiac arrhythmias. Emerging data have shown that both the sympathetic and parasympathetic limbs of the autonomic nervous system can be leveraged for arrhythmia control (Central Illustration). In this review, we describe the current state of neuromodulatory approaches for arrhythmia management, placing each technique in the context of its clinical application.

ACUTE MANAGEMENT OF ELECTRICAL STORM

CLINICAL SCENARIO. A 78-year-old man with ischemic cardiomyopathy and chronic HF with severely reduced ejection fraction (EF) presented to the emergency department for nearly 160 implantable cardioverter-defibrillator (ICD) shocks. After admission, his ICD continued to fire multiple times for incessant VT, exhausting the battery. The patient required emergent sedation and intubation as well as continuous intravenous procainamide infusion to stabilize his rhythm. This was his third hospitalization for electrical storm (ES) in 2 months, having previously failed medical therapy (metoprolol and amiodarone) and multiple catheter ablations. Cardiac sympathetic denervation (CSD) had also been attempted previously, but it had to be aborted due to extensive pleural adhesions. After extensive discussion, a mutual decision was made with the patient to pursue a trial of percutaneous left stellate ganglion



Autonomic control of the heart consists of numerous, complex reflex loops that can be divided into 3 main levels: the brain stem spinal cord (blue box); intrathoracic extracardiac ganglia (green box); and the intrinsic cardiac nervous system (tan box). The afferent limb (blue lines) carries sensory information from the heart to higher levels, where it is processed by multiple components of the central nervous system (green lines). The efferent limb (red lines) carries signals from higher levels down to the heart, to modulate cardiac function. Adapted with permission from Goldberger JJ, Arora R, Buckley U, Shivkumar K. Autonomic nervous system dysfunction: JACC Focus Seminar. J Am Coll Cardiol 2019;73:1189-206. DRG = dorsal root ganglion; ICNS = intrinsic cardiac nervous system; SG = stellate ganglion.



Neuromodulatory therapies targeting sympathetic and parasympathetic pathways have been applied at multiple levels of the cardiac autonomic nervous system to treat ventricular tachycardia (VT) and atrial fibrillation (AF). Afferent nerve fibers are omitted for simplicity. CSD = cardiac sympathetic denervation; GP = ganglionated plexi; RDN = renal artery denervation; SCS = spinal cord stimulation; SGB = stellate ganglion block; TEA = thoracic epidural anesthesia; TNS = tragus nerve stimulation; VNS = vagal nerve stimulation.

blockade (SGB). The patient tolerated the SGB well without complications and procainamide was stopped. Six weeks later, he was readmitted for another appropriate ICD shock and underwent repeat left SGB with success. He was subsequently scheduled for outpatient left SGB every 4 weeks, and 11 months after his first SGB procedure remains free of sustained VT/VF.

BETA-ADRENERGIC BLOCKADE. Sympathetic overactivity is a fundamental driver of ES (22) and is further exacerbated by pain and distress from ICD shocks. Thus, sedation and mechanical ventilation are often utilized in patients with ES for minimizing pain, as well as for their ability to blunt autonomic reflexes (23-25). Similarly, because beta-blockers also dampen sympathoexcitation, they have become a

The comparative effects of different beta-blockers on ventricular arrhythmogenesis have been recorded in the published reports for decades (31,32). Clinically, these differential effects were first demonstrated in a 2012 study, which found metoprolol to be significantly less effective than propranolol and nadolol for suppressing arrhythmias in patients with long QT syndrome (LQTS) types 1 and 2 (33). More recent data from Chatzidou et al. (34) comparing the nonselective propranolol and the beta-1-selective metoprolol in the acute management of ES in HF has helped to renew interest in the basic science of sympathetic activity in cardiovascular disease. The study found that patients treated with oral propranolol and intravenous amiodarone had a shorter length of stay with significantly reduced (2.67× decrease) arrhythmic burden compared with those treated with oral metoprolol and amiodarone. Chatzidou et al. (34) cite the selective down-regulation of beta-1 adrenergic receptors over beta-2 receptors in HF, as well as propranolol's sodium channel blockade and central nervous system effects, as underlying mechanisms for their findings.

