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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. In this review, we discuss 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.

Condensed Abstract

Autonomic dysregulation in cardiovascular disease plays a major role in the pathogenesis of arrhythmias. Cardiac disease leads to autonomic neural remodeling and imbalances in sympathetic and parasympathetic outflow with arrhythmogenic effects. Preclinical and early-stage clinical studies of neuromodulation for various cardiac arrhythmias have yielded promising results. There is a significant need for basic cardiac neurophysiology knowledge to improve the success of antiarrhythmic neuromodulatory therapies. In this review, we discuss 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.

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Tweet: New state-of-the-art review in #JACCCEP: Neuromodulation for VT and AF: A Clinical Scenario-Based Review, by #EPeeps at the @UCLAHealth Cardiac Arrhythmia Center, deciphers neurocardiology for the clinical electrophysiologist.

Keywords

cardiac autonomic nervous system; neuromodulation; cardiac sympathetic denervation; vagal nerve stimulation; stellate ganglion; cardiac ganglionated plexi

Overview of Cardiac Autonomic Control and Remodeling in Disease

The autonomic nervous system provides beat-to-beat control of cardiac function over an individual's entire lifetime. The two canonical limbs of the nervous system, sympathetic and parasympathetic, 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 which can be divided into three main levels (Figure 1): i) brainstem and spinal cord; ii) extracardiac-intrathoracic ganglia; and iii) 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 preganglionic neurons have cell bodies in the intermediolateral column of the spinal cord and project axons onto postganglionic sympathetic neurons, which are organized into the extracardiac-intrathoracic ganglia, including the middle cervical ganglia (MCG), stellate ganglia (SG, a fusion of the C8 and T1 ganglia), T2–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). Preganglionic efferent neurons of the parasympathetic system are located within the brainstem and project axons which travel via the vagus nerve and its branches to postganglionic 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 brainstem 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 (GPs) 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 brain".

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

Over the last few decades, substantial evidence has accumulated supporting the association between autonomic imbalance and cardiac arrhythmias. Emerging data has shown that both the sympathetic and parasympathetic limbs of the autonomic nervous system can be leveraged for arrhythmia control (Figure 2). 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 ICD shocks. After admission, his ICD continued to fire multiple times for incessant VT, exhausting the battery. The patient required emergent sedation/intubation as well as continuous intravenous procainamide infusion to stabilize his rhythm. This was his third hospitalization for electrical storm (ES) in the past two months, having previously failed medical therapy (metoprolol and amiodarone) and multiple catheter ablations. Cardiac sympathetic denervation (CSD) had also been attempted previously but 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 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 now remains free of sustained VT/VF, 11 months after his first SGB procedure.

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 mainstay in the management of recurrent VT/VF

and ES (26, 27). Their therapeutic mechanisms have been extensively studied – blockade of the beta-adrenergic G-protein coupled receptors inhibits downstream proarrhythmic changes to cardiac ion channel currents (28–30). Yet we may need to revisit some fundamental mechanisms of their antiarrhythmic effects.

The comparative effects of different beta blockers on ventricular arrhythmogenesis has been in the literature 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. comparing the non-selective propranolol and the beta-1-selective metoprolol in the acute management of ES in HF (34) 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 IV amiodarone had a shorter length of stay with significantly reduced (2.67 times decrease) arrhythmic burden compared with those treated with oral metoprolol and amiodarone. The authors cite the selective downregulation 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.

While this small-scale study suggests that the non-selective effects of propranolol may make it superior to metoprolol in acute management of ES, it remains unclear how non-selective beta blockade will fare beyond the acute phase. Indeed, up to a 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 like beta blockers cannot be taken for granted, and the widespread success of beta blockers still leaves significant room for improvement in neuromodulation for ES.

Stellate Ganglion 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–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 postoperative 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 greater than 80% reduction in ventricular arrhythmias in 6 out of 8 patients (47). Based on the

available data, Nademanee et al. has 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 (39).

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 two episodes of syncope after swimming. She was adopted, with unknown biological family history. Her ECG revealed a QTc interval of 612 milliseconds, 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 LQTS1. There were no tachytherapies from her ICD for the first 8 months after implantation, however she subsequently enrolled in graduate school and experienced 22 shocks over a 90-minute period. Verapamil was added, but after six 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 left-sided and bilateral CSD (BCSD) are typically performed via video-assisted thoracoscopic surgery (VATS) and involves removal of the lower half of the SG as well as the T2–T4 ganglia of the thoracic sympathetic chain (Figure 3). LCSD can usually be done in 40 minutes (and BCSD, in 120 minutes), and significantly reduces, but does not completely abolish, both efferent sympathetic and afferent neurotransmission to and from the heart, respectively (55). As the upper half of the SG and the MCG 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 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 particular 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 follow-up 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 LQT1 and LQT3 patients, consistent with the fact that the LQT1 mutation is in I_{Ks}, a delayed-rectifier potassium channel particularly sensitive to sympathetic stimulation (60, 61). The impressive, though incomplete, effect of LCSD supports the Class IIa 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 three 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 89–93% (66, 67). There were no significant complications reported in these studies, though transient Horner's syndrome was reported in a small number of patients (11%). These data suggest that for patients with primary inherited arrhythmias in whom 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 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 (ARVC) based on T wave inversions in V1–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 two endocardial/epicardial ablations, as well as

initiation of amiodarone, without success. The patient underwent bilateral CSD (BCSD) without complications. At one-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 out 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 greater than 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 (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 SGs provide some innervation to all aspects of the ventricles. In the case of ARVC, 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 and colleagues 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 (57).

While 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 (73). In this study, 121 patients with SHD (mostly non-ischemic 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 compared to 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 structural heart disease undergoing CSD for refractory VT. Further, the Cardiac Sympathetic Denervation for Prevention of Ventricular Tachyarrhythmias (PREVENT VT) 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 4) 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 postinfarct 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 0 and 0 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 anti-tachycardia pacing decreased significantly when compared to ablation alone, though mortality rates were similar in the two arms (82).

While 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 half of the SG (i.e. top half of SG, MCG, and circulating catecholamines). Recent data has 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, as well as 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 one or two leads with eight electrodes into the epidural space at the thoracic level (either at T1–T3 or T2–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-hour) periods of SCS (88–90). The spinal cord is where multiple tracts of the cardiac ANS 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 two 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 study (96) showed significant HF symptom reduction and LVEF improvement in 17 patients after SCS, however the DEFEAT-HF 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–T3 in SCS HEART, versus T2–T4 in DEFEAT-HF) of the electrodes in the thoracic spinal cord, and/or by the different stimulation parameters (12 hours per day via implanted stimulator in DEFEAT-HF versus continuously for SCS HEART). 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

While increased sympathetic tone, the main target of the aforementioned neuromodulatory therapies, is arrhythmogenic, increased parasympathetic tone is thought to be cardioprotective in SHD – 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 explains the conflicting results obtained from recent clinical trials of VNS for chronic HF (112–114), reviewed comprehensively elsewhere (115, 116), which utilized 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 implant 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 hours per 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 hours to patients with ST-elevation MI undergoing percutaneous coronary reperfusion (120). The incidence of VT/VF during the first 24 hours after reperfusion, as well as infarct size and inflammatory markers, was significantly reduced in those who underwent TNS compared to 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 undergoes 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 (PVs) was confirmed with epicardial electrograms demonstrating conduction block. Subsequently, the four major epicardial fat pads known to contain intrinsic cardiac GPs were located: anterior to the right superior PV, infero-posterior to the right inferior PV, anterior to the left superior PV and left inferior PV (between the PVs and LAA), and infer-posterior 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 ECG monitoring was negative for recurrent AF. His amiodarone was subsequently stopped and, over 15 months of additional follow-up, multiple two-week event monitors have shown no recurrent AF.

