Cardiac autonomic dysregulation is central to the development and progression of most cardiovascular diseases (hypertension, heart failure [HF], arrhythmias, and myocardial infarction). Impaired cardiac parasympathetic responsiveness and enhanced sympathetic activity are negative prognostic indicators for both morbidity and mortality associated with...
The autonomic nervous system (ANS) plays a major role in the pathophysiology of arrhythmias leading to sudden cardiac death (SCD), and neuraxial modulation is emerging as an important avenue of scientific inquiry and therapeutic intervention.3,4 Mechanism-based autonomic regulation therapy holds promise to treat both arrhythmias and HF. Improved basic scientific understanding can result in innovative low-cost therapeutic options, with a global impact, that can not only prevent death but also favorably alter the course of the underlying disease. The ANS intricately regulates cardiac excitability and contractile function. Cardiac afferents provide beat-to-beat sensory information of cardiac muscle activity to the neuraxis, additional information is conveyed by extracardiac circulatory receptors (Figures 1 and 2). The processing of this afferent information at several levels (intrinsic cardiac nervous system, extracardiac-intrathoracic ganglia, spinal cord, brain stem, and higher centers) provides an elegant mechanism for interacting feedback loops to provide physiological stability for maintaining normal rhythm and life-sustaining circulation. These nested feedback loops ensure that there is fine-tuned regulation of efferent (sympathetic and parasympathetic cardiomotor) neural signals to the heart in normal and stressed states. Concepts on cardiac neural control have been revised in recent years based on new physiological data from multiple studies that together provide an elegant framework for understanding regulatory control of the mammalian heart (Figure 2). Direct single neuron and neural network recordings from intrinsic cardiac and extracardiac ganglia provide the methods to study organ level physiology5–7 and a proper framework of interpretation of the neural control-myocyte interface.

**Pathophysiology**

Cardiac injury (e.g., infarction, focal inflammation) results in the formation of a scar at the level of the organ and likewise alters the integrative regulation of the heart.4,8 The changes at the level of the organ result in slowed and altered paths of myocardial electric propagation, which together creates the substrate for reentrant arrhythmias. The systemic effects of this scar are characterized by afferent-mediated activation of the neuroendocrine system, primarily sympathoexcitation in conjunction with withdrawal of central parasympathetic tone, which provides short-term benefits to maintain cardiac output, but at a cost.9 The recovery from acute injury is characterized by a state wherein there is continued abnormal cardiac afferent signaling (cardiocentric afferents).10 Mechanistically, such dysregulation reflects reactive and adaptive responses of the cardiac neural hierarchy leading to excessive neuronal interactive excitability and network interconnectivity from the intrinsic cardiac nervous system up to and including the insular cortex.7 This reorganization ultimately leads to conflict between central and peripheral aspects of the hierarchy. This

---

**Nonstandard Abbreviations and Acronyms**

| Abbreviation | Description |
|--------------|-------------|
| AF           | atrial fibrillation |
| ANS          | autonomic nervous system |
| BBs          | β-blockers |
| BRS          | baroreflex sensitivity |
| BS           | Brugada syndrome |
| CHF          | congestive heart failure |
| DM           | diabetes mellitus |
| HF           | heart failure |
| IVF          | idiopathic ventricular fibrillation |
| LQT          | long QT |
| NGF          | nerve growth factor |
| RDN          | renal denervation |
| RyR2         | ryanodine receptor 2 |
| SCD          | sudden cardiac death |
| Sema3A       | semaphorin 3A |
| SemaTG       | transgenic mouse expressing semaphorin |
| TWA          | T wave alternans |
| VT           | ventricular tachycardia |
| VF           | ventricular fibrillation |

---

**Figure 1.** Cardiac neurotransmission. Adapted from Jänig143 with permission of the publisher. Copyright ©2014, Elsevier. 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. CM indicates cardiomotor; and ICN, intrinsic nervous system of the heart.
leads to a maladaptive response of excessive sympathoexcitation contributing to the evolution of cardiac disease and fatal arrhythmias.

Cortical and subcortical control of the heart can be demonstrated experimentally in animal models and in humans and has been implicated in arrhythmias. The efficacy of autonomic regulation therapy such as cardiac afferent denervation after myocardial infarction and sympathectomy to treat ventricular tachycardia (VT) storm could be because of a reduction of these conflicts between levels of the cardiac nervous system. In these settings, it is likely that the intrinsic nervous system of the heart is able to provide the neural coordination and ensure electric stability without the interference of central input. The electric stability of the transplanted heart is a clear manifestation of this principle.

Determination of Cardiac Innervation Patterning by Both Neural Chemoattractants and Chemorepellents in the Heart

The heart is abundantly innervated and its performance is tightly controlled by both sympathetic and parasympathetic efferent nerves (Figure 2). Cardiac innervation density including sensory nerves is altered in diseased hearts, which can lead to unbalanced neural activation and lethal arrhythmias. In this section, we focus on the regulatory mechanisms controlling cardiac innervation and the critical roles of these processes on cardiac performance (Figure 3).

Semaphorin 3A Reduces Arrhythmia Potential Through Modulation of Sympathetic Innervation Patterning

Semaphorin 3A (sema3A) is a class 3–secreted semaphorin that has been cloned and identified as a potent neural chemorepellent and a directional guidance molecule for nerve fibers. Initially, we analyzed the kinetics and distribution of cardiac sympathetic innervation in the developing mouse ventricles. By analyzing sema3A knocked-in lacZ mice (transgenic mouse expressing semaphorin [SemaTG]), we found that sema3A is strongly expressed in the developing heart at embryonic day 12 with sema3A expression in the subendocardium, but not subepicardium, of the atria and ventricles. SemaTG mice have reduced sympathetic innervation and attenuation of the epicardial to endocardial innervation gradient. The expression of sema3A in developing hearts revealed a linear decrease from embryonic day 12 that corresponded with an increase in sympathetic innervation density. Thus, the spatial and temporal expression pattern of sema3A directly mirrors the patterning of sympathetic innervation in developing hearts. These results indicate that sema3A is a negative regulator of cardiac innervation. We also analyzed sema3A-deficient mice and found that the sympathetic nerve density is lower in the subepicardium and higher in the subendocardium. As such, these changes resulted in disruption of the innervation gradient in the ventricles. Overall, these results indicate that cardiomyocyte-derived sema3A plays a critical role in cardiac sympathetic innervation by inhibiting neural growth.

