

This Review is in a thematic series on **The Autonomic Nervous System and the Cardiovascular System**, which includes the following articles:

**Role of the Autonomic Nervous System in Modulating Cardiac Arrhythmias**

Autonomic Nervous System and Hypertension

Renal Denervation for the Treatment of Cardiovascular High Risk: Hypertension or Beyond?

Autonomic Nervous System and Heart Failure

## Role of the Autonomic Nervous System in Modulating Cardiac Arrhythmias

Mark J. Shen, Douglas P. Zipes

**Abstract:** The autonomic nervous system plays an important role in the modulation of cardiac electrophysiology and arrhythmogenesis. Decades of research has contributed to a better understanding of the anatomy and physiology of cardiac autonomic nervous system and provided evidence supporting the relationship of autonomic tone to clinically significant arrhythmias. The mechanisms by which autonomic activation is arrhythmogenic or antiarrhythmic are complex and different for specific arrhythmias. In atrial fibrillation, simultaneous sympathetic and parasympathetic activations are the most common trigger. In contrast, in ventricular fibrillation in the setting of cardiac ischemia, sympathetic activation is proarrhythmic, whereas parasympathetic activation is antiarrhythmic. In inherited arrhythmia syndromes, sympathetic stimulation precipitates ventricular tachyarrhythmias and sudden cardiac death except in Brugada and J-wave syndromes where it can prevent them. The identification of specific autonomic triggers in different arrhythmias has brought the idea of modulating autonomic activities for both preventing and treating these arrhythmias. This has been achieved by either neural ablation or stimulation. Neural modulation as a treatment for arrhythmias has been well established in certain diseases, such as long QT syndrome. However, in most other arrhythmia diseases, it is still an emerging modality and under investigation. Recent preliminary trials have yielded encouraging results. Further larger-scale clinical studies are necessary before widespread application can be recommended. (*Circ Res.* 2014;114:1004-1021.)

**Key Words:** atrial fibrillation ■ autonomic nervous system ■ ventricular fibrillation

In 1628, William Harvey hinted at a link between the brain and the heart when he wrote, "For every affection of the mind that is attended with either pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart."<sup>1</sup> For the past half century, numerous anatomic and physiological studies of cardiac autonomic nervous system (ANS)<sup>2-6</sup> have investigated this link and found it to be very complex. Autonomic activation alters not only heart rate, conduction, and hemodynamics, but also cellular and subcellular properties of individual myocytes. The characterization of extrinsic cardiac ANS and intrinsic cardiac ANS ranges from the recognition of anatomic relationships at the gross level to discovery of chemoreceptors, mechanoreceptors, and intracardiac ganglia lining specific regions along the cardiac chambers and

great vessels. Moreover, studies beginning >80 years ago<sup>7-9</sup> have demonstrated the critical role of cardiac ANS in cardiac arrhythmogenesis. This topic has garnered much recent interest because of mounting evidence showing that neural modulation either by ablation or stimulation can effectively control a wide spectrum of cardiac arrhythmias.<sup>10-13</sup> In this review, we will briefly discuss the anatomic aspects of cardiac ANS, focusing on how autonomic activities influence cardiac electrophysiology. We will also discuss specific autonomic triggers of various cardiac arrhythmias, including atrial fibrillation (AF), ventricular arrhythmias, and inherited arrhythmia syndromes. Lastly, we will discuss the latest avenues of research and clinical trials regarding the application of neural modulation in the treatment of specific cardiac arrhythmias.

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**Nonstandard Abbreviations and Acronyms**

<b>AF</b>	atrial fibrillation
<b>ANS</b>	autonomic nervous system
<b>ARVC</b>	arrhythmogenic right ventricular cardiomyopathy
<b>CPVT</b>	catecholaminergic polymorphic ventricular tachycardia
<b>EAD</b>	early afterdepolarization
<b>GP</b>	ganglionated plexi
<b>HF</b>	heart failure
<b>LCSD</b>	left cardiac sympathetic denervation
<b>LL-VNS</b>	low-level vagus nerve stimulation
<b>LQTS</b>	long QT syndrome
<b>LSG</b>	left stellate ganglion
<b>PVI</b>	pulmonary vein isolation
<b>SCD</b>	sudden cardiac death
<b>SCS</b>	spinal cord stimulation
<b>VF</b>	ventricular fibrillation

**Normal Autonomic Innervation of the Heart**

The cardiac ANS can be divided into extrinsic and intrinsic components.<sup>14</sup> The extrinsic cardiac ANS comprises fibers that mediate connections between the heart and the nervous system, whereas the intrinsic cardiac ANS consists of primarily autonomic nerve fibers once they enter the pericardial sac.

**Extrinsic Cardiac Nervous System**

The extrinsic cardiac ANS may be subdivided into sympathetic and parasympathetic components. The sympathetic fibers are largely derived from major autonomic ganglia along the cervical and thoracic spinal cord. These autonomic ganglia include superior cervical ganglia, which communicate with C<sub>1-3</sub>; the stellate (cervicothoracic) ganglia (Figure 1), which communicate with C<sub>7-8</sub> to T<sub>1-2</sub>; and the thoracic ganglia (as low as the seventh thoracic ganglion).<sup>15</sup> These ganglia house the cell bodies of most postganglionic sympathetic neurons whose axons form the superior, middle, and inferior cardiac nerves and terminate on the surface of the heart. The parasympathetic innervation originates predominantly in the nucleus ambiguus of the medulla oblongata. The parasympathetic preganglionic fibers are carried almost entirely within the vagus nerve and are divided into superior, middle, and inferior branches (Figure 2A). Most of the vagal nerve fibers converge at a distinct fat pad between the superior vena cava and the aorta (known as the third fat pad) en route to the sinus and atrioventricular nodes.<sup>16</sup>

**Intrinsic Cardiac Nervous System**

In addition to the extrinsic cardiac ANS, the heart is also innervated by an exquisitely complex intrinsic cardiac ANS. Armour et al<sup>6</sup> provided a detailed map of the distribution of autonomic nerves in human hearts. Throughout the heart, numerous cardiac ganglia, each of which contains 200 to 1000 neurons,<sup>6,17</sup> form synapses with the sympathetic and parasympathetic fibers that enter the pericardial space. The vast majority of these ganglia are organized into ganglionated plexi (GP) on the surface of the atria and ventricles.<sup>6</sup> The intrinsic cardiac ANS thus forms a complex network composed of GP, concentrated

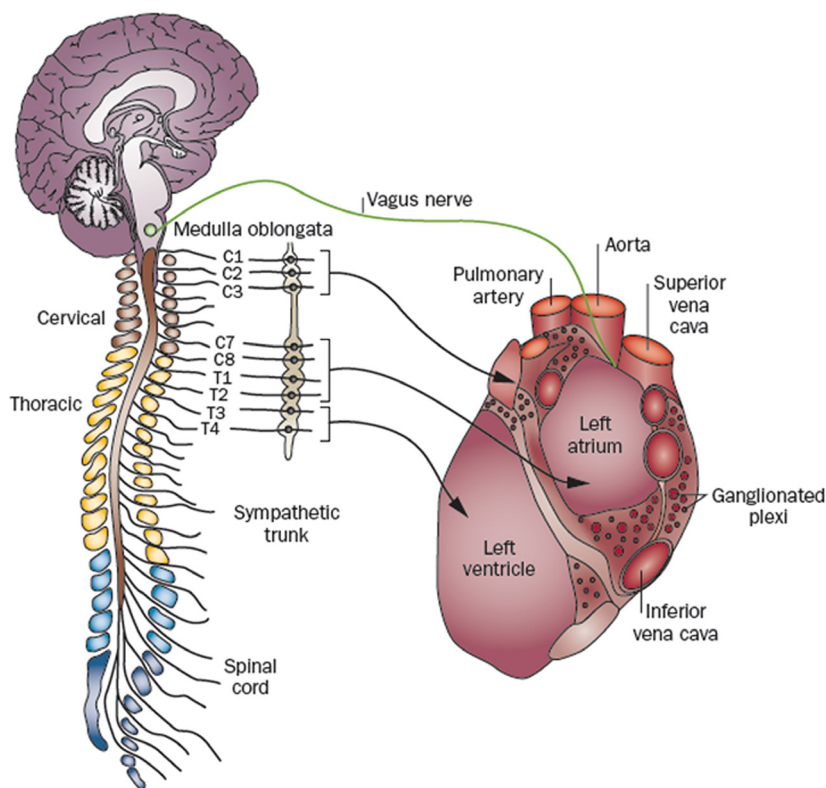
within epicardial fat pads, and the interconnecting ganglia and axons.<sup>5,6,18</sup> These GP may function as integration centers that modulate the intricate autonomic interactions between extrinsic cardiac ANS and intrinsic cardiac ANS.<sup>19</sup> Several primary groups of GP in the atria and ventricles have been identified. In the atria, GP are concentrated in distinct locations on the chamber walls.<sup>6</sup> Specifically, the sinus node is primarily innervated by the right atrial GP, whereas the atrioventricular node is innervated by the inferior vena cava–inferior atrial GP (at the junction of inferior vena cava and the left atrium).<sup>14,15,17,19</sup> Another region that is richly innervated by the ANS and has a high density of GP is the pulmonary vein–left atrium junction. The pulmonary vein–left atrium junction contains closely located adrenergic and cholinergic nerves (Figure 2B and 2C).<sup>20</sup> Although atrial GP seem to be located in multiple locations on atrial chamber walls, the ventricular GP are primarily located at the origins of several major cardiac blood vessels: surrounding the aortic root, the origins of the left and right coronary arteries, the origin of the posterior descending artery, the origin of the left obtuse marginal coronary artery, and the origin of the right acute marginal coronary artery.<sup>6,14</sup>