Pulmonary Vein Isolation and the Intrinsic Cardiac Nervous System

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 heterogenous 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 GPs of the ICNS. In canine studies, AF inducibility from vagal stimulation was eliminated after catheter ablation of several atrial fat pads, which contain the GPs conveying information from the vagus nerve to the atria (128, 129). Thus, the intrinsic cardiac GPs are attractive targets for AF therapies (Figure 5), but translating the experimental data to clinical use remains challenging.

Since Haissaguerre et al 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 (130). 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 GPs approximately match PVI ablation sites, ICN 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 compared PVI alone, ablation at expected anatomical locations of cardiac GPs, and PVI plus GP ablation (134, 135). 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 (65–86%) of AF ablation with a combined approach of PVI plus ablation of GPs and the ligament of Marshall (LOM), which serves as a pathway connecting intrathoracic cardiac neurons to the ICN. 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) 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 GPs 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 two recent trials targeting the ICNS for AF management. The AFACT 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 GPs 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 CABG showed significant reduction in AF burden compared to placebo over a three-year postoperative 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.

Vagal Nerve Stimulation 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 VNS (LL-VNS), delivered at stimulation voltages below the threshold of inducing bradycardia, prolonged the atrial and PV effective refractory periods (ERP), shortened AF

duration, and suppressed activity of the atrial GPs (145–147). Several mechanisms by which LL-VNS suppresses AF have been proposed, including anti-adrenergic suppression of left SG 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 which 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 reported the first-in-man data on LLTS in patients with drug-refractory paroxysmal AF who were referred for catheter ablation (152). With only 1 hour of LLTS, right and left atrial ERP were prolonged, AF duration was reduced, and pro-inflammatory markers such as TNF-α and C-reactive protein were decreased. This study has since been expanded to a randomized clinical trial (TREAT AF), 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 non-invasive 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, ICNS, as well as distant renal sympathetic nerves can reduce ventricular arrhythmias and atrial fibrillation. 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 which 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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University of California, Los Angeles has patents developed by KS relating to cardiac neural diagnostics and therapeutics. KS and PSR are co-founders of NeuCures, Inc. CZ and PH have no disclosures.

Abbreviations

ICNS	intrinsic cardiac nervous system
SG	stellate ganglia
GP	ganglionated plexus
CSD	cardiac sympathetic denervation
SGB	stellate ganglion block
TEA	thoracic epidural anesthesia
SCS	spinal cord stimulation
RDN	renal artery denervation
VNS	vagal nerve stimulation
TNS	tragus nerve stimulation

References

1. Andresen MC, Kunze DL, Mendelowitz D. Central nervous system regulation of the heart In: Armour JA, Ardell JL, editors. Basic and Clinical Neurocardiology. New York: Oxford University Press, 2004:187–219.
2. Armour JA. Cardiac neuronal hierarchy in health and disease. Am. J. Physiol. Regul. Integr. Comp. Physiol 2004;287:R262–271. [PubMed: 15271675]
3. Ardell JL, Andresen MC, Armour JA, et al. Translational neurocardiology: preclinical models and cardioneural integrative aspects. J. Physiol 2016;594:3877–3909. [PubMed: 27098459]
4. Jänig W Neurocardiology: a neurobiologist's perspective. J. Physiol 2016;594:3955–3962. [PubMed: 27417671]
5. Hanna P, Rajendran PS, Ajijola OA, et al. Cardiac neuroanatomy - Imaging nerves to define functional control. Auton. Neurosci. Basic Clin 2017;207:48–58.
6. Kawashima T The autonomic nervous system of the human heart with special reference to its origin, course, and peripheral distribution. Anat. Embryol. (Berl.) 2005;209:425–438. [PubMed: 15887046]
7. Hopkins DA, Armour JA. Ganglionic distribution of afferent neurons innervating the canine heart and cardiopulmonary nerves. J. Auton. Nerv. Syst 1989;26:213–222. [PubMed: 2754177]
8. Armour JA. Potential clinical relevance of the "little brain" on the mammalian heart. Exp. Physiol 2008;93:165–176. [PubMed: 17981929]
9. Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. J. Am. Coll. Cardiol 2009;54:375–385. [PubMed: 19628111]
10. Schwartz PJ, Pagani M, Lombardi F, Malliani A, Brown AM. A cardiocardiac sympathovagal reflex in the cat. Circ. Res 1973;32:215–220. [PubMed: 4685965]
11. Wang H-J, Rozanski GJ, Zucker IH. Cardiac sympathetic afferent reflex control of cardiac function in normal and chronic heart failure states. J. Physiol 2017;595:2519–2534. [PubMed: 28116751]
12. El-Sherif N Reentrant ventricular arrhythmias in the late myocardial infarction period. 6. Effect of the autonomic system. Circulation 1978;58:103–110. [PubMed: 647873]
13. Priori SG, Mantica M, Schwartz PJ. Delayed afterdepolarizations elicited in vivo by left stellate ganglion stimulation. Circulation 1988;78:178–185. [PubMed: 3383403]

14. Cao JM, Chen LS, KenKnight BH, et al. Nerve sprouting and sudden cardiac death. Circ. Res 2000;86:816–821. [PubMed: 10764417]
15. Rajendran PS, Nakamura K, Ajijola OA, et al. Myocardial infarction induces structural and functional remodelling of the intrinsic cardiac nervous system. J. Physiol 2016;594:321–341. [PubMed: 26572244]
16. Vaseghi M, Lux RL, Mahajan A, Shivkumar K. Sympathetic stimulation increases dispersion of repolarization in humans with myocardial infarction. Am. J. Physiol. Heart Circ. Physiol 2012;302:H1838–1846. [PubMed: 22345568]
17. Ajijola OA, Wisco JJ, Lambert HW, et al. Extracardiac neural remodeling in humans with cardiomyopathy. Circ. Arrhythm. Electrophysiol 2012;5:1010–1116. [PubMed: 22923270]
18. Ajijola OA, Hoover DB, Simerly TM, et al. Inflammation, oxidative stress, and glial cell activation characterize stellate ganglia from humans with electrical storm. JCI Insight 2017;2.
19. Kumar R, Woo MA, Birrer BVX, et al. Mammillary bodies and fornix fibers are injured in heart failure. Neurobiol. Dis 2009;33:236–242. [PubMed: 19022386]
20. Woo MA, Macey PM, Keens PT, et al. Aberrant central nervous system responses to the Valsalva maneuver in heart failure. Congest. Heart Fail. Greenwich Conn 2007;13:29–35.
21. Nakamura K, Ajijola OA, Aliotta E, Armour JA, Ardell JL, Shivkumar K. Pathological effects of chronic myocardial infarction on peripheral neurons mediating cardiac neurotransmission. Auton. Neurosci. Basic Clin. 2016;197:34–40.
22. Vaseghi M, Shivkumar K. The Role of the Autonomic Nervous System in Sudden Cardiac Death. Prog. Cardiovasc. Dis 2008;50:404–419. [PubMed: 18474284]
23. Geraghty L, Santangeli P, Tedrow UB, Shivkumar K, Kumar S. Contemporary Management of Electrical Storm. Heart Lung Circ. 2019;28:123–133. [PubMed: 30554598]
24. Mulpuru SK, Patel DV, Wilbur SL, Vasavada BC, Furqan T. Electrical storm and termination with propofol therapy: a case report. Int. J. Cardiol 2008;128:e6–8. [PubMed: 17692956]
25. Tsutsui K, Hayami N, Kunishima T, et al. Dexmedetomidine and clonidine inhibit ventricular tachyarrhythmias in a rabbit model of acquired long QT syndrome. Circ. J. Off. J. Jpn. Circ. Soc 2012;76:2343–2347.
26. Credner SC, Klingenheben T, Mauss O, Sticherling C, Hohnloser SH. Electrical storm in patients with transvenous implantable cardioverter-defibrillators: incidence, management and prognostic implications. J. Am. Coll. Cardiol 1998;32:1909–1915. [PubMed: 9857871]
27. European Heart Rhythm Association, Heart Rhythm Society, Zipes DP, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J. Am. Coll. Cardiol 2006;48:e247–346. [PubMed: 16949478]
28. Kowey PR, Friehling TD, Marinchak RA. Electrophysiology of beta blockers in supraventricular arrhythmias. Am. J. Cardiol 1987;60:32D–38D.
29. Dorian P Antiarrhythmic action of beta-blockers: potential mechanisms. J. Cardiovasc. Pharmacol. Ther 2005;10 Suppl 1:S15–22. [PubMed: 15965568]
30. Bangalore S, Messerli FH, Kostis JB, Pepine CJ. Cardiovascular protection using beta-blockers: a critical review of the evidence. J. Am. Coll. Cardiol 2007;50:563–572. [PubMed: 17692739]
31. Anderson JL, Rodier HE, Green LS. Comparative effects of beta-adrenergic blocking drugs on experimental ventricular fibrillation threshold. Am. J. Cardiol 1983;51:1196–1202. [PubMed: 6132549]
32. Johansson BW. Effect of beta blockade on ventricular fibrillation- and ventricular tachycardia-induced circulatory arrest in acute myocardial infarction. Am. J. Cardiol 1986;57:34F–37F.
33. Chockalingam P, Crotti L, Girardengo G, et al. Not all beta-blockers are equal in the management of long QT syndrome types 1 and 2: higher recurrence of events under metoprolol. J. Am. Coll. Cardiol 2012;60:2092–2099. [PubMed: 23083782]