Most sema3A-deficient mice died within the first postnatal week because of sinus bradycardia and abrupt sinus arrest. By comparison, SemaTG mice died suddenly without any symptoms at 10 months of age. Sustained ventricular tachyarrhythmia was induced in SemaTG mice, but not in wild-type mice, after epinephrine administration. Programmed electric stimulation also revealed that SemaTG mice were highly susceptible to ventricular tachyarrhythmias.

Together, these data indicate that the highly organized innervation patterning mediated by sema3A is critical for the...
maintenance of arrhythmia-resistant hearts. From the clinical perspective, consistent with our data, Stramba-Badiale et al. report that developmental abnormalities in cardiac innervation may play a role in the genesis of some cases of sudden infant death syndrome. In a recent study of unexplained cardiac arrest, Nakano et al. demonstrated that a polymorphism of SEMA3A (I334V) diminishes the cardiac sympathetic innervation gradient and partially contributes to the pathogenesis of sudden cardiac death with ventricular fibrillation (VF). These findings are important in elucidating the pathogenesis of cardiac sudden death and indicate the dynamic synergism between neural and cardiac development in control of cardiac electric stability.

**Nerve Growth Factor Upregulation Causes Nerve Sprouting and SCD**

Sympathetic activation is important in the genesis of SCD in diseased hearts. It has been known for decades that β-blocker (BB) therapy prevents SCD secondary to VT in ischemic heart disease or congestive HF (CHF). It is further recognized that BBs exert this effect by targeting both cardiac myocytes and elements of the cardiac nervous system.24–26

Nerve growth factor (NGF) is a prototypic member of the neurotrophin family, the members of which are critical for the differentiation, survival, and synaptic activity of the peripheral sympathetic and sensory nervous systems.27 The level of NGF expression within innervated tissue corresponds approximately to innervation density. Previous studies show that NGF expression increases during development and is altered in diseased hearts.28,29 Zhou et al. showed that NGF, which is critical for sympathetic nerve sprouting, is upregulated after myocardial infarction in animal models, resulting in the regeneration of cardiac sympathetic nerves and heterogeneous innervation.

It has also been reported that NGF is upregulated in cardiac hypertrophy, leading to sympathetic hyperinnervation.30 In addition, Cao et al. reported that NGF infusion after MI enhances myocardial nerve sprouting and results in a dramatic increase in SCD and a high incidence of ventricular tachyarrhythmias. Chen et al. have shown that overexpression of sema3A in the MI border zone could reduce the inducibility of ventricular arrhythmias by reducing sympathetic hyperinnervation after infarction. These results demonstrate that NGF-induced augmentation of sympathetic nerve sprouting in diseased hearts can lead to lethal arrhythmias and SCD.

**NGF Downregulation Is Critical for Diabetic Neuropathy and Silent Myocardial Ischemia**

Cardiac autonomic neuropathy is a frequent complication of diabetes mellitus (DM), and diabetic patients are at high risk for developing arrhythmias, silent myocardial ischemia, and SCD.31

---

**Figure 3. Regulation of cardiac innervation patterning and sudden cardiac death (SCD).** Left, Overexpression or lack of semaphorin 3A (sema3A) in endocardium causes unbalanced patterning of sympathetic nerves, which alters the potential for lethal arrhythmia. Appropriate sema3A-mediated sympathetic innervation is crucial for maintenance of arrhythmia-free heart. Middle, Upregulation of secreted nerve growth factor (NGF) from cardiomyocytes in diseased heart may cause lethal arrhythmia and SCD. Right, Downregulation of NGF in diabetic heart induces denervation of cardiac sensory nerve, which leads to silent ischemia and lethal arrhythmia. SG indicates stellate ganglia. Details of these pathways are referenced in the text.21,36,41
The cardiac ANS is composed of efferent and afferent nerves. In contrast to sympathetic innervation, little is known about sensory innervation and how it is altered in diseased hearts. A subset of the cardiac sensory innervation is responsible for pain perception. Activation of these nociceptive afferents results in multiple somatic and visceral responses during myocardial ischemia. Cardiac sensory nerve impairment causes silent myocardial ischemia and this is a likely a major cause of sudden death in patients with DM. Furthermore, there are data that indicate nerve sprouting induced by a potent stimulator of NGF after myocardial injury increases the incidence of ventricular tachyarrhythmias.

A screen of several neurotrophic factors found that the development of cardiac sensory nerves parallels the production of NGF in the heart. Cardiac nociceptive sensory nerves that are immunopositive for calcitonin gene–related peptide (including the dorsal root ganglia and the dorsal horn) are markedly retarded in NGF-deficient mice and rescued in mice overexpressing NGF specifically in the heart. Thus, NGF synthesis in the heart is critical for the development of the cardiac sensory innervation.