Although this small-scale study suggests that the nonselective effects of propranolol may make it superior to metoprolol in acute management of ES, it remains unclear how nonselective beta blockade will fare beyond the acute phase. Indeed, up to one-half of patients with ES, as in our preceding clinical scenario, will continue to have VT/VF despite antiarrhythmic drugs and guideline-directed beta blockade (35). As the propranolol versus metoprolol trial illustrates, the science behind even workhorse drugs such as betablockers cannot be taken for granted, and the widespread success of beta-blockers still leaves significant room for improvement in neuromodulation for ES.

SG BLOCKADE AND THORACIC EPIDURAL ANESTHESIA. Blockade of the SG using percutaneous local anesthetic injection was first performed in 1934 (36) for the treatment of chronic pain syndromes. The procedure can be safely done at bedside with contrast fluoroscopy for anatomic guidance, though ultrasound guidance has also been successfully used (37), as well as pulsed radiofrequency in place of local anesthetic (38). In small human studies, SG blockade has been shown to decrease sympathetically driven

cardiac excitability (39-41), likely through reducing both efferent sympathetic signals to, and afferent signals from, the heart. Thoracic epidural anesthesia (TEA) involves percutaneous injection of local anesthetic into the epidural space at the T1 to T5 spinal cord and can inhibit efferent and afferent sympathetic influences from both left and right spinal roots (42,43). TEA has previously been shown to decrease post-operative supraventricular arrhythmias in patients undergoing lung surgery, as well as to relieve anginal pain in ischemic heart disease (44,45).

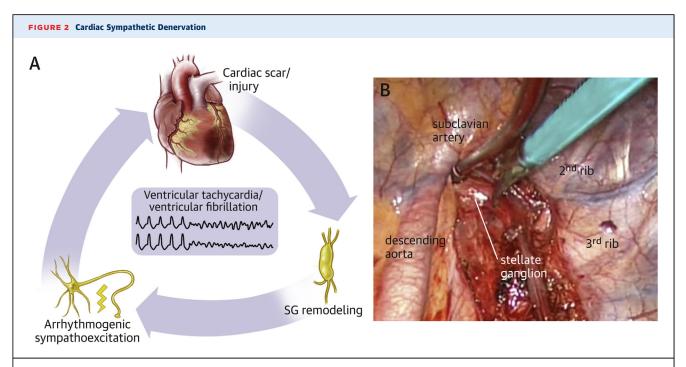
In a systematic review of 38 patients with ES who underwent SG blockade, ventricular arrhythmias were significantly reduced in 92% of subjects, from an average of 12 to 1 VT/VF episodes per day (46). A small clinical study of TEA for ES also showed a >80% reduction in ventricular arrhythmias in 6 of 8 patients (47). Based on the available data, Nademanee et al. (39) have argued that SG blockade and beta-blocker therapy may be more effective than the antiarrhythmics previously recommended by the Advanced Cardiac Life Support algorithm for ES.

Despite showing promise as temporary measures for stabilization in the acute management of ES, percutaneous SG blockade and TEA have some limitations, and their exact mechanisms of action remain to be elucidated. Both techniques have transient effects due to the inherent pharmacokinetics of local anesthetics. Additionally, the effect of SG blockade can be operator-dependent, and the procedure lacks specificity for the heart (48), potentially dampening sympathetic tone to the head, neck, and diaphragm (which restricts its concurrent application to both the left and right sides). More permanent and cardiac-specific modes of disrupting sympathetic signaling are discussed in the following sections.

INHERITED PRIMARY ARRHYTHMIA SYNDROMES

CLINICAL SCENARIO. A 24-year-old woman with no prior medical problems was referred to clinic for palpitations and 2 episodes of syncope after swimming. She was adopted, with unknown biological family history. Her electrocardiogram revealed a QTc interval of 612 ms, with broad T waves consistent with LQTS type 1. Outpatient cardiac monitoring also revealed multiple runs of polymorphic VT.