34. Chatzidou S, Kontogiannis C, Tsilimigras DI, et al. Propranolol Versus Metoprolol for Treatment of Electrical Storm in Patients With Implantable Cardioverter-Defibrillator. J. Am. Coll. Cardiol 2018;71:1897–1906. [PubMed: 29699616]
35. Sorajja D, Munger TM, Shen W-K. Optimal antiarrhythmic drug therapy for electrical storm. J. Biomed. Res 2015;29:20–34. [PubMed: 25745472]
36. Leriche R, Fontaine R. L'anesthesie isolee du ganglion etoile: sa technique, ses indications, ses resultats. Presse Méd 1934;42:849–50.
37. Gofeld M, Bhatia A, Abbas S, Ganapathy S, Johnson M. Development and validation of a new technique for ultrasound-guided stellate ganglion block. Reg. Anesth. Pain Med 2009;34:475–479. [PubMed: 19920422]
38. Hayase J, Vampola S, Ahadian F, Narayan SM, Krummen DE. Comparative efficacy of stellate ganglion block with bupivacaine vs pulsed radiofrequency in a patient with refractory ventricular arrhythmias. J. Clin. Anesth 2016;31:162–165. [PubMed: 27185701]
39. Nademanee K, Taylor R, Bailey WE, Rieders DE, Kosar EM. Treating electrical storm: sympathetic blockade versus advanced cardiac life support-guided therapy. Circulation 2000;102:742–747. [PubMed: 10942741]
40. Loyalka P, Hariharan R, Gholkar G, et al. Left stellate ganglion block for continuous ventricular arrhythmias during percutaneous left ventricular assist device support. Tex. Heart Inst. J 2011;38:409–411. [PubMed: 21841870]
41. Patel RA, Priore DL, Szeto WY, Slevin KA. Left stellate ganglion blockade for the management of drug-resistant electrical storm. Pain Med. Malden Mass 2011;12:1196–1198.
42. Mahajan A, Moore J, Cesario DA, Shivkumar K. Use of thoracic epidural anesthesia for management of electrical storm: a case report. Heart Rhythm 2005;2:1359–1362. [PubMed: 16360091]
43. Meissner A, Eckardt L, Kirchhof P, et al. Effects of thoracic epidural anesthesia with and without autonomic nervous system blockade on cardiac monophasic action potentials and effective refractoriness in awake dogs. Anesthesiology 2001;95:132–138; discussion 6A. [PubMed: 11465550]
44. Oka T, Ozawa Y, Ohkubo Y. Thoracic epidural bupivacaine attenuates supraventricular tachyarrhythmias after pulmonary resection. Anesth. Analg 2001;93:253–259, 1st contents page. [PubMed: 11473839]
45. Olausson K, Magnusdottir H, Lurje L, Wennerblom B, Emanuelsson H, Ricksten SE. Anti-ischemic and anti-anginal effects of thoracic epidural anesthesia versus those of conventional medical therapy in the treatment of severe refractory unstable angina pectoris. Circulation 1997;96:2178–2182. [PubMed: 9337187]
46. Meng L, Tseng C-H, Shivkumar K, Ajijola O. Efficacy of Stellate Ganglion Blockade in Managing Electrical Storm: A Systematic Review. JACC Clin. Electrophysiol 2017;3:942–949. [PubMed: 29270467]
47. Bourke T, Vaseghi M, Michowitz Y, et al. Neuraxial modulation for refractory ventricular arrhythmias: value of thoracic epidural anesthesia and surgical left cardiac sympathetic denervation. Circulation 2010;121:2255–2262. [PubMed: 20479150]
48. Schwartz PJ, Periti M, Malliani A. The long Q-T syndrome. Am. Heart J 1975;89:378–390. [PubMed: 234667]
49. JONNESCO T Traitment chirurgical de I' angine de poitrine par la resection du sympathetique cervicothoracique. Presse Med 1921;29:193–195.
50. Estes EH, Izlar HL. Recurrent ventricular tachycardia. A case successfully treated by bilateral cardiac sympathectomy. Am. J. Med 1961;31:493–497. [PubMed: 13697443]
51. Zipes DP, Festoff B, Schaal SF, Cox C, Sealy WC, Wallace AG. Treatment of ventricular arrhythmia by permanent atrial pacemaker and cardiac sympathectomy. Ann. Intern. Med 1968;68:591–597. [PubMed: 5643681]
52. Moss AJ, McDonald J. Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long QT interval syndrome. N. Engl. J. Med 1971;285:903–904. [PubMed: 5112730]