**Autonomic Influences on Cardiac Electrophysiology****Interplay Between Sympathetic and Parasympathetic Nervous Systems**

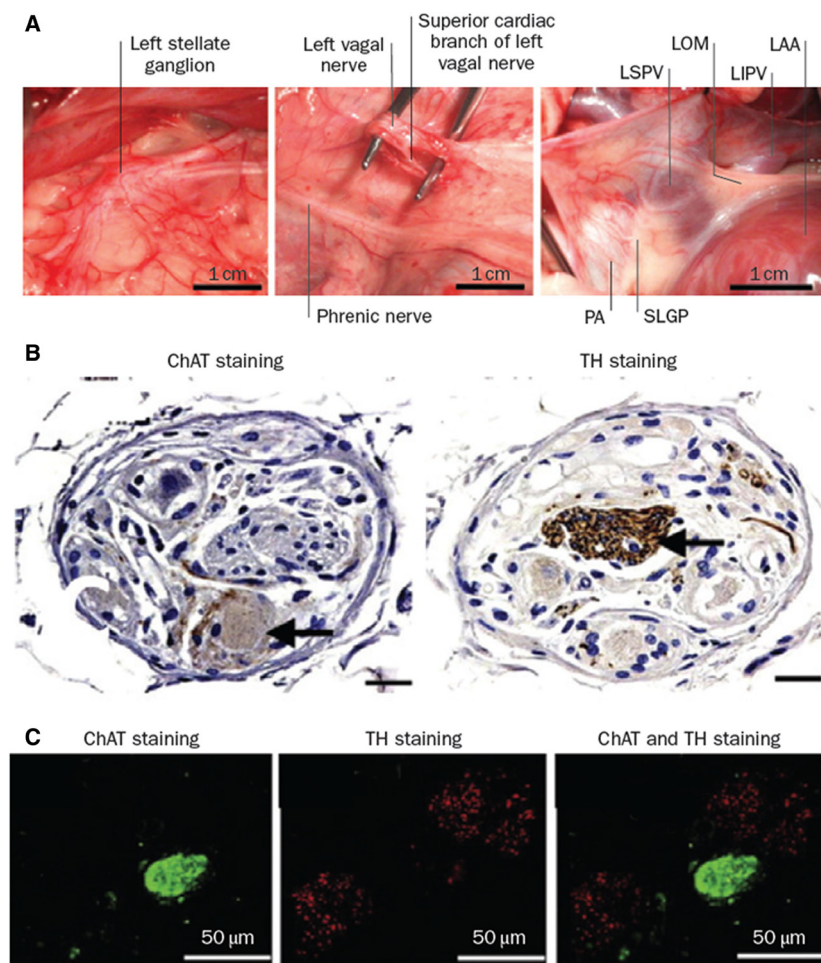
The fundamental, albeit oversimplified, characteristic of autonomic influences on the heart is its ying-yang nature,<sup>21</sup> which has been well described.<sup>2</sup> The interaction between these 2 arms of ANS is complex. In 1930s, Rosenbluth and Simeone first observed that in anesthetized cats the absolute reduction in heart rate produced by a given vagal stimulus was considerably greater under tonic sympathetic stimulation.<sup>22</sup> Similar findings were observed in anesthetized dogs by Samaan<sup>23</sup> the following year. Levy<sup>3</sup> later coined the term accentuated antagonism to describe the enhanced negative chronotropic effect of vagal stimulation in the presence of background sympathetic stimulation. This phenomenon was observed in conscious animals also.<sup>24</sup> Vagal antagonistic action, by opposing sympathetic actions at both pre- and postjunctional levels,<sup>25,26</sup> exists not only in the chronotropic effect but also in the control of ventricular performance, intracellular calcium handling, and cardiac electrophysiology.<sup>4,27,28</sup> Schwartz et al<sup>29</sup> demonstrated in chloralose anesthetized cats that afferent vagus nerve stimulation (VNS) reflexively inhibited efferent sympathetic nerve activity. About 40 years later, using an implanted device to record autonomic nerve activity continuously in ambulatory canines, Shen et al<sup>30</sup> observed that chronic left-sided cervical VNS led to a significant reduction in sympathetic nerve activity from the left stellate ganglion (LSG).

**Normal Autonomic Tone in Cardiac Electrophysiology**

Sympathetic influences on cardiac electrophysiology are complex and can be modulated by myocardial function. In the normal heart, sympathetic stimulation shortens action potential duration<sup>4</sup> and reduces transmural dispersion of repolarization.<sup>31</sup> In contrast, in pathological states such as heart failure (HF)<sup>32</sup> and long QT syndrome (LQTS),<sup>33</sup> sympathetic



**Figure 1. Scheme of autonomic innervation of the heart.** The cardiac sympathetic ganglia consist of cervical ganglia, stellate (cervicothoracic) ganglia, and thoracic ganglia. Parasympathetic innervation comes from the vagus nerves. Reprinted from Shen et al<sup>12</sup> with permission of the publisher. Copyright © 2011, Nature Publishing Group. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.



**Figure 2. Anatomy and histology of cardiac autonomic nervous system.** **A**, Photographs of the left stellate ganglion (left) and the superior cardiac branch of the left vagal nerve (middle) in the dog heart. The LOM originates from the coronary sinus and connects to the LSPV; the SLGP is located between the LAA and the LSPV (right). **B**, Colocalization of adrenergic and cholinergic nerves in the intrinsic cardiac ganglia. The same ganglion contained cholinergic ganglion cells (arrow; left) and adrenergic nerve fibers (arrow; right). **C**, Fluorescent dual labeling of TH and ChAT, visualized by confocal microscopy, showed highly colocalized ChAT-positive and TH-positive nerves within the intrinsic cardiac ganglia. ChAT indicates choline acetyltransferase; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LOM, ligament of Marshall; LSPV, left superior pulmonary vein; PA, pulmonary artery; SLGP, superior left ganglionated plexi; and TH, tyrosine hydroxylase. Panel A reprinted from Choi et al<sup>50</sup> with permission of the publisher. Copyright © 2010, Wolters Kluwer Health. Panels B and C reprinted from Tan et al<sup>20</sup> with permission of the publisher. Copyright © 2006, Elsevier Inc. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.



stimulation is a potent stimulus for the generation of arrhythmias, perhaps by enhancing the dispersion of repolarization or by generation of afterdepolarizations.<sup>21</sup>

Although sympathetic stimulation has similar effects on both atrial and ventricular myocytes, vagal stimulation does not. In the ventricles, vagal stimulation prolongs action potential duration and effective refractory period,<sup>4,34</sup> whereas in the atria, vagal activation reduces the atrial effective refractory period,<sup>35,36</sup> augments spatial electrophysiological heterogeneity,<sup>37</sup> and promotes early afterdepolarization (EAD) toward the end of phase 3 in the action potential.<sup>38</sup> This differential effect may explain why parasympathetic stimulation is proarrhythmic in the atria but antiarrhythmic in the ventricles, whereas sympathetic stimulation seems to be proarrhythmic for both chambers.<sup>39</sup>

### Measuring Autonomic Nerve Activities

Most of the abovementioned studies were performed either in vitro using a Langendorff-perfused heart or in vivo with anesthetized animals. These techniques have limited applicability in mimicking the pathophysiology of human arrhythmias because of the lack of hemodynamic reflexes and background neurohormonal influences in a perfused heart<sup>34</sup> and the relatively short-term observations without spontaneously occurring arrhythmias in acute studies. Heart rate variability analysis seems to be an attractive, noninvasive method to study cardiac autonomic activity. Power spectral analysis of heart rate variability over a period of ECG recordings to reflect cardiac sympathetic tone or sympathovagal balance has been widely used.<sup>40</sup> Another noninvasive method is by measuring baroreflex sensitivity. An increase in aortic pressure or volume can trigger the firing of stretch-sensitive neurons in the afferent baroreceptor. This sends impulses to the medulla and leads to decreased efferent sympathetic and increased efferent parasympathetic activity to restore pressure homeostasis.<sup>41</sup> These analyses provide significant prognostic value in that a depressed heart rate variability or baroreflex sensitivity after myocardial infarction is associated with higher cardiac mortality.<sup>42</sup> Nonetheless, these noninvasive analyses have substantial limitations for at least 2 reasons. First, it measures only relative changes in autonomic nerve activity rather than the absolute intensity of sympathetic or parasympathetic discharges. Second, such analyses require an intact sinus node that mediates adequate cardiac responses to autonomic activity. Patients with AF and ischemic heart disease (a major risk of ventricular arrhythmias) often have associated sinus node dysfunction,<sup>43,44</sup> rendering the analysis of heart rate variability or baroreflex sensitivity in patients with arrhythmias not always reliable. By directly comparing power spectral analysis and actual nerve recordings, Piccirillo et al<sup>45</sup> showed that the correlation was significant at baseline but not in HF, likely because of diminished sinus node responsiveness to autonomic modulation. The above limitations have made chronic direct nerve activity recordings highly desirable to demonstrate whether autonomic activity is a direct trigger of cardiac arrhythmias.