The patient underwent successful ICD implantation and was started on nadolol. Genetic testing revealed the KCNQ1 mutation Q357R, confirming LQTS type 1. There were no tachytherapies from her ICD for the first 8 months after implantation; however, she subsequently enrolled in graduate school



(A) Structural heart diseases lead to remodeling of the stellate ganglia (SG), which causes increased sympathetic outflow leading to arrhythmias. (B) Cardiac sympathetic denervation is performed by removing the bottom one-half of the SG and T2 to T4 ganglia under thoracoscopic quidance.

and experienced 22 shocks over a 90-min period. Verapamil was added, but after 6 weeks she was hospitalized again for numerous appropriate ICD shocks. She underwent left-sided CSD (LCSD) without complications. Over a 16-month follow-up period, she remained free of sustained VT and tachytherapies on device interrogations, and verapamil was tapered off. CARDIAC SYMPATHETIC DENERVATION. Pioneered more than 100 years ago for the treatment of angina, CSD has had a recent resurgence in interest for the management of arrhythmia (49). After a long period of being overshadowed by modern pharmacological advances, LCSD re-emerged in clinical practice in 1961 as a therapy for medication-refractory VT (50,51) and, subsequently, for congenital LQTS (48,52) as well as catecholaminergic polymorphic ventricular tachycardia (CPVT) (53,54).

Both LCSD and bilateral CSD (BCSD) are typically performed via video-assisted thorascopic surgery and involve removal of the lower one-half of the SG as well as the T2 to T4 ganglia of the thoracic sympathetic chain (Figure 2). LCSD can usually be done in 40 min (and BCSD in 120 min), and significantly reduces, but does not completely abolish, both efferent sympathetic and afferent neurotransmission to and from the heart, respectively (55). As the upper onehalf of the SG and the middle cervical ganglia remain intact after the procedure, some efferent sympathetic innervation is preserved to mitigate the adverse off-target effects of total stellectomy (55). Though LCSD is traditionally used for inherited primary arrhythmia syndromes, the significant contribution of right-sided sympathetic nerves to ventricular arrhythmogenesis (detailed in the next section) has long been known (56) and has been confirmed in more recent work (57,58).

At present, LQTS is the inherited primary arrhythmia in which LCSD has been best studied. The largest trial of LCSD for LQTS included 147 patients who were at particularly high risk: they had very prolonged QT intervals (mean QTc: 543ms), 48% had a prior cardiac arrest, 99% were symptomatic, and 75% of those on full-dose beta-blocker therapy remained symptomatic (59). During an 8-year followup after undergoing LCSD, cardiac events in these patients decreased by 91% and, in those with ES who had experienced multiple ICD shocks, the median number of ICD shocks decreased by 95%. Genotyping was performed for 51 patients in this study and showed that LCSD was more effective in LQTS types 1 and 3 patients, consistent with the fact that the LQTS type 1 mutation is in I_{Ks} , a delayed-rectifier potassium channel that is particularly sensitive to sympathetic stimulation (60,61). The impressive,

incomplete, effect of LCSD supports the Class II, Level of Evidence: A recommendation for its use to improve quality of life for LQTS patients with refractory syncope and multiple ICD shocks despite beta-blocker therapy (62,63).

The impact of LCSD on quality of life is also an especially important consideration in young patients with CPVT (64,65). For these patients, the risk of ES is particularly high as the distress and catecholamine release from a first ICD shock often initiates a vicious cycle of recurrent VT/VF and multiple subsequent shocks. The first study of LCSD efficacy in CPVT followed 3 patients, all with recurrent syncope and multiple ICD shocks despite beta-blocker therapy, and it showed a complete suppression of symptoms for more than 10 years after LCSD (53). Subsequent larger studies have also shown LCSD to reduce major cardiac events and ICD shocks by 89% to 93% (66,67). There were no significant complications reported in these studies, though transient Horner syndrome was reported in a small number of patients (11%). These data suggest that for patients with primary inherited arrhythmias who had the first-line therapy of beta blockade is incompletely effective, LCSD should be considered, perhaps even before implantation of an ICD (54).

STRUCTURAL HEART DISEASE

CLINICAL SCENARIO. A 16-year-old male patient with no past medical history presented to the emergency department with palpitations after running and was found to be in monomorphic VT. He was diagnosed with arrhythmogenic right ventricular cardiomyopathy based on T-wave inversions in V1 to V4, left-bundle inferior-axis VT, a sibling who died suddenly in his early 20s while exercising, and subtricuspid right ventricular dyskinesia with right ventricular EF of 30%. Genetic testing revealed a pathogenic c.2489+1G>A splice donor variant in the desmosomal gene *PKP2*.