53. Wilde AAM, Bhuiyan ZA, Crotti L, et al. Left cardiac sympathetic denervation for catecholaminergic polymorphic ventricular tachycardia. N. Engl. J. Med 2008;358:2024–2029. [PubMed: 18463378]
54. De Ferrari GM, Dusi V, Spazzolini C, et al. Clinical Management of Catecholaminergic Polymorphic Ventricular Tachycardia: The Role of Left Cardiac Sympathetic Denervation. Circulation 2015;131:2185–2193. [PubMed: 26019152]
55. Irie T, Yamakawa K, Hamon D, Nakamura K, Shivkumar K, Vaseghi M. Cardiac sympathetic innervation via middle cervical and stellate ganglia and antiarrhythmic mechanism of bilateral stellectomy. Am. J. Physiol. Heart Circ. Physiol 2017;312:H392–H405. [PubMed: 28011590]
56. Verrier RL, Thompson PL, Lown B. Ventricular vulnerability during sympathetic stimulation: role of heart rate and blood pressure. Cardiovasc. Res 1974;8:602–610. [PubMed: 4434365]
57. Vaseghi M, Zhou W, Shi J, et al. Sympathetic innervation of the anterior left ventricular wall by the right and left stellate ganglia. Heart Rhythm 2012;9:1303–1309. [PubMed: 22465457]
58. Yagishita D, Chui RW, Yamakawa K, et al. Sympathetic nerve stimulation, not circulating norepinephrine, modulates T-peak to T-end interval by increasing global dispersion of repolarization. Circ. Arrhythm. Electrophysiol 2015;8:174–185. [PubMed: 25532528]
59. Schwartz PJ, Priori SG, Cerrone M, et al. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long-QT syndrome. Circulation 2004;109:1826–1833. [PubMed: 15051644]
60. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation 2001;103:89–95. [PubMed: 11136691]
61. Norbert Jost, Virág László Bitay Miklós, et al. Restricting Excessive Cardiac Action Potential and QT Prolongation. Circulation 2005;112:1392–1399. [PubMed: 16129791]
62. Schwartz PJ, Ackerman MJ. The long QT syndrome: a transatlantic clinical approach to diagnosis and therapy. Eur. Heart J 2013;34:3109–3116. [PubMed: 23509228]
63. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 2013;10:1932–1963. [PubMed: 24011539]
64. Antiel RM, Bos JM, Joyce DD, et al. Quality of life after videoscopic left cardiac sympathetic denervation in patients with potentially life-threatening cardiac channelopathies/cardiomyopathies. Heart Rhythm 2016;13:62–69. [PubMed: 26341607]
65. Schwartz PJ. When the risk is sudden death, does quality of life matter? Heart Rhythm 2016;13:70–71. [PubMed: 26407898]
66. Collura CA, Johnson JN, Moir C, Ackerman MJ. Left cardiac sympathetic denervation for the treatment of long QT syndrome and catecholaminergic polymorphic ventricular tachycardia using video-assisted thoracic surgery. Heart Rhythm 2009;6:752–759. [PubMed: 19467503]
67. Roston TM, Vinocur JM, Maginot KR, et al. Catecholaminergic polymorphic ventricular tachycardia in children: analysis of therapeutic strategies and outcomes from an international multicenter registry. Circ. Arrhythm. Electrophysiol 2015;8:633–642. [PubMed: 25713214]
68. Yanowitz F, Preston JB, Abildskov JA. Functional distribution of right and left stellate innervation to the ventricles: production of neurogenic electrocardiographs changes by unilateral alteration of sympathetic tone. Circ. Res 1966;18:416–428. [PubMed: 4952701]
69. Wichter T, Hindricks G, Lerch H, et al. Regional myocardial sympathetic dysinnervation in arrhythmogenic right ventricular cardiomyopathy. An analysis using 123I-meta-iodobenzylguanidine scintigraphy. Circulation 1994;89:667–683. [PubMed: 8313555]
70. Schwartz PJ, Verrier RL, Lown B. Effect of stellectomy and vagotomy on ventricular refractoriness in dogs. Circ. Res 1977;40:536–540. [PubMed: 870234]
71. Cinca J, Evangelista A, Montoyo J, et al. Electrophysiologic effects of unilateral right and left stellate ganglion block on the human heart. Am. Heart J 1985;109:46–54. [PubMed: 3966332]
72. García-Calvo R, Chorro FJ, Sendra M, et al. The effects of selective stellate ganglion manipulation on ventricular refractoriness and excitability. Pacing Clin. Electrophysiol. PACE 1992;15:1492–1503. [PubMed: 1383961]

73. Vaseghi M, Barwad P, Malavassi Corrales FJ, et al. Cardiac Sympathetic Denervation for Refractory Ventricular Arrhythmias. J. Am. Coll. Cardiol 2017;69:3070–3080. [PubMed: 28641796]
74. ClinicalTrials.gov. Identifier NCT01013714, Cardiac Sympathetic Denervation for Prevention of Ventricular Tachyarrhythmias - (PREVENT VT). 2009 Available at: https://clinicaltrials.gov/ct2/show/NCT01013714. Accessed May 16, 2019.
75. Bernard C Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme. Tome II. 1859;2.
76. Starling EH. THE CHEMICAL CONTROL OF THE BODY. J. Am. Med. Assoc 1908;L:835–840.
77. Shivkumar K, Ajijola OA, Anand I, et al. Clinical neurocardiology defining the value of neuroscience-based cardiovascular therapeutics. J. Physiol 2016;594:3911–3954. [PubMed: 27114333]
78. DiBona GF, Esler M. Translational medicine: the antihypertensive effect of renal denervation. Am. J. Physiol. Regul. Integr. Comp. Physiol 2010;298:R245–253. [PubMed: 19955493]
79. Tung R, Shivkumar K. Neuraxial modulation for treatment of VT storm. J. Biomed. Res 2015;29:56–60. [PubMed: 25745476]
80. Jackson N, Gizurarson S, Azam MA, et al. Effects of Renal Artery Denervation on Ventricular Arrhythmias in a Postinfarct Model. Circ. Cardiovasc. Interv 2017;10:e004172. [PubMed: 28258128]
81. Armaganijan LV, Staico R, Moreira DAR, et al. 6-Month Outcomes in Patients With Implantable Cardioverter-Defibrillators Undergoing Renal Sympathetic Denervation for the Treatment of Refractory Ventricular Arrhythmias. JACC Cardiovasc. Interv 2015;8:984–990. [PubMed: 26088516]
82. Evranos B, Canpolat U, Kocyigit D, Coteli C, Yorgun H, Aytemir K. Role of Adjuvant Renal Sympathetic Denervation in the Treatment of Ventricular Arrhythmias. Am. J. Cardiol 2016;118:1207–1210. [PubMed: 27600464]
83. Bradfield JS, Vaseghi M, Shivkumar K. Renal denervation for refractory ventricular arrhythmias. Trends Cardiovasc. Med 2014;24:206–213. [PubMed: 25017919]
84. Liu K, Do D, Sorg J, et al. Abstract 16805: Renal Sympathetic Denervation as an Adjunctive Therapy to Radiofrequency Ablation and Cardiac Sympathetic Denervation for Refractory Ventricular Tachycardia. Circulation 2018;138:A16805–A16805.
85. Steinberg J Evaluate Renal Artery Denervation In Addition to Catheter Ablation To Eliminate Atrial Fibrillation (ERADICATE-AF) Trial Late Breaking Clinical Trial presented at: Heart Rhythm Scientific Sessions; 5 9, 2019; San Francisco, CA.
86. Mannheimer C, Camici P, Chester MR, et al. The problem of chronic refractory angina; report from the ESC Joint Study Group on the Treatment of Refractory Angina. Eur. Heart J 2002;23:355–370. [PubMed: 11846493]
87. Zhang TC, Janik JJ, Grill WM. Mechanisms and models of spinal cord stimulation for the treatment of neuropathic pain. Brain Res. 2014;1569:19–31. [PubMed: 24802658]
88. Wang S, Zhou X, Huang B, et al. Spinal cord stimulation protects against ventricular arrhythmias by suppressing left stellate ganglion neural activity in an acute myocardial infarction canine model. Heart Rhythm 2015;12:1628–1635. [PubMed: 25778432]
89. Odenstedt J, Linderoth B, Bergfeldt L, et al. Spinal cord stimulation effects on myocardial ischemia, infarct size, ventricular arrhythmia, and noninvasive electrophysiology in a porcine ischemia-reperfusion model. Heart Rhythm 2011;8:892–898. [PubMed: 21255678]
90. Lopshire JC, Zipes DP. Spinal cord stimulation for heart failure: preclinical studies to determine optimal stimulation parameters for clinical efficacy. J Cardiovasc. Transl. Res 2014;7:321–329. [PubMed: 24569871]
91. Foreman RD, Linderoth B, Ardell JL, et al. Modulation of intrinsic cardiac neurons by spinal cord stimulation: implications for its therapeutic use in angina pectoris. Cardiovasc. Res 2000;47:367–375. [PubMed: 10946073]
92. Latif OA, Nedeljkovic SS, Stevenson LW. Spinal cord stimulation for chronic intractable angina pectoris: a unified theory on its mechanism. Clin. Cardiol 2001;24:533–541. [PubMed: 11501604]