In 2006, Jung et al<sup>46</sup> pioneered the technique of continuously recording the activity of stellate ganglia in healthy dogs using implanted radiotransmitters for an average of 41.5 days. The results showed the feasibility of chronic cardiac nerve recordings and demonstrated a circadian variation of

sympathetic outflow to the heart.<sup>46</sup> Multiple subsequent studies<sup>30,47–51</sup> with direct nerve activity recordings in diseased animal models have provided insights into the understanding of the role of cardiac ANS in arrhythmogenesis.

## Abnormal Autonomic Tone in Cardiac Arrhythmias

### Atrial Fibrillation

AF is the most common arrhythmia in developed countries and affects ≈2.3 million people in the United States alone.<sup>52</sup> The importance of autonomic nerve activity in the genesis and maintenance of AF has long been recognized. Coumel et al<sup>53</sup> in 1978 first reported that cardiac autonomic activities might predispose patients to develop paroxysmal atrial arrhythmias. Subsequent studies<sup>54–56</sup> with heart rate variability analysis indicate that, rather than being triggered by either vagal or sympathetic activity, the onset of AF can be associated with simultaneous discharge of both limbs, leading to an imbalance between these 2 arms of cardiac ANS. With implanted radiotransmitters, spontaneous simultaneous sympathetic (from LSG) and parasympathetic (from thoracic vagus nerve) nerve activity was observed to precede the onset of paroxysmal AF in ambulatory dogs with rapid atrial pacing (Figure 3A)<sup>48</sup> and HF.<sup>57</sup> Cryoablation of bilateral stellate ganglia and of the superior cardiac branches of the left vagus nerve eliminated all episodes of paroxysmal AF, consistent with a causal relationship.<sup>48,57</sup> These direct nerve activity recordings echo the concept that was termed calcium transient triggering by Patterson et al.<sup>58,59</sup> Sympathetic activation causes increasing calcium transient.<sup>60</sup> Vagal activation can reduce the atrial effective refractory period.<sup>36</sup> The discrepancy between action potential duration and intracellular calcium transient, which are normally tightly coupled, leads to increased forward Na/Ca exchanger current, which contributes to the generation of EAD and triggered activity<sup>58</sup> (Figure 4). This is particularly evident in pulmonary veins, of which focal activities are critically important in the initiation of AF in humans.<sup>61</sup>

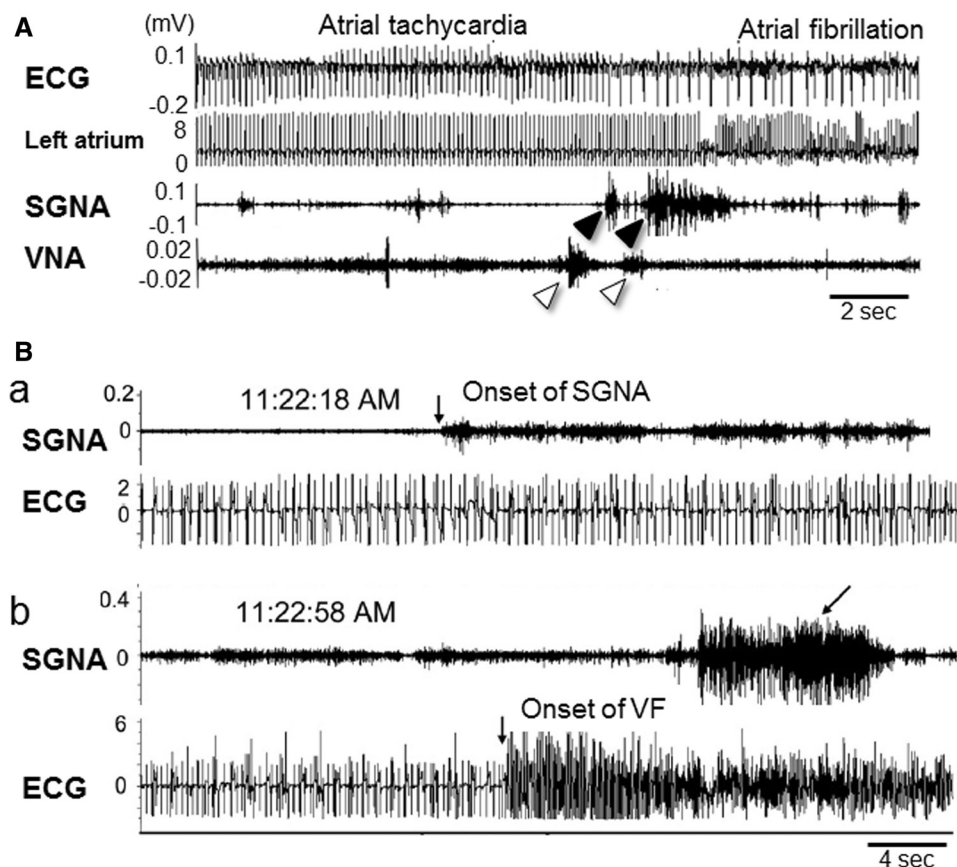
From the abovementioned direct nerve recordings, it is clear that extrinsic cardiac ANS (from the stellate ganglion and vagus nerve) plays a vital role in the initiation of AF. However, it is not clear whether both extrinsic and intrinsic cardiac ANS are required, or whether intrinsic cardiac ANS can function independently to initiate AF. To address this question, Choi et al<sup>50</sup> first directly recorded nerve activities from intrinsic cardiac ganglia with implanted radiotransmitters. In addition to the LSG and the left thoracic vagus nerve, nerve activities from the superior left GP and the ligament of Marshall (Figure 2A, right panel) were monitored in dogs subjected to intermittent, rapid atrial pacing. A surprising finding of this study is that although the majority of AF episodes were preceded by simultaneous firings of both extrinsic and intrinsic cardiac ANS, 11% of AF was triggered by activities from intrinsic cardiac ANS alone without higher input. In fact, ungoverned intrinsic cardiac ANS may be deleterious. This is supported by a recent study by Lo et al<sup>62</sup> that showed AF burden increased after extrinsic cardiac ANS and intrinsic cardiac ANS were disconnected by ablating the GP within the third fat pad.<sup>16</sup>

### Ventricular Tachyarrhythmias

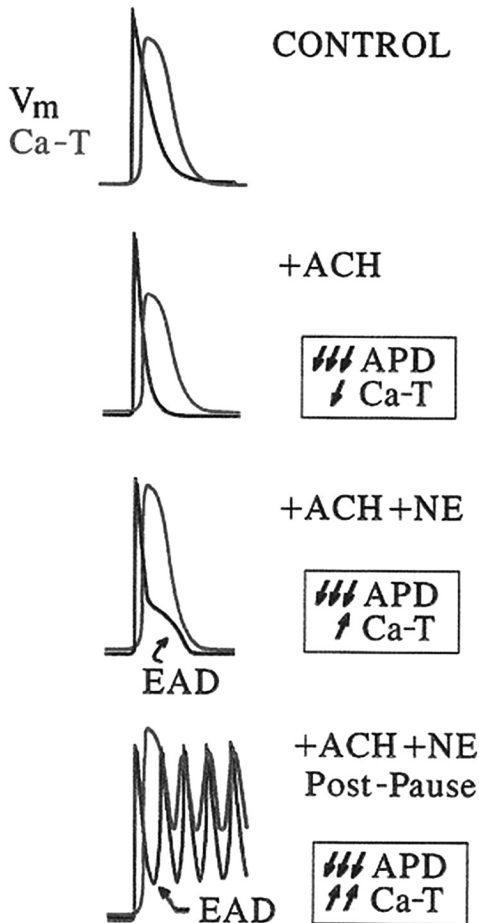
Sudden cardiac death (SCD) resulting from ventricular arrhythmias, including ventricular fibrillation (VF), continues to be a significant unsolved clinical problem with an annual death toll of 250 000 to 450 000 annually in the United States.<sup>63</sup> Experimentally, sympathetic stimulation induces changes in ECG repolarization and reduction of fibrillation threshold, facilitating the initiation of VF.<sup>64</sup> These effects are magnified in the presence of cardiac ischemia.<sup>65</sup> The ischemic and infarcted myocardium becomes a substrate exquisitely sensitive to arrhythmia triggers because of not only regional cellular and tissue remodeling<sup>66</sup> but also heterogeneity of sympathetic nervous system innervation.<sup>67</sup> Contributing to the heterogeneity is the phenomenon of nerve sprouting.<sup>68,69</sup> By examining explanted hearts, Cao et al<sup>70</sup> found that patients who had a history of ventricular arrhythmias had augmented sympathetic nerve sprouting (mainly in the border of normal myocardium and scar tissues; Figure 5) as compared with patients with similar structural heart disease but no arrhythmias. Both infusion of nerve growth factor into the LSG<sup>68</sup> and sub-threshold electric stimulation of the LSG<sup>71</sup> in dogs with myocardial infarction resulted in sympathetic nerve sprouting

and increased VF and SCD, suggesting a causal relationship. Follow-up studies demonstrated that myocardial infarction causes the upregulation of proteins that contributed to nerve growth (nerve growth factor, growth-associated protein 43, and synaptophysin) in both the infarcted site<sup>72</sup> and the more upstream bilateral stellate ganglia.<sup>73</sup> Interestingly, sympathetic nerve sprouting itself can lead to an increased incidence of VF without concomitant cardiac ischemia. It was found that rabbits given a high-cholesterol diet developed myocardial hypertrophy and cardiac sympathetic hyperinnervation without coronary artery disease along with an increased vulnerability to VF.<sup>74</sup>