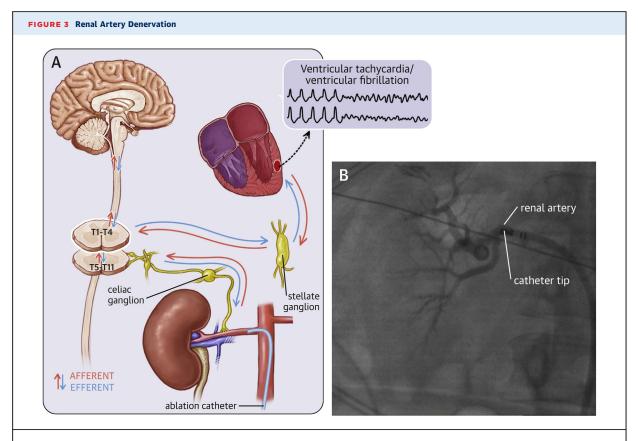
The patient received a dual-chamber ICD and was discharged on metoprolol. Over the next few months, he was hospitalized numerous times for frequent appropriate ICD shocks while exercising and subsequently underwent 2 endocardial-epicardial ablations, as well as initiation of amiodarone, without success. The patient underwent BCSD without complications. At 1-year follow-up, the patient remained asymptomatic on metoprolol, and routine device interrogations showed no VT therapies.

BILATERAL CARDIAC SYMPATHETIC DENERVATION. The safety and success of LCSD in inherited primary arrhythmias has led to the expansion of its use to

structural heart disease (SHD). However, the initial case series describing LCSD for refractory VT/VF storm in patients with SHD showed that only 5 of 9 patients benefited from the procedure (47). Interestingly, the patients in the study who underwent TEA, which affects both left- and right-sided sympathetic cardiac innervation, showed a greater response, with 75% having a >80% reduction in their ventricular arrhythmia burden. These results raised the question of whether, for SHD, bilateral cardiac sympathectomy may be more effective than LCSD alone.

The anatomical contribution of both left stellate ganglia (LSG) and right stellate ganglia (RSG) to sympathetic innervation of the left ventricle has been described since the 1960s (68), with canine models showing predominant RSG innervation of the anterior aspects of the ventricles while the LSG predominated the posterior aspects, though both SG types provide some innervation to all aspects of the ventricles. In the case of arrhythmogenic right ventricular cardiomyopathy, abnormal sympathetic innervation of the right ventricle has been described since the disease was first reported (69). What remains unclear is the distinct functional effect of the RSG versus the LSG at the ventricular level. Conflicting studies have shown either no change in the refractory period of the anterior left ventricular wall with RSG stimulation or a paradoxical decrease in ventricular refractory period with RSG removal (70-72). A more recent study in a porcine model by Vaseghi et al. (57) found that innervation of the anterior left ventricular wall and effect on repolarization is shared by the bilateral SGs, though LSG stimulation may be more proarrhythmic by increasing dispersion of the refractory period across the ventricular wall.

Whereas the precise role of the RSG in arrhythmogenesis remains to be elucidated, a 2017 retrospective analysis suggested that BCSD may be more effective for treatment for VT in SHD than LCSD alone is (73). In this study, 121 patients with SHD (mostly nonischemic etiologies) underwent either LCSD (19%) or BCSD (81%) for refractory VT or VT storm. In these patients, LCSD was always performed first in case BCSD could not be tolerated due to hemodynamic instability. Over a median follow-up period of 1.1 years, those who underwent BCSD had significantly longer ICD-shock-free and transplant-free survival than did those who underwent LCSD only, though the overall endpoints of recurrent ICD shocks and freedom from sustained VT were similar. Thus far, this has been the largest series of patients with predominantly SHD undergoing CSD for refractory VT. Furthermore, the PREVENT VT (Cardiac Sympathetic



(A) Renal artery denervation exerts its antiarrhythmic effect by decreasing renal afferent signals, which in turn decreases efferent sympathetic outflow to the heart. (B) Renal artery denervation is performed via catheter ablation under guidance by contrast angiography.

Denervation for Prevention of Ventricular Tachyarrhythmias) trial (74) has been planned to investigate the antiarrhythmic effects of BCSD.