To investigate whether NGF is involved in diabetic neuropathy, type 1 DM was induced with streptozotocin in wild-type and transgenic mice overexpressing NGF in the heart. DM-induced wild-type mice show downregulation of NGF, calcitonin gene–related peptide–immunopositive cardiac sensory denervation and atrophic changes in the dorsal root ganglia. These defects are prevented in DM-induced NGF-transgenic mice. Cardiac sensory function, as measured by myocardial ischemia–induced c-Fos expression in the dorsal root ganglia, is also downregulated by DM in wild-type mice, but not by DM in NGF-transgenic mice. Direct gene transfer of NGF into diabetic rat hearts improves the impaired cardiac sensory innervation and function, as determined by the electrophysiological activity of cardiac afferent nerves during myocardial ischemia. These findings demonstrate that the development of the cardiac sensory nervous system depends on the synthesis of NGF in the heart, and that DM-induced suppression of NGF expression may lead to cardiac sensory neuropathy. In human clinical trials of recombinant human NGF administered to diabetic patients with polyneuropathy, none of adverse events such as ventricular arrhythmias were reported. However, a better understanding of the regulation of these pathways and precise studies on reliable and efficient methods of gene therapy and optimal dosage or the regulation of these pathways and precise studies on reliable and efficient methods of gene therapy and optimal dosage are required for further clinical trials.

### Abnormalities and Alteration of Cardiac Sympathetic Nerve Profile in HF

Recently, crosstalk, through various humoral factors, between cardiomyocyte and cardiac sympathetic nerves has been demonstrated. Axon growth, denervation, and functional alternation of sympathetic nerves have been noted in HF. Using molecular biological approaches, a new concept about the adaptation mechanism of the ANS in HF has been developed. With this understanding, new interventional therapies targeted for the ANS and based on a concept with multiple organ linkage have emerged. In this section, we focus on a framework to understand cardiac sympathetic nerve abnormalities in HF and implications for therapy of HF and SCD prevention strategies that target autonomic nerves (Figure 4).

### Systemic Autonomic Nerve Dysfunction as Related to Central and Peripheral Neural Interactions

There is strong evidence that sympathetic efferent neuronal activity is increased in CHF. Such sympathetic activation in HF can also trigger malignant arrhythmias. One of the mechanisms proposed to explain sympathetic activation in HF involves abnormalities in baroreceptors. Signals from baroreceptors are transmitted to the central nervous system via afferent nerves, and after central processing is transduced back to the heart to suppress sympathetic efferent activity. An impairment of carotid baroreflex sensitivity (BRS) has been shown to be a marker of the risk of mortality or a cardiovascular event in HF. The HOPE-4HF (Health Outcomes Prospective Evaluation for Heart Failure With EF ≥ 40%) trial (ClinicalTrials.gov Identifier: NCT00957073) is a prospective randomized trial, where patients will be randomized in a 2:1 ratio to receive baroreceptor activation therapy (device arm) or optimal medical therapy alone (medical arm).

Mechanisms mediated by the chemoreceptor reflex that sense hypoxic and hypercapnic conditions could also be involved in sympathetic activation. Recently, Del Rio et al showed that carotid chemoreceptor ablation reduces respiratory dysfunction and improves survival during HF in rats. In addition, Niewinski et al showed that surgical removal of the carotid body from a patient with systolic HF significantly decreased sympathetic tone.

Brain stem and suprabulbar regions of the central nervous system are critical elements for integrated cardiovascular control. It is well established that the paraventricular nucleus of the hypothalamus and the rostral ventrolateral medulla are involved in the enhanced central sympathetic outflow in HF. Reduced nitric oxide, increased oxidative stress, and activation of angiotensin II type 1 receptors in the rostral ventrolateral medulla all contribute to sympathetic drive. Further oxidative stress can alter cardiac cholinergic control. It is important to note that cardiac afferents are activated after cardiac injury and play a major role in cardiac dysfunction and remodeling. Wang et al using resiniferatoxin a potent analog of capsaicin to delete transient receptor potential vaniloid 1 receptor–expressing cardiac afferent nerves, have demonstrated attenuation of remodeling and fibrosis in a rat HF model.

Animal and human studies suggest that activation of both efferent and afferent renal nerves play a role in the pathogenesis and progression of disease states such as hypertension and CHF. Renal denervation (RDN), which is a novel catheter-based ablation therapy, interrupts efferent sympathetic and afferent renal sensory nerves. It is being studied as an option for patients with resistant hypertension and HF. Physiological cardiovascular control involves afferent signals from the kidneys which are processed in the hypothalamus as well as in the nucleus of the solitary tract, insular cortex, anterior cingulate cortex, and based on functional MRI studies in the infralimbic cortex. Alterations in afferent input would
als59–62 demonstrated decrease ambulatory blood pressure in TrkA, tropomyosin-related kinase A. RVLM, rostral ventrolateral medulla; SG, stellate ganglia; and PVN, paraventricular nucleus; ROS, reactive oxygen species; DRG, dorsal root ganglia; NE, norepinephrine; NTS, solitary tract; acetylcholine; BP, blood pressure, CG, intrinsic cardiac ganglia; cholinergic (choline transporter [CHT], choline acetyltransferase [ChAT]) and juvenile (polysialylated neural cell adhesion molecule [PSA-NCAM]) increased. Ach indicates acetylcholine; TH and DBH, tyrosine hydroxylase (TH) and dopamine-β-hydroxylase (DBH) reduced and of cholinergic (choline transporter [CHT]), choline acetyltransferase [ChAT]) and juvenile (polysialylated neural cell adhesion molecule [PSA-NCAM]) increased. Ach indicates acetylcholine; BP, blood pressure, CG, intrinsic cardiac ganglia; DRG, dorsal root ganglia; NE, norepinephrine; NTS, solitary tract; PVN, paraventricular nucleus; ROS, reactive oxygen species; RVLM, rostral ventrolateral medulla; SG, stellate ganglia; and TrkA, tropomyosin-related kinase A. Currently, RDN is being evaluated as a potential adjunctive therapy in a spectrum of sympathetically modulated cardiovascular diseases, including left ventricular hypertrophy and diastolic dysfunction, CHF, obstructive sleep apnea, and atrial fibrillation (AF). RDN has also been proposed as a possible treatment strategy in patients with recurrent ventricular arrhythmias. Consequently, there are several ongoing clinical trials (Symplicity-HF and REACH [Renal Artery Denervation in Chronic Heart Failure Study]) investigating the safety and efficacy of RDN in patients with CHF and VT (Reset VT).