Despite histological evidence and data from anesthetized animals indicating that sympathetic nerve activity is vital in the development of ventricular arrhythmias, a direct temporal relationship in conscious individuals has not been established. Increased sympathetic activity, as suggested by heart rate variability analysis, was found to be in the 30 minutes before the onset of ventricular tachyarrhythmias.<sup>75</sup> With direct nerve activity recordings in a canine model of SCD, Zhou et al<sup>49</sup> observed that VF and SCD were immediately preceded by spontaneous sympathetic nerve discharge from the LSG (Figure 3B). Although increased stellate ganglion nerve



**Figure 3. Autonomic nervous system and cardiac arrhythmias.** **A**, Atrial fibrillation (AF). During an episode of atrial tachycardia, simultaneous sympathetic (black arrowheads) and parasympathetic (hollow arrowheads) coactivation preceded the conversion of atrial tachycardia to AF. **B**, Ventricular fibrillation and sudden cardiac death. Increased stellate ganglion nerve activity preceded the onset of ventricular fibrillation for  $\approx 40$  s. **A** and **B** are continuous recordings. SGNA indicates stellate ganglion nerve activity; SLGPNA, superior left ganglionated plexi nerve activity; VF, ventricular fibrillation; and VNA, vagal nerve activity. Panel **A** reprinted from Tan et al<sup>48</sup> with permission of the publisher. Copyright © 2008, Wolters Kluwer Health. Panel **B** reprinted from Zhou et al<sup>49</sup> with permission of the publisher. Copyright © 2008, Elsevier Inc. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.



**Figure 4. Schematic of the arrhythmia mechanism in atrial fibrillation.** Membrane voltage ( $V_m$ ) is shown in black, and calcium transient ( $Ca-T$ ) is shown in gray.  $Ca-T$  transient outlasts  $V_m$  even under control conditions. The difference between  $V_m$  and  $Ca-T$  is increased with action potential duration (APD) shortening observed after acetylcholine (ACH). Early afterdepolarization (EAD) formation is not observed because  $Ca-T$  is also reduced in amplitude. With the addition of norepinephrine (NE),  $Ca-T$  is enhanced in amplitude, whereas APD remains abbreviated. The disparity between  $V_m$  and  $Ca-T$  is thus increased, with inward sodium-calcium exchange current producing an EAD. If even further enhancement of  $Ca-T$  is observed after a tachycardia pause interval, a second action potential is initiated.  $Ca-T$  initiated by the first ectopic beat initiates the second ectopic beat, and so on, producing a repetitive rhythm. Reprinted from Patterson et al<sup>58</sup> with permission of the publisher. Copyright © 2006, Elsevier Inc. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

activity contributes to VF and SCD in myocardial infarction, acute myocardial infarction itself can cause an increase in nerve activity and nerve density of the LSG—electroanatomic remodeling.<sup>73</sup> This generates a vicious cycle that can lead to more ischemia, VF, and SCD.

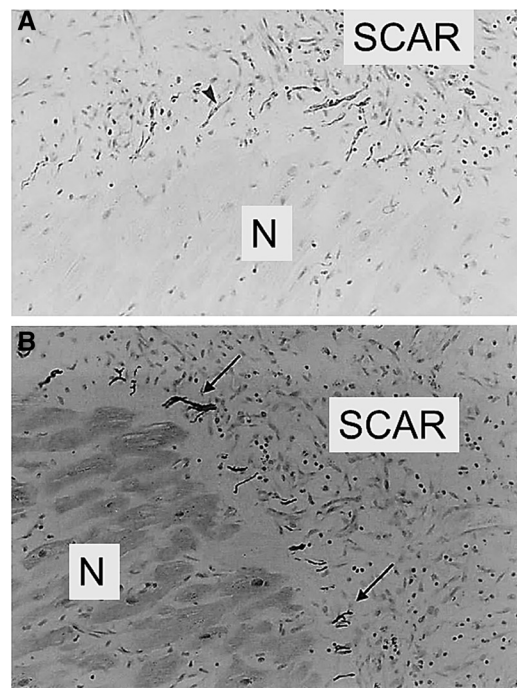
### Inherited Arrhythmia Syndromes

In the past decade, the discovery that ventricular arrhythmias and SCD in young individuals could be caused by genetic substrate has defined a new subset of cardiac conditions: inherited arrhythmia syndromes.<sup>76,77</sup> These inherited arrhythmias have characteristic ECG changes reflecting electric heterogeneities

of ventricular depolarization or repolarization. Autonomic influences play an important role in unmasking the electrocardiographic phenotype and precipitating lethal arrhythmias.<sup>78</sup> Experimentally, the arrhythmias are often triggered or suppressed by intravenous infusion of sympathomimetic or parasympathomimetic drugs. These measures have limitations in clinical applicability because intravenous catecholamine administration, by providing homogeneous drug distribution, reduces the dispersion of repolarization throughout the ventricles. In contrast, autonomic nerve discharges (as in real-world situations) lead to the local release of neurotransmitters that heterogeneously abbreviates the refractory period and thereby increases the dispersion of repolarization.<sup>79</sup> This provides an ideal substrate for potentially fatal ventricular arrhythmias.

### Long QT Syndrome

LQTS is characterized by a prolonged QT interval and risk for developing polymorphic ventricular tachycardia, known as torsades de pointes, causing SCD.<sup>80,81</sup> The primary arrhythmogenic trigger is thought to be EAD-induced triggered activity. Once triggered by EADs, torsades de pointes can be maintained by a reentrant mechanism.<sup>82,83</sup> Enhanced sympathetic activity can substantially increase the spontaneous inward current through L-type calcium channels to increase the



**Figure 5. Sympathetic nerve sprouting.** **A**, Regional cardiac hyperinnervation in patients with cardiomyopathy and ventricular tachyarrhythmias as demonstrated with positive S100 staining (arrowheads). S100-positive nerve fascicles are scattered in swarm-like pattern at the junction between necrotic (SCAR) and normal myocardium (N). **B**, Another example showing nerve twigs between scar tissues and normal myocardium in a human heart. Panel **A** reprinted from Cao et al<sup>70</sup> with permission of the publisher. Copyright © 2000, Wolters Kluwer Health. Panel **B** reprinted from Chen et al<sup>69</sup> with permission of the publisher. Copyright © 2001, Oxford University Press. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.



likelihood of EAD development and initiation of reentry.<sup>33,84</sup> Therefore, sympathetic stimulation can create the substrate for EAD-induced triggered activity as well as the substrate for reentry in the LQTS.<sup>33</sup> In normal individuals, high adrenergic tone or sympathetic stimulation shortens the ventricular action potential duration and hence the QT interval.<sup>31</sup> In contrast, in congenital LQTS types 1 and 2, increased adrenergic tone can prolong the QT interval. However, there is some variability in terms of the degree of response to sympathetic activation depending on the type of LQTS and, thus, the type of channel and current affected. Noda et al<sup>85</sup> observed that sympathetic stimulation by infusion of epinephrine caused more prominent and prolonged effects on QT prolongation in patients with congenital LQTS type 1 (characterized by an abnormality in KCNQ1 and the  $I_{Ks}$  current; Figure 6A) than in type 2 (characterized by an abnormality in KCNH2 and the  $I_{Kr}$  current). In contrast, type 3 (characterized by an abnormality in SCN5A and the  $I_{Na}$  current) has much less QT prolongation effect with sympathetic stimulation. In fact, patients with LQTS type 3 have ventricular tachyarrhythmias triggered by increased vagal tone.<sup>86</sup> This is similar to other channelopathies involving sodium channel, such as Brugada syndrome.

### Brugada Syndrome

The Brugada syndrome is an autosomal-dominant inherited arrhythmic disorder characterized by its typical ECG alterations (right bundle branch block and persistent ST-segment elevation) and an increased risk of VF and SCD in young individuals with probably structurally normal hearts.<sup>87,88</sup> Most episodes of VF in patients with Brugada syndrome are observed during periods of high vagal tone, such as at rest, during sleep, or from 12 AM to 6 AM.<sup>89,90</sup> With heart rate variability analysis, Kasanuki et al<sup>91</sup> reported a sudden increase of vagal activity just before the episodes of VF in a patient with Brugada syndrome. Furthermore, characteristic ECG changes of Brugada syndrome can be augmented by parasympathomimetic agents (edrophonium), while mitigated by sympathomimetic agents (isoproterenol; Figure 6C).<sup>92</sup> These data suggest that an increased vagal tone or a decreased sympathetic function may be important mechanisms in the arrhythmogenesis of this lethal disease. Another hypothesis would be that the right ventricular outflow tract serves as a substrate that mediates and sustains ventricular arrhythmias triggered by altered autonomic tones. In many instances, the arrhythmia origin seems to be in the epicardium of the right ventricular outflow tract,<sup>93</sup> where ablation can eliminate the arrhythmia.<sup>94,95</sup> Conduction abnormalities can be present, and fractionated conduction has been shown to be a risk factor.<sup>96</sup>

### Idiopathic VF/J-Wave Syndrome

Recently, several studies have reported that J-point and ST-segment elevation in the inferior or lateral leads, which is also called early repolarization pattern, can be associated with VF and SCD in patients without apparent structural heart diseases, that is, idiopathic VF.<sup>97–99</sup> However, J-wave elevation is fairly commonly seen in young healthy individuals (estimated prevalence, 1%–9%) and frequently considered to be benign.<sup>97,98</sup> To identify high-risk patients within the broad population of healthy individuals is an important task.