93. Wu M, Linderoth B, Foreman RD. Putative mechanisms behind effects of spinal cord stimulation on vascular diseases: a review of experimental studies. Auton. Neurosci. Basic Clin 2008;138:9–23.
94. Ardell JL. Heart failure: Mechanisms of spinal cord neuromodulation for heart disease. Nat. Rev. Cardiol 2016;13:127–128. [PubMed: 26843288]
95. Grimaldi R, de Luca A, Kornet L, Castagno D, Gaita F. Can spinal cord stimulation reduce ventricular arrhythmias? Heart Rhythm 2012;9:1884–1887. [PubMed: 22877745]
96. Tse H-F, Turner S, Sanders P, et al. Thoracic Spinal Cord Stimulation for Heart Failure as a Restorative Treatment (SCS HEART study): first-in-man experience. Heart Rhythm 2015;12:588–595. [PubMed: 25500165]
97. Zipes DP, Neuzil P, Theres H, et al. Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Systolic Heart Failure: The DEFEAT-HF Study. JACC Heart Fail. 2016;4:129–136. [PubMed: 26682789]
98. Li M, Zheng C, Sato T, Kawada T, Sugimachi M, Sunagawa K. Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats. Circulation 2004;109:120–124. [PubMed: 14662714]
99. Ando Motonori, Katare Rajesh G., Kakinuma Yoshihiko, et al. Efferent Vagal Nerve Stimulation Protects Heart Against Ischemia-Induced Arrhythmias by Preserving Connexin43 Protein. Circulation 2005;112:164–170. [PubMed: 15998674]
100. Zhang Y, Popovic ZB, Bibevski S, et al. Chronic vagus nerve stimulation improves autonomic control and attenuates systemic inflammation and heart failure progression in a canine high-rate pacing model. Circ. Heart Fail 2009;2:692–699. [PubMed: 19919995]
101. Waxman MB, Wald RW. Termination of ventricular tachycardia by an increase in cardiac vagal drive. Circulation 1977;56:385–391. [PubMed: 884795]
102. Uthman BM, Reichl AM, Dean JC, et al. Effectiveness of vagus nerve stimulation in epilepsy patients: a 12-year observation. Neurology 2004;63:1124–1126. [PubMed: 15452317]
103. Shuchman M Approving the vagus-nerve stimulator for depression. N. Engl. J. Med 2007;356:1604–1607. [PubMed: 17442903]
104. De Ferrari GM, Crijns HJGM, Borggrefe M, et al. Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. Eur. Heart J 2011;32:847–855. [PubMed: 21030409]
105. Zuanetti G, De Ferrari GM, Priori SG, Schwartz PJ. Protective effect of vagal stimulation on reperfusion arrhythmias in cats. Circ. Res 1987;61:429–435. [PubMed: 3621502]
106. Vanoli E, De Ferrari GM, Stramba-Badiale M, Hull SS, Foreman RD, Schwartz PJ. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. Circ. Res 1991;68:1471–1481. [PubMed: 2019002]
107. Yamakawa K, So EL, Rajendran PS, et al. Electrophysiological effects of right and left vagal nerve stimulation on the ventricular myocardium. Am. J. Physiol. Heart Circ. Physiol 2014;307:H722–731. [PubMed: 25015962]
108. Yamakawa K, Rajendran PS, Takamiya T, et al. Vagal nerve stimulation activates vagal afferent fibers that reduce cardiac efferent parasympathetic effects. Am. J. Physiol. Heart Circ. Physiol 2015;309:H1579–1590. [PubMed: 26371172]
109. Vaseghi M, Salavatian S, Rajendran PS, et al. Parasympathetic dysfunction and antiarrhythmic effect of vagal nerve stimulation following myocardial infarction. JCI Insight 2017;2.
110. Ardell JL, Rajendran PS, Nier HA, KenKnight BH, Armour JA. Central-peripheral neural network interactions evoked by vagus nerve stimulation: functional consequences on control of cardiac function. Am. J. Physiol. Heart Circ. Physiol 2015;309:H1740–1752. [PubMed: 26371171]
111. Ardell JL, Nier H, Hammer M, et al. Defining the neural fulcrum for chronic vagus nerve stimulation: implications for integrated cardiac control. J. Physiol 2017;595:6887–6903. [PubMed: 28862330]
112. Zannad F, De Ferrari GM, Tuinenburg AE, et al. Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) randomized controlled trial. Eur. Heart J 2015;36:425–433. [PubMed: 25176942]

113. Premchand RK, Sharma K, Mittal S, et al. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial. J. Card. Fail 2014;20:808–816. [PubMed: 25187002]

114. Hauptman PJ, Schwartz PJ, Gold MR, et al. Rationale and study design of the increase of vagal tone in heart failure study: INOVATE-HF. Am. Heart J 2012;163:954–962.e1. [PubMed: 22709747]

115. Byku M, Mann DL. Neuromodulation of the Failing Heart. JACC Basic Transl. Sci 2016;1:95–106. [PubMed: 27525317]

116. Hanna P, Shivkumar K, Ardell JL. Calming the Nervous Heart: Autonomic Therapies in Heart Failure. Card. Fail. Rev 2018;4:92–98. [PubMed: 30206483]

117. Yamaguchi N, Yamakawa K, Rajendran PS, Takamiya T, Vaseghi M. Antiarrhythmic effects of vagal nerve stimulation after cardiac sympathetic denervation in the setting of chronic myocardial infarction. Heart Rhythm 2018;15:1214–1222. [PubMed: 29530832]

118. Spuck S, Tronnier V, Orosz I, et al. Operative and technical complications of vagus nerve stimulator implantation. Neurosurgery 2010;67:489–494. [PubMed: 21099577]

119. Yu L, Wang S, Zhou X, et al. Chronic Intermittent Low-Level Stimulation of Tragus Reduces Cardiac Autonomic Remodeling and Ventricular Arrhythmia Inducibility in a Post-Infarction Canine Model. JACC Clin. Electrophysiol 2016;2:330–339. [PubMed: 29766893]

120. Yu L, Huang B, Po SS, et al. Low-Level Tragus Stimulation for the Treatment of Ischemia and Reperfusion Injury in Patients With ST-Segment Elevation Myocardial Infarction: A Proof-of-Concept Study. JACC Cardiovasc. Interv 2017;10:1511–1520. [PubMed: 28797427]

121. Garrey WE. Auricular fibrillation. Physiol. Rev 1924;4:215–250.

122. Allessie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The “leading circle” concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ. Res 1977;41:9–18. [PubMed: 862147]

123. Allessie MA, Lammers WJ, Bonke IM, Hollen J. Intra-atrial reentry as a mechanism for atrial flutter induced by acetylcholine and rapid pacing in the dog. Circulation 1984;70:123–135. [PubMed: 6723008]

124. Burn JH, Williams EMV, Walker JM. The effects of acetylcholine in the heart-lung preparation including the production of auricular fibrillation. J. Physiol 1955;128:277–293. [PubMed: 14392608]

125. Zipes DP, Mihalick MJ, Robbins GT. Effects of selective vagal and stellate ganglion stimulation of atrial refractoriness. Cardiovasc. Res 1974;8:647–655. [PubMed: 4434368]

126. Liu L, Nattel S. Differing sympathetic and vagal effects on atrial fibrillation in dogs: role of refractoriness heterogeneity. Am. J. Physiol 1997;273:H805–816. [PubMed: 9277498]