Finally, considering its systemic relationship with the peripheral sympathetic nerves, the involvement of the central nervous system in sympathetic dysfunction is of considerable interest and further studies in this area are anticipated in the future.52

Figure 4. Systemic autonomic interactions and crosstalk between cardiomyocyte and sympathetic nerve terminal via humoral factors in diseased heart. This figure shows that central and peripheral mechanism of the heart and brain interaction including the cardiac autonomic efferent (sympathetic and parasympathetic) and afferent (sensory) nerves. Representative promising interventional therapies are also described in the figure. In addition, alteration of cardiac sympathetic nerves occurs in postganglionic fiber. Failing cardiomyocytes induces nerve growth factor (NGF) via endothelin-1 (ET-1)–mediated pathway and leukemia inhibitory factor (LIF). NGF and LIF lead to hyperinnervation (anatomic modulation) and rejuvenation/cholinergic differentiation (functional modulation), respectively. This phenomenon shows the expression of catecholaminergic markers such as tyrosine hydroxylase (TH) and dopamine-β-hydroxylase (DBH) reduced and of cholinergic (choline transporter [CHT], choline acetyltransferase [ChAT]) and juvenile (polysialylated neural cell adhesion molecule [PSA-NCAM]) increased. Ach indicates acetylcholine; BP, blood pressure, CG, intrinsic cardiac ganglia; DRG, dorsal root ganglia; NE, norepinephrine; NTS, solitary tract; PVN, paraventricular nucleus; ROS, reactive oxygen species; RVLM, rostral ventrolateral medulla; SG, stellate ganglia; and TrkA, tropomyosin-related kinase A.

be expected to alter set-points and sensitivities for reflex control of blood pressure.

Treatment of drug-resistant hypertension was the initial therapeutic use of RDN. Both preclinical and clinical trials demonstrated decrease ambulatory blood pressure in medication refractory hypertension. However, the recently reported prospective Symplicity HTN-3 trial did not meet the expected antihypertensive end points and was terminated early.

CHF leads to upregulation of a range of growth factors and cytokines in the heart. Leukemia inhibitory factor and other members of the interleukin-6 family, which can induce fetal gene expression (so-called rejuvenation) in adult cardiomyocytes, are upregulated during CHF.31 In the cardiac sympathetic nervous system in CHF, strong expression of growth-associated protein 43 and highly polysialylated neural cell adhesion molecule has been noted.31 We also found that this neural rejuvenation can be induced by leukemia inhibitory factor expressed in hypertrophied hearts (unpublished data). These observations are supported by several other studies, which showed that leukemia inhibitory factor changes the neuropeptide phenotype or increases the degradation of tyrosine hydroxylase through the ubiquitin-proteasome system. Taken together, these results suggests that cardiac sympathetic nervous system dysfunction is accompanied by neuronal rejuvenation, the so-called functional denervation because of rejuvenation mechanism.

Cardiac sympathetic properties are also altered in CHF as mediated by changes in cardiac-derived humoral factors. In a HF model using Dahl salt-sensitive rats and in autopsy specimens from patients with HF, decreased density of tyrosine hydroxylase–positive neurons was seen. Furthermore, many neurons in the stellate ganglia and left ventricle also expressed parasympathetic markers such as choline transporter...
and choline acetyltransferase. This was thought to represent cholinergic transdifferentiation of cardiac adrenergic neurons into cholinergic neurons, induced by leukemia inhibitory factor via a gp130 signaling pathway.78 The diverse potential of sympathetic neurons in terms of plasticity (adaptability to changes in the environment) is implied by the functional changes to cardiac sympathetic neurons in HF.

It remains controversial whether cardiac sympathetic differentiation induced by gp130-mediated cytokines in CHF is a favorable or unfavorable event for cardiac performance and prognosis. We found significantly improved survival rate and ventricular function in reference mice when compared with sympathetic nerve specific, gp130-deficient mice, suggesting a protective role for the transdifferentiation seen in the model of hypoxia-induced HF mice.78 Together, these results indicate that interleukin-6 family cytokines secreted from the failing myocardium act as negative modulators of sympathetic function by rejuvenation and cholinergic differentiation via a gp130 signaling pathway, possibly affecting cardiac performance and prognosis.78

Modulation of parasympathetic function can exert profound effects on sympathetic function in the heart. Previous reports have demonstrated that the vagal nerve stimulation suppresses arrhythmia and prevents sudden death in CHF after myocardial infarction with dogs or rats.79,80 Indeed, in recent reported clinical trial, vagal nerve stimulation improves cardiac function and quality of life with tolerable safety profile in patients with CHF.81 However the recent results of another multicenter trial of vagal stimulation failed to demonstrate benefits with regards to cardiac remodeling and functional capacity despite improvement in quality-of-life measures.82

Long-term exposure of high plasma norepinephrine concentration caused a reduction in myocardial NGF and associated sympathetic fiber loss in severe decompensated HF animals, the so-called anatomic denervation because of depletion of NGF.74 Recently, Rana et al83 showed that mechanical stretch and α-1 adrenergic stimulation attenuated NGF expression via the calcineurin-nuclear factor of activated T-cell signaling pathway in cultured neonatal cardiomyocytes. The spatial and temporal innervation pattern and activity of sympathetic nerves directly affect the pathogenesis in HF (Figure 3). We think that better understanding of the mechanisms of cardiac sympathetic anatomic and functional innervation patterning represents an important approach for future development of therapies to avoid SCD.