Though significant preclinical and retrospective data have supported promising roles for LCSD and BCSD in the management of refractory VT, the efficacy of these relatively invasive procedures remains incomplete. Thus, efforts toward successful antiarrhythmic neuromodulation in SHD are being expanded to other limbs of the cardiac autonomic nervous system, which are discussed in the following sections.

RENAL ARTERY DENERVATION. The effects of modulating renal sympathetic innervation have long been studied, from the experiments of Claude Bernard and Ernest Starling in the late 19th century (75,76) to more recent work on its potential in treating hypertension (77,78). Renal artery sympathetic fibers run parallel to the artery ostially to distally in the adventitial layer. Renal artery denervation (RDN) is performed via selective angiography and catheter

ablation (Figure 3) and is aimed at inhibiting the afferent renal sympathetic pathway, which in turn decreases efferent sympathetic influence on the heart (79).

RDN has been shown to decrease VT/VF burden in a porcine post-infarct model (80) and in small human studies. In a 2015 observational study of 10 patients who underwent RDN for refractory VT/VF, ventricular arrhythmias and ICD shocks were both reduced from 28.5 and 8 episodes in the 6 months before RDN to o and o episodes over the 6 months after RDN, respectively (81). Another retrospective study of 32 patients showed that in those who underwent catheter ablation of VT plus adjunctive RDN, the number of VT/VF episodes as well as ICD shocks and antitachycardia pacing decreased significantly than when treated with ablation alone, though mortality rates were similar in the 2 arms (82).

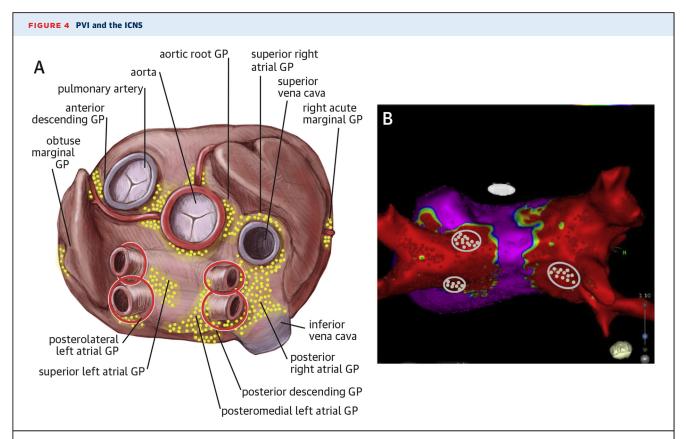
Although RDN has not been compared directly to LCSD or BCSD for VT/VF treatment, its advantages include avoidance of thoracotomy, as well as potential to suppress reflexive sympathetic signaling from sources other than the bottom one-half of the SG (i.e., top one-half of SG, middle cervical ganglia, and circulating catecholamines). Recent data have suggested RDN may be considered as adjunctive therapy to CSD for ablation-refractory cases of VT/VF (83,84). The small amount of data on RDN as antiarrhythmic therapy, including a recent trial on its use for atrial fibrillation (AF) (85), shows promise, but the procedure has yielded mixed results in its trials for hypertension treatment, likely due to inconsistent degrees of technical success and suboptimal anatomical targets (77). These challenges must be overcome if RDN is to be effectively applied to the treatment of ventricular arrhythmias.

SPINAL CORD STIMULATION. Relatively accessible anatomic location and previously demonstrated safety and efficacy in treating angina and chronic pain (86,87) have made thoracic spinal cord stimulation (SCS) a potential therapy for ventricular arrhythmias in SHD. SCS is achieved by inserting 1 or 2 leads with 8 electrodes into the epidural space at the thoracic level (either at T1 to T3 or T2 to T4) and applying a small current at approximately the paresthesia threshold. Prior canine and porcine studies showed significant reduction in ischemia-driven ventricular arrhythmias, even with brief (approximately 1-h) periods of SCS (88-90). The spinal cord is where multiple tracts of the cardiac autonomic nervous system converge, but the specific beneficial mechanisms underlying SCS remain poorly understood and may relate to both decreased sympathetic outflow and increased vagal tone (88,91-94).