127. Smeets JL, Allessie MA, Lammers WJ, Bonke FI, Hollen J. The wavelength of the cardiac impulse and reentrant arrhythmias in isolated rabbit atrium. The role of heart rate, autonomic transmitters, temperature, and potassium. Circ. Res 1986;58:96–108. [PubMed: 3943157]

128. Chiou CW, Eble JN, Zipes DP. Efferent vagal innervation of the canine atria and sinus and atrioventricular nodes. The third fat pad. Circulation 1997;95:2573–2584. [PubMed: 9184589]

129. Schauerte P, Scherlag BJ, Pitha J, et al. Catheter ablation of cardiac autonomic nerves for prevention of vagal atrial fibrillation. Circulation 2000;102:2774–2780. [PubMed: 11094046]

130. Haïssaguerre M, Jaïs P, Shah DC, et al. Spontaneous Initiation of Atrial Fibrillation by Ectopic Beats Originating in the Pulmonary Veins. N. Engl. J. Med 1998;339:659–666. [PubMed: 9725923]

131. Tsai CF, Chen SA, Tai CT, et al. Bezold-Jarisch-like reflex during radiofrequency ablation of the pulmonary vein tissues in patients with paroxysmal focal atrial fibrillation. J. Cardiovasc. Electrophysiol 1999;10:27–35. [PubMed: 9930906]

132. Hsieh MH, Chiou CW, Wen ZC, et al. Alterations of heart rate variability after radiofrequency catheter ablation of focal atrial fibrillation originating from pulmonary veins. Circulation 1999;100:2237–2243. [PubMed: 10577997]

133. Tan AY, Li H, Wachsmann-Hogiu S, Chen LS, Chen P-S, Fishbein MC. Autonomic innervation and segmental muscular disconnections at the human pulmonary vein-atrial junction:

implications for catheter ablation of atrial-pulmonary vein junction. J. Am. Coll. Cardiol 2006;48:132–143. [PubMed: 16814659]

134. Katritsis DG, Giazitzoglou E, Zografos T, Pokushalov E, Po SS, Camm AJ. Rapid pulmonary vein isolation combined with autonomic ganglia modification: a randomized study. Heart Rhythm 2011;8:672–678. [PubMed: 21199686]
135. Katritsis DG, Pokushalov E, Romanov A, et al. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: a randomized clinical trial. J. Am. Coll. Cardiol 2013;62:2318–2325. [PubMed: 23973694]
136. Steinberg JS, Pokushalov E, Mittal S. Renal denervation for arrhythmias: hope or hype? Curr. Cardiol. Rep 2013;15:392. [PubMed: 23881576]
137. Han FT, Kasirajan V, Kowalski M, et al. Results of a minimally invasive surgical pulmonary vein isolation and ganglionic plexi ablation for atrial fibrillation: single-center experience with 12-month follow-up. Circ. Arrhythm. Electrophysiol 2009;2:370–377. [PubMed: 19808492]
138. Edgerton JR, Brinkman WT, Weaver T, et al. Pulmonary vein isolation and autonomic denervation for the management of paroxysmal atrial fibrillation by a minimally invasive surgical approach. J. Thorac. Cardiovasc. Surg 2010;140:823–828. [PubMed: 20299028]
139. Krul SPJ, Driessen AHG, van Boven WJ, et al. Thoracoscopic video-assisted pulmonary vein antrum isolation, ganglionated plexus ablation, and periprocedural confirmation of ablation lesions: first results of a hybrid surgical-electrophysiological approach for atrial fibrillation. Circ. Arrhythm. Electrophysiol 2011;4:262–270. [PubMed: 21493960]
140. Báez-Escudero JL, Keida T, Dave AS, Okishige K, Valderrábano M. Ethanol infusion in the vein of Marshall leads to parasympathetic denervation of the human left atrium: implications for atrial fibrillation. J. Am. Coll. Cardiol 2014;63:1892–1901. [PubMed: 24561151]
141. Pauza DH, Skripka V, Pauziene N, Stropus R. Morphology, distribution, and variability of the epicardiac neural ganglionated subplexuses in the human heart. Anat. Rec 2000;259:353–382. [PubMed: 10903529]
142. Driessen AHG, Berger WR, Krul SPJ, et al. Ganglion Plexus Ablation in Advanced Atrial Fibrillation: The AFACT Study. J. Am. Coll. Cardiol 2016;68:1155–1165. [PubMed: 27609676]
143. Romanov A, Pokushalov E, Ponomarev D, et al. Long-term suppression of atrial fibrillation by botulinum toxin injection into epicardial fat pads in patients undergoing cardiac surgery: Three-year follow-up of a randomized study. Heart Rhythm 2018.
144. Tai CT, Chiou CW, Wen ZC, et al. Effect of phenylephrine on focal atrial fibrillation originating in the pulmonary veins and superior vena cava. J. Am. Coll. Cardiol 2000;36:788–793. [PubMed: 10987601]
145. Li S, Scherlag BJ, Yu L, et al. Low-level vagosympathetic stimulation: a paradox and potential new modality for the treatment of focal atrial fibrillation. Circ. Arrhythm. Electrophysiol 2009;2:645–651. [PubMed: 19948505]
146. Sha Y, Scherlag BJ, Yu L, et al. Low-level right vagal stimulation: anticholinergic and antiadrenergic effects. J. Cardiovasc. Electrophysiol 2011;22:1147–1153. [PubMed: 21489033]
147. Sheng X, Scherlag BJ, Yu L, et al. Prevention and reversal of atrial fibrillation inducibility and autonomic remodeling by low-level vagosympathetic nerve stimulation. J. Am. Coll. Cardiol 2011;57:563–571. [PubMed: 21272747]
148. Shen MJ, Cheng H-C, Park H-W, et al. Low-level vagus nerve stimulation upregulates small conductance calcium-activated potassium channels in the stellate ganglion. Heart Rhythm 2013;10:910–915. [PubMed: 23357541]
149. Stavrakis S, Scherlag BJ, Fan Y, et al. Antiarrhythmic effects of vasostatin-1 in a canine model of atrial fibrillation. J. Cardiovasc. Electrophysiol 2012;23:771–777. [PubMed: 22487376]
150. Salavatian S, Beaumont E, Longpré J-P, et al. Vagal stimulation targets select populations of intrinsic cardiac neurons to control neurally induced atrial fibrillation. Am. J. Physiol. - Heart Circ. Physiol 2016;311:H1311–H1320. [PubMed: 27591222]
151. Yu L, Scherlag BJ, Li S, et al. Low-level transcutaneous electrical stimulation of the auricular branch of the vagus nerve: a noninvasive approach to treat the initial phase of atrial fibrillation. Heart Rhythm 2013;10:428–435. [PubMed: 23183191]

152. Stavrakis S, Humphrey MB, Scherlag BJ, et al. Low-level transcutaneous electrical vagus nerve stimulation suppresses atrial fibrillation. J Am Coll Cardiol 2015;65:867–75. [PubMed: 25744003]

153. Stavrakis S Transcutaneous Electrical Vagus Nerve Stimulation To Suppress Atrial Fibrillation (TREAT AF): A Randomized Clinical Trial Late Breaking Clinical Trial presented at: Heart Rhythm Scientific Sessions; 5 9, 2019; San Francisco, CA.

154. Rajendran PS, Challis RC, Fowlkes CC, et al. Identification of peripheral neural circuits that regulate heart rate using optogenetic and viral vector strategies. Nature Communications 2019;10:1944.

List of 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 ventricular tachycardia and atrial fibrillation.
- Further investigation into basic mechanisms of cardiac neural control is needed to improve antiarrhythmic therapies.