Translational Relevance of Cardiac and Extracardiac Neural Remodeling

The electrophysiological effects of neural remodeling have been the subject of recent human and animal studies. Data from epicardial and endocardial recordings in patients referred for interventional cardiac electrophysiology procedures demonstrate that there is global cardiac remodeling in humans (analysis of infarcted regions, peri-infarct regions, and remote/normal parts of the ventricle).84 This study showed that in humans, sympathetic stimulation increased regional differences in repolarization. The myocardium remote from the infract demonstrated abnormal neural control consistent with denervation (lack of action potential shortening with neural stimulation). This functional denervation is also seen in experimental infarction replicating the human condition.84,85 Dispersion of action potential duration in response to sympathetic stimulation (heterogeneity in response) is significantly increased in cardiomyopathic hearts which explains the proclivity to lethal arrhythmias. To mechanistically evaluate this disease-induced remodeling, a porcine model of myocardial infarction was developed that reproduces all key aspects of disease observed in humans.85 From these animal models, we found that remote (noninfarcted) myocardium in these hearts shows abnormal regulation and the stellate ganglia show neuronal remodeling and adrenergic transdifferentiation (greater tyrosine hydroxylase–positive cells in stellate ganglia).86 We have recently extended this work to human and have found that in addition to cardiac changes, extracardiac neural structures undergo significant neural remodeling in the presence of myocardial dysfunction.87 Evaluating the stellate ganglia removed from patients with refractory arrhythmias, we found that remote (noninfarcted) myocardium in these hearts shows abnormal regulation and the stellate ganglia show neuronal remodeling and adrenergic transdifferentiation (greater tyrosine hydroxylase–positive cells in stellate ganglia).86 We have recently extended this work to human and have found that in addition to cardiac changes, extracardiac neural structures undergo significant neural remodeling in the presence of myocardial dysfunction.87 Evaluating the stellate ganglia removed from patients with refractory arrhythmias, we found morphological changes (enlargement of neurons), as well as changes in growth-associated protein 43 and synaptophysin consistent with increased activity.87 Such changes likely reflect the pathophysiological changes in response to neural

![Temporal changes in cardiac innervation with disease progression.](image-url)
transduction in the stressed heart and the removal of these structures is beneficial by interrupting efferent and afferent pathways.\textsuperscript{17,88} It is of interest that vagal stimulation, which is being evaluated as a treatment for HF to prevent sudden death, leads to cholinergic transdifferentiation of stellate ganglion in dogs (Figure 6).\textsuperscript{39}

**Clinical Correlates**

Several studies have highlighted the value of autonomic indices to identify patients at risk for sudden death. These typically have related to measurable indices of sympathetic and parasympathetic function. Although several tests are valuable, they have not surpassed simpler measures of risk such as ventricular function assessment. However, the physiological basis of these tests will be alluded to briefly.

**Identifying High-Risk Patients for SCD in Diseased Heart by Evaluation of the ANS**

Higher sympathetic tone and lower parasympathetic tone promote fatal arrhythmas by multiple mechanisms including reducing ventricular refractory period and VF threshold, promoting triggered activity and automaticity. To identify patients at high risk for SCD, evaluation of the ANS has received attention during the years primarily because of the limitations of only using left ventricular ejection fraction. Multifaceted evaluation using different risk markers is expected to increase the accuracy for detecting cardiac risk and also provides opportunities to initiate protective therapy and continues to be a matter of clinical debate. In this section, we summarize available cardiac autonomic testing strategies including heart rate variability, BRS, heart rate turbulence, heart rate deceleration capacity, and T wave alternans (TWA) to place them in the context of cardiac interventions (Table 1).

**Heart Rate Variability**

Sinus node automaticity is modulated by both sympathetic and parasympathetic nervous systems. Modulation of heart rate by respiration is well-known phenomenon mediated by cardiopulmonary afferent inputs and central interactions between cardiovascular and respiratory networks.\textsuperscript{90,91} Alterations of the heart rate is easily measured clinically from ECG recordings and is used to quantify cardiac autonomic modulation as heart rate variability. Heart rate variability is measured by multiple different methods. The most popular methods are time domain or frequency domain analysis.

**Baroreflex Sensitivity**

BRS is an index of autonomic input to the sinus node and measured by the reflex changes in R-R interval in response to induced changes in blood pressure. It is usually measured by characterizing the magnitude of induced bradycardia in response to a pressor (phenylephrine) challenge. BRS decreases with advancing age and is reduced in patients with hypertension or HF.\textsuperscript{14,92} The Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study showed that, after myocardial infarction, the SD of the average of normal sinus to normal sinus intervals <70 ms or BRS <3.0 ms/mm Hg with left ventricular ejection fraction <35% carried a significant risk of cardiac mortality.\textsuperscript{84} Daily exercise prevents VF induced by acute myocardial infarction by decreasing sympathetic and increasing parasympathetic tone.\textsuperscript{93}

**Heart Rate Turbulence**

Heart rate turbulence is an index of changes in sinus rate after a premature ventricular complex followed by a compensatory pause. Normally, the sinus rate initially accelerates and slows thereafter but this phenomenon is disturbed in various heart diseases. Abnormal heart rate turbulence is associated with increased total mortality and sudden death in patients with coronary artery disease and dilated cardiomyopathy.\textsuperscript{24} From the substudy of ATRAMI study, relative risk for abnormal values of heart rate turbulence was a strong predictor.\textsuperscript{95}

**Heart Rate Deceleration Capacity**

Heart rate deceleration capacity is based on a signal processing algorithm to separately characterize deceleration and acceleration of heart rate, which in turn distinguish between vagal and sympathetic factors. Heart rate deceleration capacity is reported to be a better predictor of mortality after myocardial infarction than left ventricular ejection fraction and SD of normal sinus to normal sinus.\textsuperscript{96}

**T Wave Alternans**

TWA is beat-to-beat variability in the amplitude or morphology of T waves. TWA reflects temporal heterogeneity or dispersion in ventricular repolarization. TWA is primary used as a tool for the risk stratification for SCD in patients with ischemic and nonischemic heart diseases. Negative predictive value of this test is high and a negative test strongly predicts freedom from VT and VF.\textsuperscript{97}