At present, data on SCS and ventricular arrhythmias in humans are limited to case series and small clinical trials. In 2012, a case series of 2 patients who underwent SCS showed reduced VT burden, from 128 and 90 episodes of VT over 2 months before SCS, to 6 and 0 episodes over 2 months after SCS (95). Two randomized trials primarily evaluating the effect of SCS in HF have had conflicting results and either failed or had insufficient power to show significant effect on ventricular arrhythmia burden. The SCS HEART (Thoracic Spinal Cord Stimulation for Heart Failure as a Restorative Treatment) study (96) showed significant HF symptom reduction and left ventricular EF improvement in 17 patients after SCS; however, the DEFEAT-HF (Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Systolic Heart Failure) study (97) did not show improved clinical outcomes for 66 patients who underwent SCS. There was also no significant reduction in ventricular arrhythmias based on limited data from ICD interrogations in DEFEAT-HF. The conflicting results could possibly be explained by the different anatomical locations (T1 to T3 in SCS HEART vs. T2 to T4 in DEFEAT-HF) of the electrodes in the thoracic spinal cord, by the different stimulation parameters (12 h/day via implanted stimulator in DEFEAT-HF versus continuously for SCS HEART), or both. If SCS is to have reproducible success as antiarrhythmic therapy, future studies will need to investigate the distinct neurohormonal and electrophysiological effects of varying anatomical locations and stimulation protocols.

VAGAL NERVE STIMULATION. Whereas increased sympathetic tone, the main target of the aforementioned neuromodulatory therapies, is arrhythmogenic, increased parasympathetic tone is thought to be cardioprotective in SHD by maintaining electrical stability via preservation of gap junction communication between myocytes, reducing heterogeneity of action potential duration, and decreasing circulating catecholamines and inflammatory markers (98-100). Clinically, augmenting parasympathetic tone to terminate VT was demonstrated as early as 1977 (101). This provides the mechanistic basis for investigating the effect of vagal nerve stimulation (VNS) on ventricular arrhythmias. VNS is achieved via surgical implantation of a pulse generator powering a cuff electrode around the vagus nerve. Left-sided VNS has already been in clinical use for drug-refractory epilepsy (102) and depression (103). Initial feasibility studies for right-sided VNS in the treatment of HF yielded promising data for safety, tolerability, and preliminary efficacy (104).

In animal models, VNS has been shown to significantly reduce VT/VF occurrence and inducibility after coronary artery occlusion and reperfusion (105) and healed myocardial infarction (106), likely by decreasing heterogeneity of repolarization and stabilizing infarct border zones (107-109). Interestingly, adjustments in the frequency, pulse width, and current used for VNS changes the balance between increased efferent parasympathetic output and afferent inhibition of parasympathetic output (110). This suggests that VNS does not simply turn on parasympathetic input to the heart like a bimodal switch. There may be optimal parameters to achieve a therapeutic effect-a "neural fulcrum" at which the reflexive afferent decrease in central parasympathetic drive is counterbalanced by direct efferent increase in vagal parasympathetic outflow (111). Variable effects from altering stimulation parameters likely explain the conflicting results obtained from recent clinical trials of VNS for chronic HF (112-114), reviewed comprehensively elsewhere (115,116), which utilized



(A) A dense network of intrinsic cardiac ganglionated plexi (GP) (yellow dots) correlates anatomically with major cardiac vessels. These GP also crudely match ablation sites targeted by most pulmonary vein isolation (PVI) techniques (red circles) for atrial fibrillation. (B) Electroanatomic map of PV after atrial fibrillation ablation, showing correlation of ablation sites with intrinsic cardiac GP (encircled gray dots). ICNS = intrinsic cardiac nervous system.

different VNS frequencies and pulse amplitudes. This more nuanced understanding of vagal stimulation parameters led to a 2018 study of preferentially efferent VNS in pigs with chronic MI after BCSD (117). After BCSD, VT was inducible in all infarcted animals during isoproterenol infusion, but VNS reduced this inducibility by 67%.