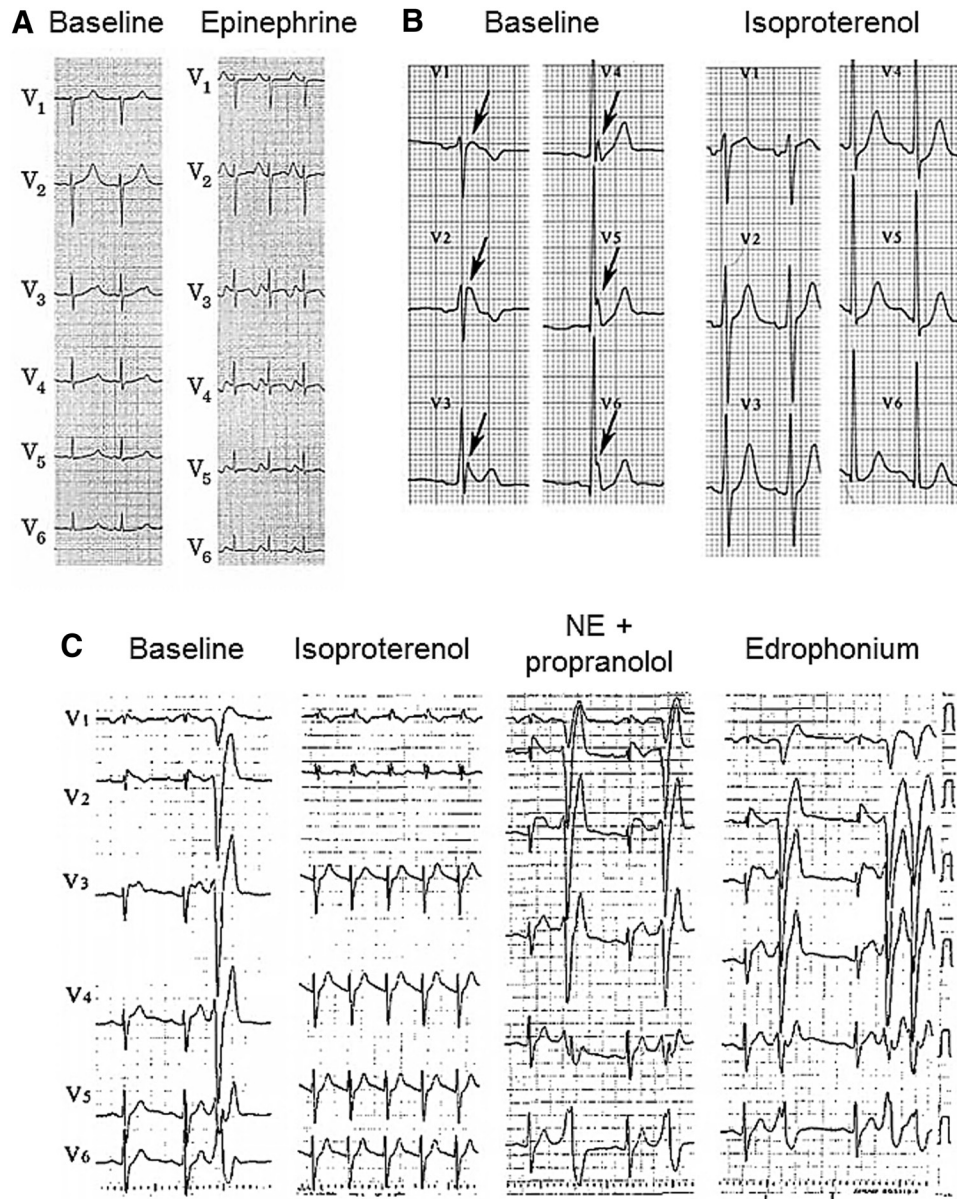
Experimentally, J-waves are well explained by the transmural voltage gradient of the myocardial cells in phase 1 of the action potential, which is created by transient outward potassium currents ( $I_{to}$ ).<sup>100,101</sup> Bradycardia can lead to accentuated  $I_{to}$ <sup>101</sup> and, in turn, result in the augmentation of J-wave amplitude on surface ECG in patients with idiopathic VF.<sup>102</sup> In contrast, isoproterenol infusion may eliminate J-waves (Figure 6B) and suppress VF.<sup>103</sup> It is important to note that sympathetic stimulation precipitates or worsens virtually all ventricular tachyarrhythmias, except in Brugada and J-wave syndromes where it can prevent them. An observational study found that among patients with J-wave elevation and idiopathic VF, episodes of VF occur most frequently at night, when vagal tone is dominant.<sup>104</sup> In addition, J-wave elevation could be more strongly affected in patients with idiopathic VF than in control subjects under similar conditions of autonomic tone.<sup>105</sup> For example, Mizumaki et al<sup>106</sup> recently observed that in patients with idiopathic VF as compared with control subjects, J-wave augmentation was associated with an increase in vagal activity. These data suggest a critical role of cardiac ANS in the occurrence of VF in patients with J-wave syndromes. The differential responses of characteristic ECG changes to autonomic input also may provide a useful tool in the identification of high-risk patients within the broad population of healthy individuals with this specific ECG pattern.

### Catecholaminergic Polymorphic Ventricular Tachycardia

As the name suggests, the hallmark of catecholaminergic polymorphic ventricular tachycardia (CPVT) includes bidirectional or polymorphic ventricular arrhythmias under conditions of increased sympathetic activity in young patients with structurally normal hearts and a normal 12-lead ECG.<sup>107</sup> About 60% of patients with CPVT have mutations in the genes encoding proteins that are involved in the release of calcium from the sarcoplasmic reticulum.<sup>108</sup> The resultant inappropriate calcium leak<sup>109</sup> leads to cytosolic calcium overload that generates delayed afterdepolarizations, triggered activity, and ventricular arrhythmias, particularly under conditions of increased  $\beta$ -adrenergic tone.<sup>110,111</sup>  $\beta$ -Blockade either with  $\beta$ -blocker pharmacotherapy or left-sided stellotomy (which also interrupts  $\alpha$  stimulation) has been shown to have great efficacy in preventing cardiac events.<sup>112,113</sup> Another successful treatment is with flecainide to block the ryanodine receptor.<sup>114</sup>

### Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) was first observed in a case series in late 1970s as an underlying disease in young patients with ventricular arrhythmias and SCD.<sup>115</sup> These arrhythmias are often precipitated by increased sympathetic activity such as physical exercise, mental stress, and intravenous catecholamine infusion during electrophysiological study and frequently suppressed by an antiarrhythmic drug regimen with antiadrenergic properties.<sup>116</sup> Using positron emission tomography for quantification, Wichter et al<sup>117</sup> demonstrated in patients with ARVC that there was a significant reduction of myocardial  $\beta$ -adrenergic receptor density, which has been theorized to be due to



**Figure 6. Autonomic neural modulation in inherited arrhythmia syndromes.** **A**, Long QT syndrome. Twelve-lead ECGs under baseline conditions and at peak of epinephrine in a patient with long QT syndrome type 1. The corrected QT interval was markedly prolonged from 602 to 729 ms. **B**, J-wave syndrome. Baseline ECG shows the appearance of prominent J-waves (arrows) across the precordial leads. Isoproterenol infusion eliminated the J-waves and completely suppressed ventricular fibrillation. **C**, Brugada syndrome. Characteristic ECG criteria are noted in a patient with Brugada syndrome. ST elevation seen in leads V<sub>1</sub> to V<sub>3</sub> at baseline is eliminated by  $\beta$ -adrenergic stimulation with isoproterenol, while augmented by selective  $\alpha$ -adrenoceptor stimulation with norepinephrine (NE) in the presence of propranolol or by muscarinic stimulation with intravenous edrophonium. Panel **A** reprinted from Noda et al<sup>85</sup> with permission of the publisher. Copyright © 2002, Oxford University Press. Panel **B** reprinted from Nam et al<sup>103</sup> with permission of the publisher. Copyright © 2010, Oxford University Press. Panel **C** reprinted from Miyazaki et al<sup>92</sup> with permission of the publisher. Copyright © 1996, Elsevier Inc. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

(downregulation) increased firing of efferent sympathetic nerves. These data suggest the importance of sympathetic hyperactivity in triggering life-threatening arrhythmias in patients with ARVC. Extremely vigorous exercise can not only enhance sympathetic activity but also lead to phenotypic ARVC without an identifiable genetic predisposition.<sup>118</sup> This was thought to be partly due to structural remodeling resulting from right ventricular volume overload and stretch from increased venous return.