**Disease-Specific Treatment by Sympathetic or Parasympathetic Modulation for Patients at High Risk for SCD**

**Atrial Fibrillation**

Several mechanisms have been proposed to explain the pathogenesis of AF suggesting a strong link to the ANS.\textsuperscript{98} The clinical correlation of an autonomic influence was noted by Coumel et al\textsuperscript{99} and has since then been the subject of several studies. Electric stimulation of autonomic nerves during the atrial refractory period has been shown to produce rapid ectopic beats from the pulmonary veins and superior vena cava, which in turn can initiate AF.\textsuperscript{100–102} It is now generally accepted that the ANS has an important contribution to the pathogenesis of AF.\textsuperscript{103,104} However, AF still remains poorly understood and the specific mechanisms underlying the relationship between the ANS and AF have yet to be fully elucidated. Imbalances in the intrinsic nervous system of the heart (Figure 2) are thought to be involved in the pathogenesis of AF and therefore strategies have been developed to modify the synaptic efficacy of these structures by spinal cord stimulation,\textsuperscript{105} ablate ganglionated plexi,\textsuperscript{106} or the vein of Marshall.\textsuperscript{107} Recent studies have used an alternative neuromodulation-based strategy for control of the atrial arrhythmic substrate, spinal cord stimulation.\textsuperscript{105} High thoracic spinal cord stimulation stabilizes neural processing within the intrinsic cardiac nervous system, reducing the potential for neurally induced AF. Moreover, the efficacy of such therapy increases with time and is related to induced changes in intrinsic cardiac neural network function.\textsuperscript{7,102,105}
Ganglionated plexus ablation has been proposed as a strategy for management of AF based on experimental models and human studies. These treatments have the potential to impact ventricular electrophysiology and arrhythmogenesis. Studies have shown significantly increased risk of ventricular arrhythmias in the setting of acute myocardial ischemia heart compared with normal hearts,\textsuperscript{108} and there is some evidence of this having relevance to humans post ablation suggesting the need for careful follow-up (Table 2).\textsuperscript{109}

### Table 1. Cardiac Autonomic Testing

| Test | Description |
|------|-------------|
| Heart rate variability | Baroreflex sensitivity |
| Heart rate turbulence | Heart rate deceleration capacity |
| T wave alternans |  |

**Figure 6.** Functional remodeling of cardiac innervation in an experimental infarct model and humans with postinfarct cardiomyopathy. Innervation patterns of the mammalian heart are altered after myocardial infarction. **Left upper,** Polar maps of global epicardial activation recovery intervals (ARIs) recorded from a control and an infarcted porcine heart at baseline (BL), and during stimulation of the right, left, and bilateral stellate ganglion (RSG, LSG, and BSG, respectively). The focal region of myocardial infarction in the anteroapical left ventricle is indicated by the dashed circle in bottom row. The altered pattern of ARI distribution in the infarcted heart extends beyond the region of focal myocardial infarction. **Right upper,** Graphical representation of the regional responses of the porcine heart to stimulation of RSG, LSG, and BSG in control and infarcted hearts, respectively. The anterior and posterior predominance of RSG and LSG stimulations, respectively, are completely lost after infarction. **Left lower,** ARIs recorded from a patient with ischemic cardiomyopathy and a large anteroapical scar. The location of the recording multielectrode catheter on fluoroscopy in the right and left anterior oblique (RAO and LAO, respectively) projections; and the corresponding electroanatomic map is shown. On the electroanatomic map, the purple regions indicate tissue with normal voltage (nonscar tissue), whereas the dense gray regions represent dense scar. All other colors represent border zones (tissue with voltage $\geq 0.5$ mV but $\leq 1.5$ mV). **Right lower,** The degree of change in ARI from baseline in response to direct (isoproterenol) and indirect reflex-mediated (nitroprusside) sympathetic stimulation in cardiomyopathic and normal hearts is shown. With isoproterenol, ARI shortening is exaggerated in normal voltage regions in cardiomyopathic hearts (CM-NL) and scarred tissue regions of the cardiomyopathic heart (CM-scar). Border zone regions are slightly less responsive to isoproterenol. With nitroprusside, CM-NL and CM-scar zones paradoxically demonstrate ARI increase when compared with the border zone regions. These observations, when compared with normal hearts, indicate the severe degree of adrenergic nerve dysfunction in human hearts with ischemic cardiomyopathy. AICD indicates automatic internal cardioverter defibrillator lead; AP, apex; CS, coronary sinus electrode; LV, left ventricle; and RV, right ventricular lead.
phase of coronary occlusion, re-entry caused by heterogeneity of the ischemic myocardium is considered as major mechanism. Reperfusion arrhythmias are caused by washout of various ions such as lactate, potassium, and toxic metabolic substances from the ischemic zone and also oxidative stress alters autonomic function. Reflex activation of the cardiac nervous system, leading to heterogeneous sympathetic activation, contributes to the arrhythmogenic substrate.

VT is often encountered in patients with a healed myocardial infarction. These VTs are mostly monomorphic and caused by re-entry involving a region of infarcted scar. Myocardial scars are most commonly caused by an old myocardial infarction but can also be seen in arrhythmogenic right ventricular cardiomyopathy, sarcoidosis, and other nonischemic cardiomyopathies. Fibrotic scar creates areas of slow conduction or block between surviving myocytes and promotes re-entry. Schwartz et al reported that the presence of a reduced BRS is associated with a greater susceptibility to VF in a canine model of healed myocardial infarction. These data indicate that there are inherent and acquired differences in the neural substrate for cardiac control that contribute to the potential for SCD in the setting of acute and chronic ischemic heart disease.

BBs are essential pharmacological treatment in patients with coronary artery disease and HF. BBs reduce O2 requirements in myocardium by decreasing heart rate and exercise induced increases in blood pressure. Because BBs block arrhythmogenic sympathetic myocardial stimulation, antiarrhythmic effects also contribute to a favorable outcome. BBs exert this cardioprotective effect by targeting elements of the cardiac nervous system as well as the end-effectors of the heart.