A disadvantage of cervical VNS is its invasiveness and side effects such as voice changes, discomfort at implantation site, and infection have been described (118). A noninvasive alternative to cervical VNS, tragus nerve stimulation (TNS), is also being studied for VT/VF. TNS targets the cutaneous, auricular branch of the vagus nerve at the tragus. In a canine post-MI model, chronic intermittent TNS lasting 2 h/day for 2 months reduced inducibility of ventricular arrhythmias, LSG neuronal activity, as well as nerve remodeling at the infarct border zone (119). A recent human study of TNS in 128 patients applied the treatment for 2 h to patients with ST-segment elevation MI undergoing percutaneous coronary reperfusion (120). The incidence of VT/VF during the first

24 h after reperfusion, as well as infarct size and inflammatory markers, was significantly reduced in those who underwent TNS versus sham intervention. Though there has been progress in utilizing stimulation of the vagus nerve and its auricular branch, achieving convincing clinical benefit will require future studies to better incorporate our evolving understanding of the basic mechanisms underlying the neural fulcrum.

ATRIAL FIBRILLATION

clinical scenario. A 68-year-old man with severe rheumatic mitral regurgitation, chronic HF with preserved EF, and chronic persistent AF on amiodarone underwent mitral valve replacement surgery with maze procedure and left atrial appendage exclusion. After completion of these main procedures, the patient was in normal sinus rhythm. Using a decapolar coronary sinus catheter, electrical isolation of the pulmonary veins (PV) was confirmed with epicardial electrograms demonstrating conduction block.

Subsequently, the 4 major epicardial fat pads known to contain intrinsic cardiac GP were located: anterior to the right superior PV; inferoposterior to the right inferior PV; anterior to the left superior PV and left inferior PV (between the PV and left atrial appendage); and inferoposterior to the left inferior PV. Botulinum toxin was injected into each of these fat pads, and the surgery was concluded.

The patient had an uncomplicated recovery. Three months later, he reported his exercise tolerance was significantly improved and ambulatory electrocardiographic monitoring was negative for recurrent AF. His amiodarone was subsequently stopped, and over 15 months of additional follow-up, multiple 2-week event monitors showed no recurrent AF.

PV ISOLATION AND THE ICNS. Parasympathetic signaling has long been implicated in the pathogenesis of certain forms of AF (121). High-level vagal stimulation or the administration of cholinergic agonists lead to inducibility of sustained AF (122-124) via spatially heterogeneous shortening of atrial refractoriness (125,126) and shortening of atrial propagation wavelength (127). Vagal signaling to the heart is thought to be relayed by the GP of the ICNS. In canine studies, AF inducibility from vagal stimulation was eliminated after catheter ablation of several atrial fat pads, which contain the GP conveying information from the vagus nerve to the atria (128,129). Thus, the intrinsic cardiac GP are attractive targets for AF therapies (Figure 4), but translating the experimental data to clinical use remains challenging.

Since Haïssaguerre et al. (130) first demonstrated the success of pulmonary vein isolation (PVI) for catheter ablation of AF, there has been widespread acceptance of the technique and its underlying mechanistic assumption—that PV ectopic foci are triggers of AF. Soon after the advent of PVI, it was observed to have autonomic effects, namely bradycardic events (131) and long-term alterations of heart rate variability (132). Given that the anatomical locations of intrinsic cardiac GP approximately match PVI ablation sites, ICNS denervation may play an important role in the efficacy of PVI (133).

Studies of PVI in conjunction with targeted ICN ablation have shown that the procedures may be synergistic. Two randomized trials by Katritsis et al. (134,135) compared PVI alone, ablation at expected anatomical locations of cardiac GPs, and PVI plus GP ablation. The combined approach resulted in approximately 1.5-fold higher success rates of eliminating paroxysmal AF. A similar comparison study showed that PVI plus GP ablation was superior to PVI

plus linear lesions (136). Surgical case series (137-139) have also described impressive success rates (65% to 86%) of AF ablation with a combined approach of PVI plus ablation of GP and the ligament of Marshall (LOM), which serves as a pathway connecting intrathoracic cardiac neurons to the ICNS. Percutaneous approaches of targeting the LOM via ethanol infusion in the vein of Marshall (VOM) have also been validated in humans (140), and a randomized, multicenter trial (VOM-R01 [Vein of Marshall Ethanol Infusion for Persistent Atrial Fibrillation]) is currently underway to investigate the role of VOM ethanol ablation in persistent AF.