## Autonomic Modulation for Treatment of Arrhythmias

### Atrial Fibrillation

#### Neural Ablation

In 1998, Haïssaguerre et al<sup>61</sup> discovered that AF can emerge as a result of depolarizations in the pulmonary veins and established the fundamental role of pulmonary vein isolation (PVI) in the treatment of patients with AF. To date, PVI remains the



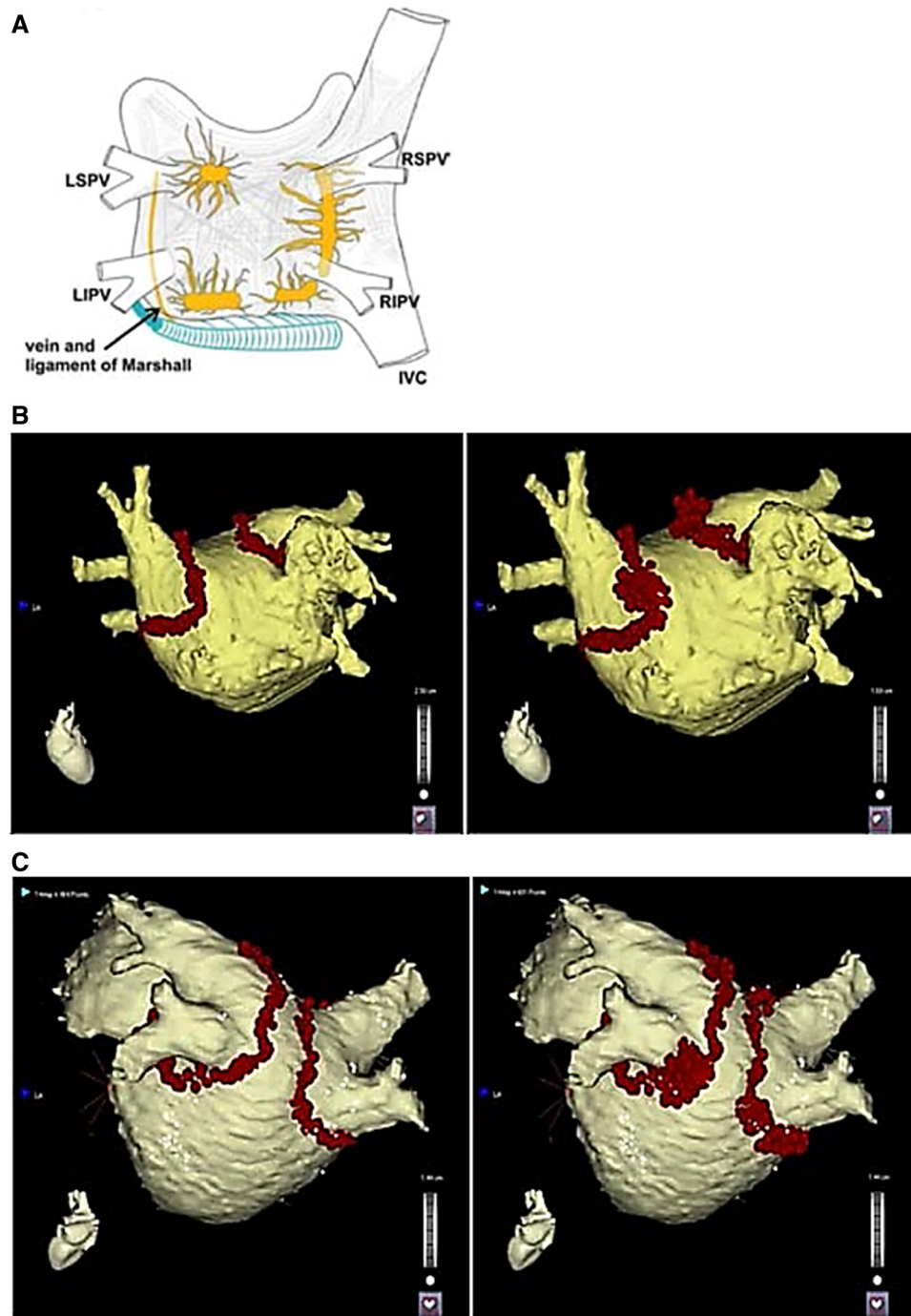
most widely used ablation approach to treat AF. However, with a 5-year success rate in some series <30% after a single procedure,<sup>119</sup> and <40% off antiarrhythmic drugs,<sup>120</sup> PVI alone can be insufficient to maintain sinus rhythm. AF can be further categorized into paroxysmal, persistent, and long-term persistent, each with potentially different substrates and responses to therapy. Nevertheless, given the importance of autonomic tone in AF, autonomic modulation has become a target of investigation. Elvan et al<sup>121,122</sup> demonstrated that radiofrequency catheter ablation in the atria can eliminate pacing-induced sustained AF in part by denervation of efferent vagal nerves of the atria. Because linear lesions from standard pulmonary vein-directed ablation run through areas with high concentrations of GP,<sup>123</sup> autonomic modification or denervation might be a potential mechanism that contributes to the effectiveness of PVI<sup>124,125</sup> and has become the target of investigation in multiple subsequent clinical studies.<sup>126–129</sup> Nevertheless, autonomic denervation targeting the GP around the base of the pulmonary veins, whether as an adjunctive procedure<sup>126,127</sup> or as a standalone treatment,<sup>128,129</sup> has yielded inconsistent results.<sup>124,127,130–132</sup> Scherlag et al<sup>132</sup> showed that GP ablation in addition to PVI increased ablation success from 70% to 91% among patients with paroxysmal or persistent AF after 12 months of follow-up. Other studies have shown less optimistic results. For instance, Lemery et al<sup>130</sup> found that only 50% of patients with paroxysmal and persistent AF were free from recurrent AF after undergoing combined GP ablation and PVI. These conflicting findings can be explained by individual variability in autonomic triggers, with some patients having more pronounced autonomic triggers compared with others.<sup>133</sup> Alternatively, the traditional approach of selective ablation of GP directed by high-frequency stimulation may fail to effectively eliminate all intrinsic cardiac nerves in the atria. For example, Pokushalov et al<sup>134</sup> demonstrated that an anatomic, regionally extensive approach for the ablation of GP confers better clinical outcomes compared with selective ablation directed by high-frequency stimulation. The conflicting results of smaller clinical studies and the complexity inherent in the genesis of AF among different patients highlight the importance of clinical trials for the comparison of different ablation strategies. A recent randomized, multicenter clinical trial that enrolled 242 patients compared the efficacy of PVI, GP ablation alone, and PVI followed by GP ablation (Figure 7) after 2 years of follow-up.<sup>135</sup> Freedom from AF was achieved in 56%, 48%, and 74%, respectively, after 2 years of follow-up. These results suggest that the addition of GP ablation to PVI confers a significantly higher success rate compared with either PVI or GP alone in patients with PAF.

An alternative approach of neural ablation is to ablate the extrinsic cardiac nerves, particularly the LSG. The ablation of LSG is known to reduce the incidence of ventricular arrhythmias in patients with LQTS,<sup>136,137</sup> but the technique has been less vigorously investigated clinically for the treatment of atrial tachyarrhythmias. In animal models, this approach has been shown to abolish episodes of atrial tachyarrhythmias.<sup>47,48</sup> These findings argue that the ablation of extrinsic cardiac nerves might be an effective alternative therapy to the ablation of intrinsic cardiac ganglia for the treatment of AF.<sup>12</sup> An area

gaining clinical interest is renal denervation. Catheter-based renal sympathetic denervation is most widely applied clinically as a treatment for resistant hypertension.<sup>138</sup> The effects of renal denervation on cardiac electrophysiology have been shown in animal models and humans. In a porcine model of obstructive sleep apnea, renal denervation was shown to attenuate the shortening of atrial effective refractory period that is presumably caused by combined sympathovagal activation.<sup>139</sup> Renal denervation leads to a reduction in heart rate and atrioventricular conduction in patients with resistant hypertension.<sup>140</sup> It has been proposed that renal denervation can be an adjunct therapy for AF. Mechanistically, renal denervation ablates both efferent and afferent renal sympathetic nerves as they run together. By ablating the efferent nerves, renal denervation decreases renal norepinephrine spillover by 47%<sup>141</sup> and attenuates the activity of renin–angiotensin–aldosterone system,<sup>142</sup> which can be important in the pathogenesis of AF.<sup>143</sup> More importantly, from a cardiac standpoint, afferent renal sympathetic denervation leads to decreased feedback activation to the central nervous system and thereby decreased sympathetic input to the heart. As a result, renal denervation results in a reduction of left ventricular mass,<sup>144</sup> which is associated with decreased incidence of new-onset AF in patients with resistant hypertension.<sup>145</sup> To test the antiarrhythmic property of renal denervation directly, Pokushalov et al<sup>146</sup> compared the efficacy of combined renal denervation with PVI to PVI alone in a study enrolling 27 patients of paroxysmal or persistent AF. They found that at 1-year follow-up, 69% of patients who received both procedures were free of AF, compared with 29% of those in the PVI-only group. This small trial and the pivotal Symplicity HTN-1 trial<sup>147</sup> that followed patients with resistant hypertension for 24 months demonstrate sustained efficacy in spite of the possibility of postganglionic sympathetic reinnervation after the procedure. However, despite the promising results, large multicenter randomized trials are needed before a widespread application of renal denervation in the treatment of AF may be advised. Furthermore, whether the antiarrhythmic property of renal denervation is beyond normalization of blood pressure is yet to be determined. For example, whether renal denervation can directly inhibit arrhythmogenic atrial autonomic activities is unclear and warrants further studies.