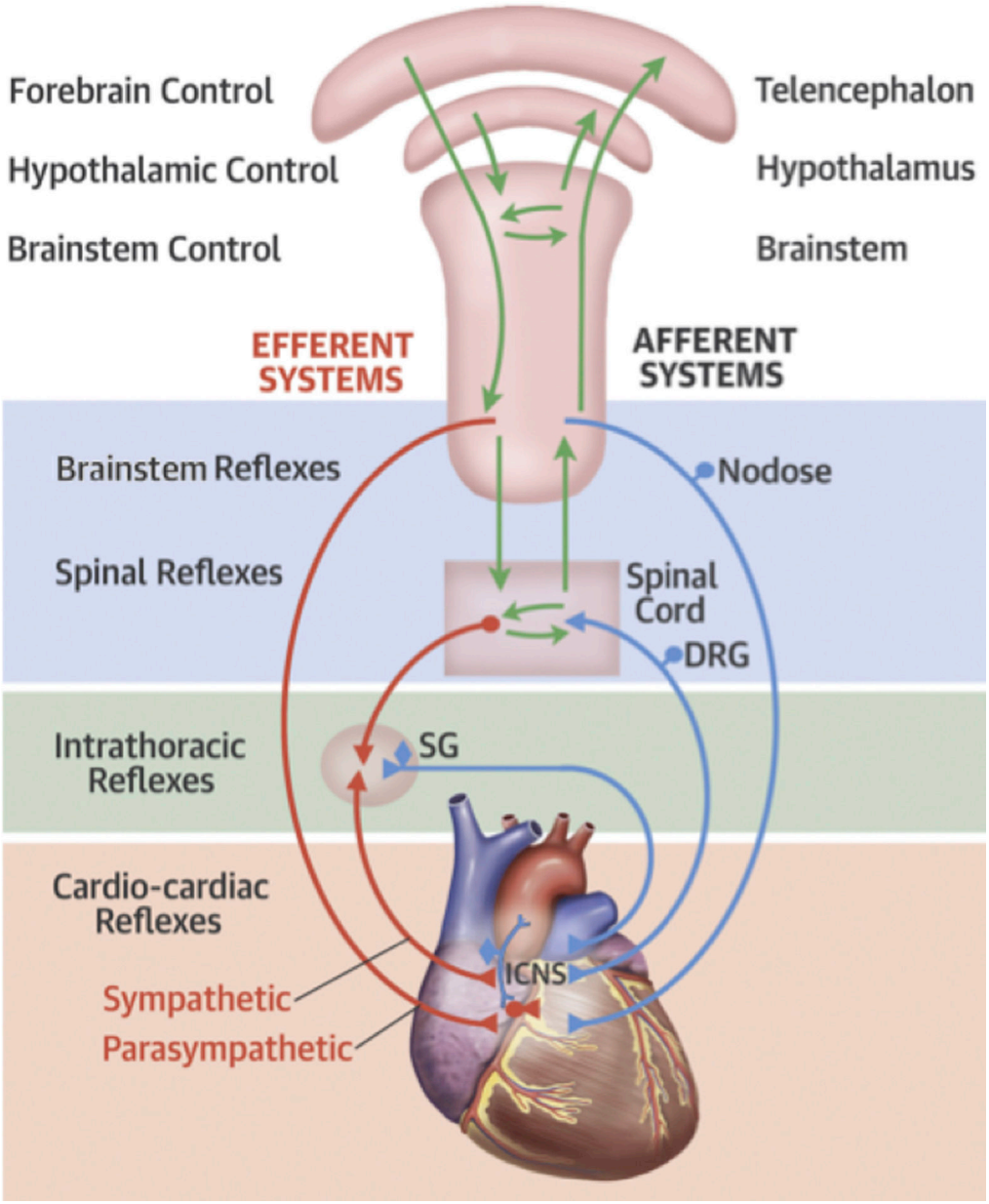


Figure 1.

Cardiac Autonomic Control. 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.

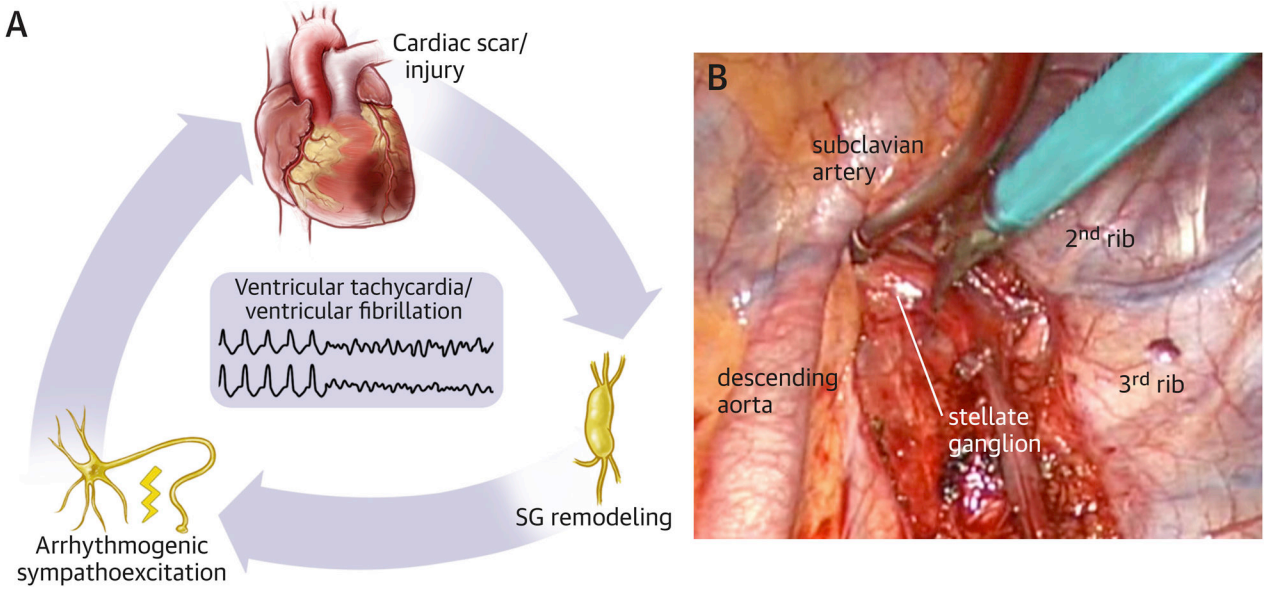


Figure 2.

Cardiac Sympathetic Denervation. **(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 guidance.