Cardiomyopathy
Cardiomyopathies including dilated cardiomyopathy, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy can be associated with VTs. The mechanism of VTs in these patients is re-entry, involving the fibrotic scar with slow conduction. Although TWA may be a useful marker of risk stratification in patients with dilated cardiomyopathy, it is difficult to predict patients at high risk of sudden death. The effect of antiarrhythmic drugs is uncertain and implantable cardioverter defibrillator is indicated for primary and secondary prevention of SCD in these patients. In addition to BBs, neuraxial therapy has been valuable in the management of arrhythmias in these patients.

Heart Failure
Increased sympathetic tone in the failing heart causes diastolic Ca2+ leak through ryanodine receptor 2 (RyR2) resulting in localized and transient increases in Ca2+ in cardiomyocytes. Focally increased Ca2+ initiates more Ca2+ release and propagates as Ca2+ waves. These Ca2+ waves can cause delayed afterdepolarizations resulting in a ventricular premature beats and sustained VT. The effect of β-adrenergic receptor blockers on the survival in patients with HF was proven by multiple placebo-controlled multicenter trials. BBs combined with angiotensin-converting enzyme-I produce reverse remodeling of LV, improve patient symptoms, lower hospitalization and prolong survival.

Inherited Arrhythmia
The ANS plays an important role in the development of various inherited arrhythmias.

| Disease-Specific Treatment by Sympathetic or Parasympathetic Modulation to Prevent Sudden Cardiac Death | Trigger | Treatment |
|------------------------------------------------------|--------|----------|
| Ventricular tachyarrhythmias | Sympathetic | BB, ARB, ACE-I, aspirin, RFCA, ICD, BCSD |
| ischemia and myocardial infarction | Sympathetic | BB, ARB, ACE-I, ICD, BCSD |
| Cardiomyopathy | DCM | BB, Ca-B, III, ICD, BCSD |
| HCM | Sympathetic | BB, Ca-B, III, ICD, BCSD |
| ARVC | Sympathetic | BB, ARB, ACE-I, III, ICD, BCSD |

Long-QT Syndrome
Long-QT (LQT) syndromes are characterized by a prolonged QT interval on the ECG and an increased risk of sudden death by polymorphic VT/torsades de pointes. In congenital LQT syndrome, several clinical phenotypes have been well described including the autosomal dominant Romano–Ward syndrome and the autosomal recessive Jervell and Lange–Nielsen syndrome with or without associated deafness. To date, >17 genotypes have identified but great majority (90%) of cases are LQT1–3. Phenotype–genotype relationships are well studied and the onset of syncope or torsade de pointes (TdP) is initiated by exercise in LQT1 and by noise, sudden wakening from sleep by an alarm clock or telephone rings in LQT2; there are also cardiac changes associated with sleep stages. Patients with LQT3 develop events when at rest or asleep. In LQT1 and LQT2, β-adrenergic stimulation enhances transmural dispersion of repolarization and induced TdP. BBs are effective especially in LQT1 but indicated in all LQT patients including genotyped patients with normal QTc. Therapeutic importance of cardiac innervation is evidenced by the fact that left cardiac sympathetic denervation is valuable in high-risk patients who are intolerant or refractory to BBs alone.

Brugada Syndrome
Brugada syndrome (BS) is characterized by ST elevation in the precordial leads and associated with syncope or sudden
death because of VF.\textsuperscript{124} VF in BS patients is known to develop more frequently at night than during the remainder of the day. Enhanced vagal tone including a full stomach provokes ST elevation. A decreased nocturnal SD of the average of normal sinus to normal sinus measured in Holter recordings is one of the markers of risk stratification of BS. Sympathetic stimulation such as exercise, isoproterenol infusion improves ST elevation and suppresses syncopal or fibrillatory events.

**Diagnosis of idiopathic VF (IVF) is made if patients survive cardiac arrest and the pathogenesis cannot be determined by all available testing. Clinical evaluation should be performed to exclude coronary artery disease, cardiomyopathy, or primary electric disease including BS, LQT, or catecholaminergic polymorphic VT. Although IVF patients are heterogeneous, among the non–Brugada IVF patient, some patients demonstrate similar phenotype with BS. Such patients have higher incidence of J waves. IVF patients with J waves were highlighted as early repolarization syndrome and isoproterenol and quinidine is effective in suppressing VF episodes. There exists a circadian pattern of VF in IVF patients and the presence of J waves was associated with nocturnal occurrence.\textsuperscript{125}**

**Catecholaminergic Polymorphic VT**

Catecholaminergic polymorphic VT is characterized by adrenergically induced polymorphic VT which can be reproducibly induced by physical or emotional stress. Mutations in the cardiac RyR2 gene underlie autosomal dominant catecholaminergic polymorphic VT,\textsuperscript{126} whereas cardiac calsequestrin mutations underlie autosomal recessive catecholaminergic polymorphic VT.\textsuperscript{127} Intracellular calcium overload triggered by adrenergic stimulation is the disease mechanism. Discontinuation of exercise is required and \(\beta\)-blocking agents are the first line of therapy. Flecainide is alternative pharmacological therapy for patients when cardiac events are not controlled with BBs alone.\textsuperscript{128} Left cardiac sympathetic denervation has been reported to be effective in patients with drug refractory ventricular arrhythmias.\textsuperscript{129}