### Neural Stimulation

Acupuncture has been used for thousands of years to treat humans with various cardiac diseases. One effect of acupuncture is the modulation of autonomic nerves.<sup>148</sup> For instance, the stimulation of median afferent nerve (corresponding to the Neiguan acupoint) improves myocardial ischemia caused by reflexively induced sympathetic excitation in cats.<sup>149</sup> This indicates that the beneficial effects of acupuncture may be explained by its inhibition of sympathetic activity. In a recent, small-scale clinical trial, acupuncture achieved an AF recurrence rate after cardioversion similar to amiodarone treatment, and lower than in acupuncture-sham and control groups.<sup>150</sup> In another study, acupuncture resulted in a significant reduction in the number and duration of symptomatic AF episodes in a small group of patients with paroxysmal AF.<sup>151</sup> These preliminary data need to be validated in a larger population, but suggest a potential role of acupuncture in the treatment of AF.



**Figure 7. Major left atrial ganglionated plexi (GP) proposed for ablation.** **A**, Anatomic location of the 4 GPs. Schematic posterior view of the left and right atria showed 5 major left atrial autonomic GP, and axons (SLGP, ILGP, ARGP, IRGP, and ligament of Marshall) are shown in yellow, whereas coronary sinus is shown in blue. **B**, Anatomic ablation of SLGP and ARGP. **C**, Anatomic ablation of ILGP and IRGP. After pulmonary vein isolation, ablation lesions are expanded to cover the anatomic site of presumed GP clusters. ARGP indicates anterior right GP; ILGP, inferior left GP; IRGP, inferior right GP; IVC, inferior vena cava; LIPV, left inferior pulmonary vein; LSPV, left superior PV; RIPV, right inferior PV; RSPV, right superior PV; and SLGP, superior left GP. Panel **A** reprinted from Calkins et al<sup>203</sup> with permission of the publisher. Copyright © 2012, Elsevier Inc. Panels **B** and **C** reprinted from Katritsis et al<sup>135</sup> with permission of the publisher. Copyright © 2013, Elsevier Inc. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

More recently, cervical VNS has emerged as a target of investigation for its potential anti-AF property. Despite its profibrillatory effects in the atria and being a reliable method to induce AF experimentally, cervical VNS at a stimulus strength 1 V below the threshold needed to reduce heart

rate—low-level VNS (LL-VNS)—can lower intrinsic cardiac nerve activity and, paradoxically, suppress electrically induced AF in open-chest, anesthetized dogs.<sup>152</sup> Even if the stimulus strength is 50% below the threshold, LL-VNS still possesses the same effects.<sup>153</sup> Shen et al<sup>30</sup> used direct nerve recordings to

demonstrate that continuous LL-VNS suppressed paroxysmal atrial tachyarrhythmias in ambulatory, conscious dogs via the reduction of stellate ganglion nerve activity. This reduction was most apparent in the early morning, when the incidence of AF is highest.<sup>154</sup> Histologically, LL-VNS resulted in a significant reduction of ganglion cells in the LSG that were stained positive for tyrosine hydroxylase, an enzyme critical in the biosynthesis of adrenalin (Figure 8A). A subsequent study by the same group showed that in the LSG, LL-VNS also resulted in the upregulation of small-conductance calcium-activated potassium channel type 2 and increased its expression in the cell membrane (Figure 8B and 8C).<sup>155</sup> These changes may facilitate hyperpolarization of the ganglion cells and reduce the frequency of neuronal discharges.<sup>156</sup> Thus, LL-VNS can functionally and structurally remodel the LSG, which might explain some of its antiarrhythmic effects.

Spinal cord stimulation (SCS) is also being investigated in the treatment of AF. Olgin et al<sup>157</sup> demonstrated that SCS at T<sub>1</sub>-T<sub>2</sub> enhances parasympathetic activity by showing its ability to slow the sinus rate and prolong AV nodal conduction. The authors demonstrated that this effect was abolished after transection of bilateral cervical vagus nerves but not of an-sae subclaviae (sympathectomy), suggesting that the effect of SCS is via the vagus nerves. More recently, Bernstein et al<sup>158</sup> demonstrated that acute application of SCS at T<sub>1</sub>-T<sub>5</sub> level prolonged atrial effective refractory period without a noticeable effect on heart rate and atrioventricular conduction. The authors thought that the contrast between their results and those of Olgin et al could be explained by a broader region of SCS that may provide more balanced autonomic modulation. More importantly, early application of SCS at this level substantially decreased AF burden and inducibility by rapid atrial pacing.<sup>158</sup>

What makes these results of neural stimulation attractive is that both VNS and SCS have long been used clinically for drug refractory epilepsy<sup>159</sup> and angina,<sup>160</sup> respectively. Despite the invasive nature, the level of invasiveness is not much greater than a routine cardiac pacemaker implantation.<sup>161</sup>

## Ventricular Tachyarrhythmias

### Neural Ablation

$\beta$ -Blockers have been shown to reduce the incidence of recurrent ventricular tachyarrhythmias,<sup>162,163</sup> reinforcing the crucial role of sympathetic nerve activity in the pathogenesis of ventricular tachyarrhythmias, particularly in the setting of cardiac ischemia.<sup>65,66,164</sup> In fact, a more aggressive measure by direct ablation of sympathetic nerves, sympathectomy, has been explored for the treatment of drug-resistant ventricular tachycardia and, in contrast to drugs that just block  $\beta$ -receptors, provided  $\alpha$  interruption as well. Almost 100 years ago, Jonnesco<sup>165</sup> first performed left stellectomy in a patient with angina pectoris complicated by serious ventricular arrhythmias and succeeded in terminating both angina and arrhythmias. Two case reports in the 1960s by Estes and Izlar<sup>166</sup> and Zipes et al<sup>167</sup> demonstrated that the removal of bilateral stellate ganglia or upper thoracic ganglia successfully suppressed patients with drug-resistant ventricular tachycardia fibrillation. Subsequently, left cardiac sympathetic denervation (LCSD) was shown to prevent cardiac death in high-risk

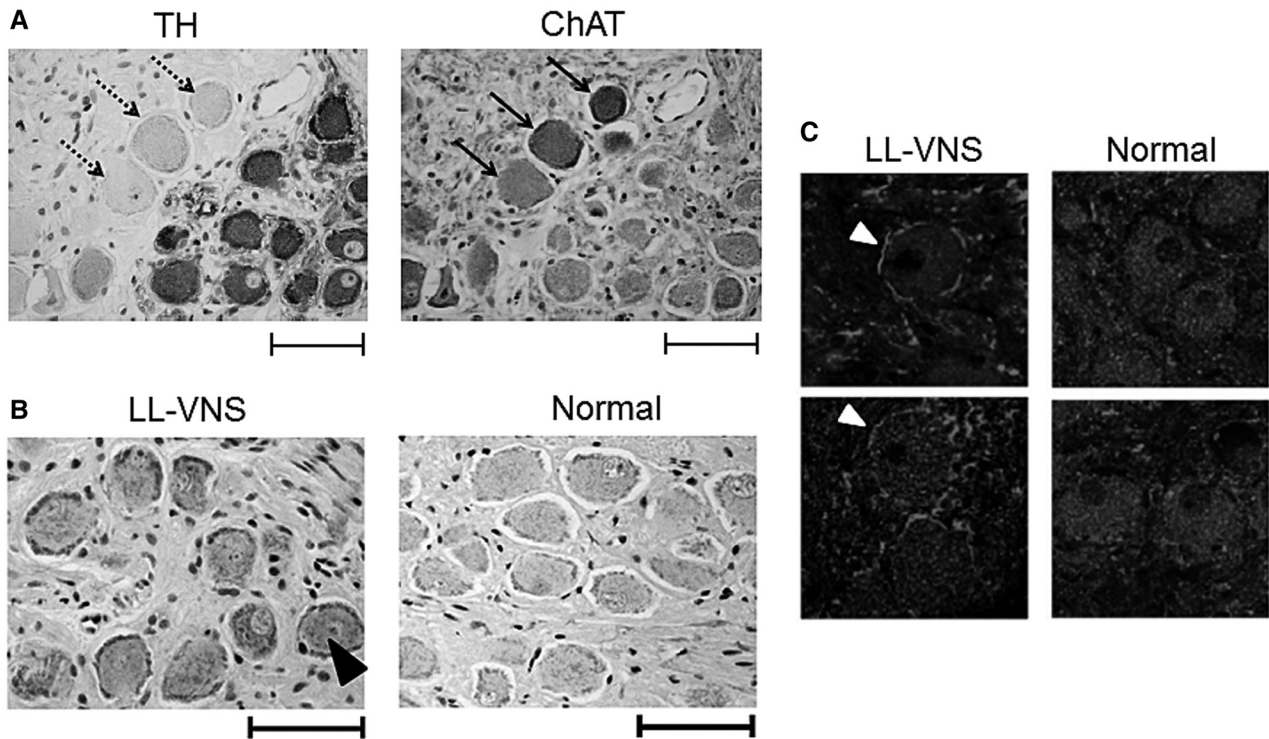
patients after myocardial infarction and was proposed to be an alternative measure in high-risk patients with contraindications to  $\beta$ -blockers.<sup>168</sup> Although LCSD has been mostly applied in patients with inherited arrhythmia syndromes with significant success,<sup>13,112,137</sup> denervation has been used to treat acquired ventricular arrhythmia storm as well.<sup>169</sup> Bilateral cardiac sympathetic denervation was recently investigated in humans and found to be more effective than LCSD in preventing ventricular arrhythmias.<sup>170</sup> Conclusions from the latter study must be interpreted cautiously because of its small sample size, inclusion of only patients with ischemic cardiomyopathy, and possible negative inotropic effects from bilateral sympathetic denervation.