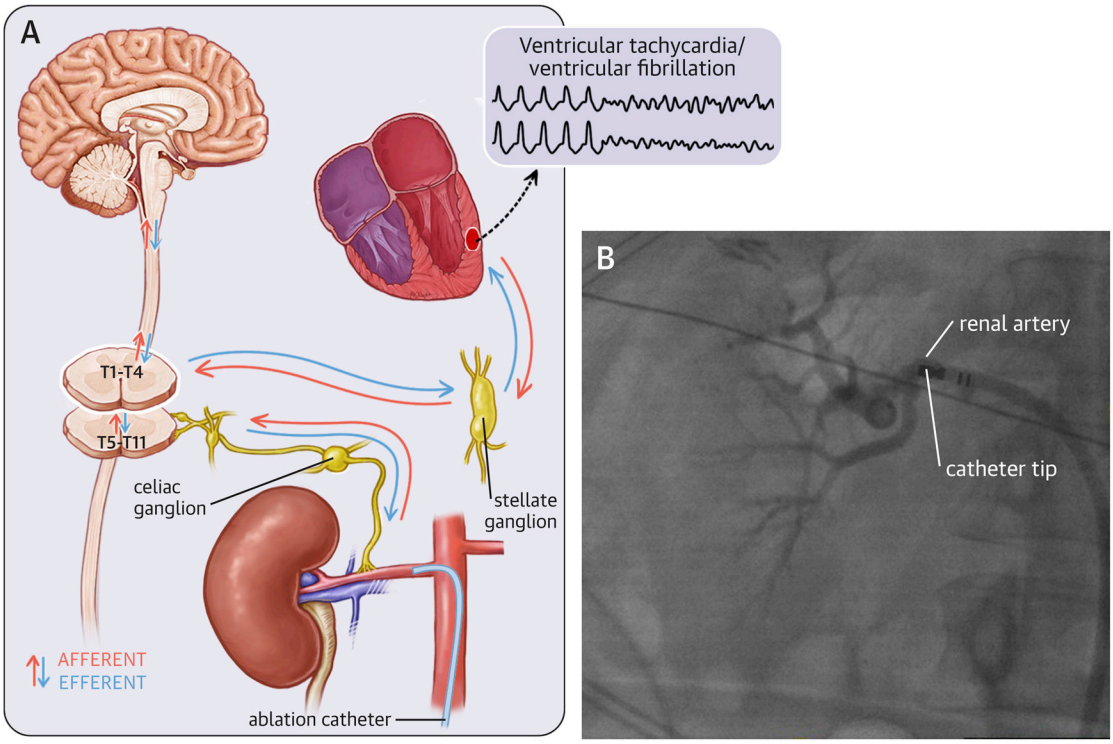


Figure 3.

Renal Artery Denervation. **(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.

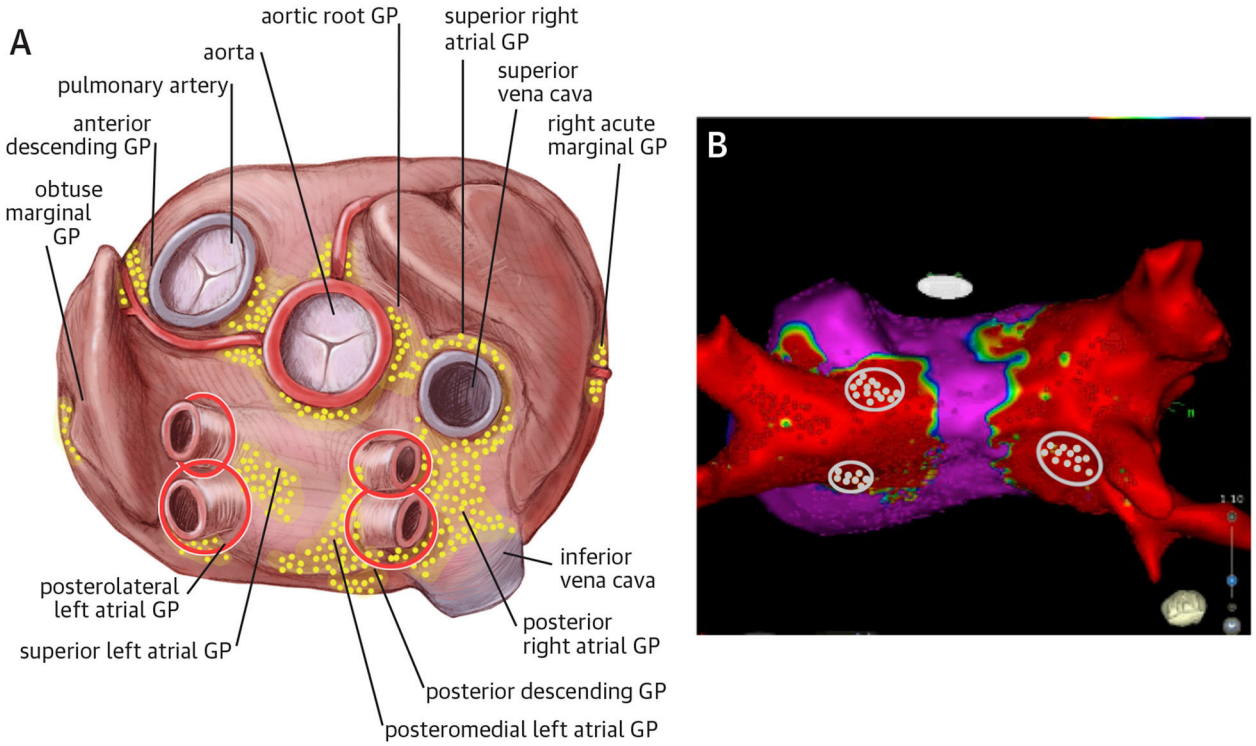
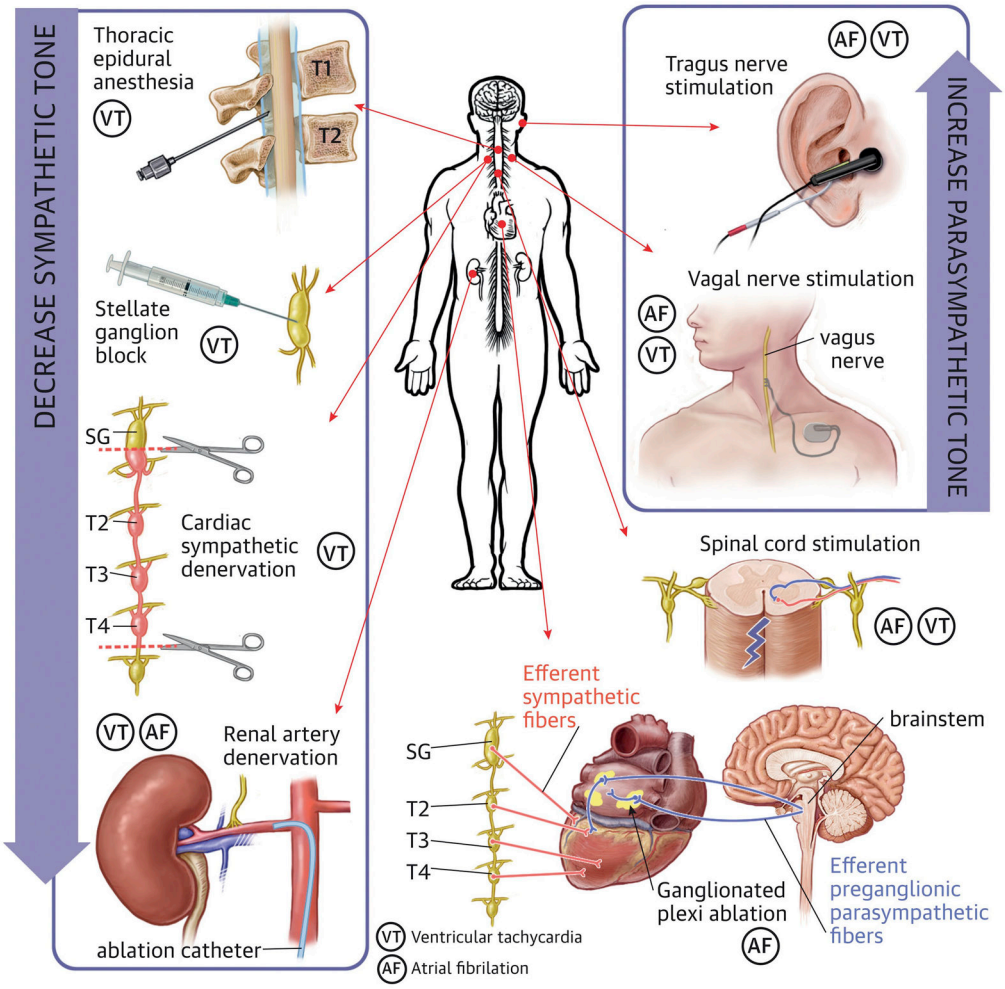


Figure 4.

PVI and the ICNS. **(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.



CENTRAL ILLUSTRATION:
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