The current clinical approaches to modulate the ICNS lack specificity, as the cardiac GP contain diverse neuronal populations and neurotransmitter types (141). Thus, GP destruction is a crude approach with variable outcomes, which is readily apparent in the results of 2 recent trials targeting the ICNS for AF management. The AFACT (Atrial Fibrillation Ablation and Autonomic Modulation Via Thorascopic Surgery) trial (142) was a study of 240 patients in which patients with paroxysmal AF underwent PVI and those with persistent AF underwent PVI plus additional lines (Dallas lesion set). These patients were then randomized to receive either additional thoracoscopic epicardial ablation of GP and LOM or no extra ablation. The additional GP and LOM ablation had no significant effect on AF recurrence and actually caused more adverse events such as major bleeding and sinus node dysfunction requiring pacemaker implantation. In contrast, a randomized study of botulinum toxin injection into epicardial fat pads in patients with paroxysmal AF undergoing coronary artery bypass graft showed significant reduction in AF burden compared with placebo over a 3-year post-operative follow-up period (143). The conflicting results of these trials highlight the profound knowledge gap in how ICNS physiology regulates atrial impulse propagation, which must be addressed to define the role for ICNS modulation in AF therapy.

VNS FOR ATRIAL ARRHYTHMIAS. While high-level vagal stimulation has been shown to cause AF inducibility, mild-to-moderate enhancement of vagal efferent activity has been observed to suppress PV firing even without inducing bradycardia (144). This paradox illustrates the complexity of cardiac autonomic pathways, where efferent and afferent signals, as well as central-peripheral nervous system interactions, exist in a delicate balance (111). In animal models, low-level (LL)-VNS, delivered at stimulation

voltages below the threshold of inducing bradycardia, prolonged the atrial and PV effective refractory periods, shortened AF duration, and suppressed activity of the atrial GP (145-147). Several mechanisms by which LL-VNS suppresses AF have been proposed, including antiadrenergic suppression of LSG activity (148) and release of the neurotransmitter vasostatin-1 (149). Interestingly, a recent canine study showed that LL-VNS mitigated inducibility of AF by preferentially targeting neurons of the ICNS that receive both efferent and afferent information, or so-called convergent neurons (150).

The antiarrhythmic effects of LL-VNS led to investigation of noninvasive low-level tragus stimulation (LLTS), which was also shown to suppress AF in animal models of rapid atrial pacing (151). In 2015, Stavrakis et al. (152) reported the first-in-man data on LLTS in patients with drug-refractory paroxysmal AF who were referred for catheter ablation. With only 1 h of LLTS, right and left atrial effective refractory periods were prolonged, AF duration was reduced, and proinflammatory markers such as tumor necrosis factor-α and C-reactive protein were decreased. This study has since been expanded to a randomized clinical trial (TREAT AF [Transcutaneous Electrical Vagus Nerve Stimulation to Suppress Atrial Fibrillation]), with promising preliminary results (153). The voltage threshold at which patient discomfort was reported was also significantly higher than that required to achieve the antiarrhythmic effects, which is encouraging for the potential of LLTS as a noninvasive treatment for paroxysmal AF.

CONCLUSIONS

Since the revival of CSD to treat inherited arrhythmia syndromes in the 1960s, significant progress has been made in developing neuromodulatory techniques for heart rhythm disorders. LCSD continues to improve outcomes for those with LQTS and CPVT, and BCSD is now becoming more widely used for its effectiveness in refractory VT/VF cases, especially in patients with SHD. Small clinical studies also have shown that modulation at the spinal cord, vagus, SG, and ICNS, as well as distant renal sympathetic nerves can reduce ventricular arrhythmias and AF. But despite these optimistic early results, the efficacy of cardiac neuromodulation clearly needs further study. Case selection for likely responders is limited by our lack of understanding of the cardiac autonomic nervous system, a multilevel hierarchy with complex feedback loops that we are only beginning to unravel.

Some specific questions that still require experimental investigation include:

- · What is the mechanism of benefit provided by increasingly used neuromodulatory procedures such as CSD?
- Do patients have differing baseline autonomic states that require individualized therapies toward the optimal sympathovagal balance?
- How can we effectively titrate neuromodulatory therapy using electrical readouts from the heart and/or biomarkers?

Recent advances in neurosciences such as optogenetics have been applied to fundamental questions in electrophysiology and cardiac neural control (154) and could pave the way to valuable clinical insights.

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