Recently, renal denervation has also been investigated as a potential treatment modality for ventricular arrhythmias. Ukena et al<sup>171</sup> first demonstrated that renal denervation successfully reduced ventricular tachyarrhythmia episodes in 2 patients with cardiomyopathy and drug-resistant VT/VF. In a recent small case series, renal denervation was shown to decrease VT burden in 3 patients with recurrent refractory VT.<sup>172</sup> Linz et al<sup>173</sup> observed that in anesthetized pigs during acute coronary artery occlusion, renal denervation significantly decreased the occurrence of VF associated with decreased premature ventricular contractions. The authors reckoned that this latter effect, among others previously mentioned,<sup>138,141,142</sup> might explain its anti-VF effects in that premature ventricular contractions may arise from delayed afterdepolarization-related triggered activity, which is important in the initiation of VF, especially in cardiac ischemia.<sup>174</sup> These preliminary studies provide exciting and promising data. Nevertheless, whether to sedate the nervous kidney<sup>175</sup> may be a possible game changer in the management of ventricular tachyarrhythmias related to cardiac ischemia still requires further investigation.

### Neural Stimulation

More than 150 years ago, Einbrodt<sup>176</sup> first demonstrated that cervical VNS increased the threshold of experimentally induced VF. Subsequently, studies with anesthetized dogs have shown that VNS reduces the occurrence of ventricular tachyarrhythmias after acute coronary artery occlusion.<sup>177,178</sup> In dogs that survived an acute myocardial infarction, Vanoli et al<sup>179</sup> demonstrated that VNS during the process of coronary artery occlusion reduced the occurrence of VF from 100% to 10%. The antiarrhythmic effects of VNS are not entirely known. Atropine, a nonselective muscarinic receptor antagonist, increased the occurrence of coronary artery occlusion-induced VF in several studies.<sup>178</sup> This suggests that the activation of muscarinic receptors of the ventricular cardiomyocytes can in part explain the antiarrhythmic effects of VNS. VNS can directly antagonize sympathetic actions at both pre- and postjunctional levels.<sup>25,26</sup> It causes histological remodeling of the LSG that in turns decreases the sympathetic outflow to the heart.<sup>30,155</sup> Additionally, VNS leads to a reduction of heart rate, which may be protective because this may attenuate rate-dependent alterations in ventricular action potential duration, refractoriness, and dispersion of both factors. However, the anti-VF effect of VNS is reduced but not abolished during constant cardiac pacing,<sup>34,179</sup> suggesting that the decrease in heart rate is an important but not the only protective mechanism.





**Figure 8. Histological remodeling of left stellate ganglion (LSG) after low-level vagus nerve stimulation (LL-VNS).** **A**, After LL-VNS, there is a significant increase in the number of TH-negative ganglion cells (dashed arrows). These cells stain positive for ChAT (arrows). This cholinergic transformation in the LSG is accompanied by a decrease of stellate ganglion nerve activity by LL-VNS. Calibration bar, 50  $\mu$ m. **B**, In dogs that underwent LL-VNS, there is also an upregulation of ganglion cells that are stained more strongly positive for small-conductance calcium-activated potassium channel subtype 2 (SK2; black arrowhead). This channel is responsible for the hyperpolarization of ganglion cells and reduces the frequency of neuronal discharges. Calibration bar, 50  $\mu$ m. **C**, Immunofluorescence confocal microscopy images show an increase in the expression of SK2 protein in the periphery of the cells (white arrowheads), whereas a decrease in cytosol. This intracellular trafficking of SK2 protein to the cell membrane is evident after LL-VNS. ChAT indicates choline acetyltransferase; and TH, tyrosine hydroxylase. Reprinted from Shen et al<sup>155</sup> with permission of the publisher. Copyright © 2013, Elsevier Inc. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

VNS is shown to attenuate systemic inflammation.<sup>180,181</sup> VNS, via the modulation of nitric oxide,<sup>182</sup> may reduce the slope of action potential duration restitution curve,<sup>183</sup> which is important in the initiation of VF.<sup>184</sup> VNS can also significantly increase the expression of connexin-43,<sup>185</sup> which is downregulated in failing human hearts and thereby arrhythmogenic.<sup>186</sup> More recently, the cardioprotection of VNS has been demonstrated to be associated with its prevention of mitochondrial dysfunction during ischemia/reperfusion.<sup>187</sup> After Schwartz et al<sup>188</sup> and De Ferrari et al<sup>189</sup> demonstrated the safety and efficacy of VNS in patients with HF, 2 international multicenter randomized clinical trials (Increase of Vagal Tone in Chronic Heart Failure [INOVA-HF]<sup>190</sup> and Neural Cardiac Therapy for Heart Failure Study [NECTAR-HF]<sup>191</sup>) are ongoing to examine the application of chronic VNS in the treatment of HF. Clearly, there is a need for additional studies on the potential benefits of VNS in the prevention of arrhythmias in HF, especially given that arrhythmia-related deaths remain a significant clinical burden in patients with HF in spite of advances in treatment.<sup>192</sup>

For the past decade, SCS has also been investigated for its role in treating ventricular arrhythmias. Issa et al<sup>193</sup> observed that SCS stimulation during transient myocardial ischemia can reduce the combined VT and VF events from 59% to 23%

in a canine model prone to developing ischemia-induced ventricular arrhythmias. This antifibrillatory effect was associated with a reduction in sinus rate, prolongation of PR interval, and lowering of blood pressure, consistent with antisympathetic properties that were demonstrated in a previous study by Olgin et al.<sup>157</sup> Lopshire et al<sup>194</sup> investigated the chronic effect of SCS. By studying 28 dogs that survived left anterior descending artery occlusion for >10 weeks, the authors documented that SCS significantly reduced the events of spontaneous ventricular tachyarrhythmias with better efficacy compared with  $\beta$ -blockers. With direct nerve recordings in ambulatory dogs, Garlie et al<sup>195</sup> demonstrated that SCS could attenuate the augmented stellate ganglion nerve activity after myocardial infarction and tachypacing-induced HF. In a recent case series involving 2 patients with high VT/VF burden, SCS chronically for 2 months was associated with a reduction of VT/VF events.<sup>196</sup> More studies are definitely needed to validate the findings of this preliminary study. A multicenter, prospective clinical trial, Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure (DEFEAT-HF), is underway to evaluate the effects of SCS in HF.<sup>197</sup> The observations of arrhythmias in that trial may provide us with a direction on the use of SCS as an antiarrhythmic strategy.

## Inherited Arrhythmia Syndromes

Life-threatening ventricular arrhythmias in patients with LQTS (particularly type 1)<sup>198</sup> and CPVT<sup>199</sup> are frequently triggered by increased sympathetic activity, such as emotional stress and physical exercise. Therefore, to prevent cardiac events,  $\beta$ -blocker pharmacotherapy is the cornerstone of medical therapy.<sup>113,200</sup> However, some patients are either intolerant or refractory to this therapy. LCSD, in which lower half of the LSG (to avoid Horner syndrome) and the first 3 to 4 thoracic ganglia are removed, has emerged to become a treatment modality for patients with LQTS,<sup>137</sup> and more recently CPVT,<sup>112</sup> who continue to have cardiac events despite high-dose  $\beta$ -blocker therapy, and has been proved to be a safe and effective treatment option.<sup>201</sup> Recently, Coleman et al<sup>202</sup> studied 27 patients with a wide spectrum of arrhythmogenic diseases that include CPVT (n=13), Jervell and Lange-Nielsen syndrome (n=5), idiopathic VF (n=4), left ventricular noncompaction (n=2), hypertrophic cardiomyopathy (n=1), ischemic cardiomyopathy (n=1), and ARVC (n=1). Their results during early follow-up showed a marked reduction in the frequency of cardiac events postdenervation, suggesting that the antifibrillatory effect of LCSD may be substrate-independent and extend beyond the traditional application in LQTS.

## Conclusions

The cardiac ANS has a significant impact on cardiac electrophysiology and arrhythmogenesis. This impact is diverse: different types of arrhythmias have different autonomic triggers. With growing knowledge in the identification of those specific triggers, appropriate treatment modalities through neural modulation can be applied accordingly. In certain diseases, cardiac ANS modulation has been substantiated. However, in most other arrhythmia diseases, the application of neural modulation is nascent or still under investigation. Future work in this field, from basic laboratories and clinical trials, is needed to contribute to a better understanding of specific autonomic triggers and to validate the promising results of preliminary smaller-scale studies.

## Review Criteria

The initial literature review was conducted using the PubMed database using the search terms autonomic nervous system, ganglionated plexi, sympathetic, vagal, neural mechanisms, atrial fibrillation, ventricular fibrillation, inherited arrhythmia syndromes, long QT syndrome, Brugada syndrome, Idiopathic VF, J-wave syndrome, CPVT, ARVC, arrhythmia, ablation, and renal denervation. Full-text articles published in English from 1930 to 2013 were included. Reference lists of comprehensive review articles were further examined for additional references.

## Disclosures

None.

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