**VT and Fibrillation Storm in Patients With Structural Heart Disease**

Patients with a wide variety of cardiac structural disease present with VT and sometimes this occurs in a cluster (storm) which is associated with a high mortality.\textsuperscript{130} Typically these patients are managed with supportive measures, antiarrhythmic drugs, and catheter ablation. The presence of a scar in the heart provides the substrate for VT, but it is not always seen and the pathophysiological role is unclear in patients with dilated cardiomyopathies suggesting a role for functional factors that govern impulse propagation.\textsuperscript{112} However, even scar-based reentrant arrhythmias require obligate areas of functional block/conduction changes that allow impulse propagation in preferential directions.\textsuperscript{85,131,132} Thus, clinical occurrence of VT reflects the balance between macro structure and functional control. The importance of understanding why only some VTs are clinically encountered when a scar can have multiple circuits is highlighted by the clinical data showing that targeting of the clinical VT is crucial for improved outcomes (not just an arbitrary circuit modification achieved by catheter ablation).\textsuperscript{133} In instances when the cardiac substrate is not amenable to catheter modification or refractory to such approaches, neuraxial strategies such as thoracic epidural anesthesia and bilateral cardiac sympathetic denervation have been beneficial.\textsuperscript{134} Patients who undergo such procedures can show changes in cardiac interoception and objective measures of reduced sympathetic outflow to the heart.\textsuperscript{14} This again highlights another aspect of the brain heart connection.\textsuperscript{12,13}

**Perspective on Neuromodulation to Prevent SCD Based on Improved Understanding of Cardiac Innervation**

Cardiac disease results in adaptations of afferent and efferent input to various levels of the neuraxis.\textsuperscript{2,10} Such adaptations result in changes to the integrated neural function within central and peripheral aspects of the cardiac nervous system. For stress-induced changes in cardiac electric stability, there are interdependent interactions within the nervous system and at the neural–myocyte interface. The following points summarize the current state of the field for neurocardiology with respect to the evolving potential for neuromodulation-based antiarrhythmic therapy based on a better understanding of cardiac innervation.

- Afferent sensory transduction of the pathologically stressed heart results in a reflex-driven adrenergic efferent postganglionic neuronal output to the heart.
- The reflex response of the higher centers to the sensory inputs from stressed heart, especially from ischemic myocardium, is inherently proarrhythmic resulting in augmented norepinephrine release.
- Chronic heart disease adversely remodels multiple levels of the cardiac neuraxis with a resultant shift toward discordant cardiocardiac reflexes, an adaptation by itself that can be proarrhythmic.
- Cardiac neuromodulation/autonomic regulation therapy at different levels of the cardiac neuraxis has the potential to exert antiarrhythmic effects while still preserving basic integrated reflex control the heart.

Recent work has demonstrated that targeting select elements within the cardiac nervous system by electric stimulation or transection and pharmacological manipulation is effective in select cardiac disease states including myocardial ischemia/infarction,\textsuperscript{135–137} atrial arrhythmias,\textsuperscript{102,105,138,139} and ventricular arrhythmias.\textsuperscript{3,8,13} With appropriate neuromodulation therapy, myocytes are rendered stress resistant, autonomically responsive for control of the heart is preserved, and the potential for fatal arrhythmias is reduced.\textsuperscript{135–137,140–142} Current autonomic regulation therapy therapies are delivered in the open-loop configuration (no feedback) and with the cardiac nervous system considered a black box. To rectify this critical deficit in knowledge, future studies should evaluate reactive and adaptive changes in network function from successive levels of the cardiac neuraxis. This is likely to help develop approaches for mechanism-based targeted neuromodulation for effective cardiac therapeutics.
Conclusions

The emerging field of neurocardiology is predicated on the dynamic interactions between the substrate of the heart and the neurohumoral control systems that regulate it. As detailed herein, there are inherent and acquired adaptations in both the heart and the nervous system that affect the progression of cardiac disease. With each year new insights are gained into these adaptations at the molecular, cellular, organ, and whole body level. Such information is critical to (1) identifying patients at high risk for future adverse outcome and (2) providing novel targets to pre-emptively manage such patients. Neuromodulation strategies show promise of sustaining cardiac function while maintaining electric stability.

Sources of Funding

Dr Shivkumar is supported by the National Heart, Lung, and Blood Institute (NHLBI; R01HL084261) and Dr Ardell was supported by NHLBI (R01 HL071830). Dr Ardell has grant funding from the St. Luke’s Medical, Glaxo Smith Klein, and Cyberonics Inc.

Disclosures

Dr Ardell serves as a consultant to Cyberonics Inc. The other authors report no conflicts.

References

1. Chugh SS, Reinier K, Teodorescu E, Evanado A, Kehr E, Al Samara M, Mariani R, Gunson K, Jui J. Epidemiology of sudden cardiac death: clinical and research implications. Prog Cardiovasc Dis. 2008;51:213–228. doi: 10.1016/j.pcad.2008.06.003.
2. Shen MJ, Zipes DP. Role of the autonomic nervous system in modulating cardiac arrhythmias. Circ Res. 2014;114:1004–1021. doi: 10.1161/CIRCRESAHA.113.302549.
3. Schwartz PJ. Cardiac sympathetic denervation to prevent life-threatening arrhythmias. Nat Rev Cardiol. 2014;11:346–350. doi: 10.1038/nrcardio.2014.19.
4. Vaseghi M, Shivkumar K. The role of the autonomic nervous system in sudden cardiac death. Prog Cardiovasc Dis. 2008;50:404–419. doi: 10.1016/j.pcad.2008.01.003.
5. Armour JA. Cardiac neuronal hierarchy in health and disease. Am J Physiol Regul Integr Comp Physiol. 2004;287:R262–R271. doi: 10.1152/ajpregu.00183.2004.
6. Armour JA. Potential clinical relevance of the 'little brain' on the mammalian heart. Exp Physiol. 2008;93:165–176. doi: 10.1113/epjphysiol.2007.041178.
7. Beaumont E, Salavatian S, Southerland EM, Vinet A, Jacquemet V, Armour JA, Ardell JL. Network interactions within the canine intrinsic cardiac nervous system: implications for reflex control of regional cardiac function. J Physiol. 2013;591:4515–4533. doi: 10.1113/jphysiol.2013.259382.
8. Rubart M, Zipes DP. Mechanisms of sudden cardiac death. J Clin Invest. 2005;115:2305–2315. doi: 10.1172/JCI26381.
9. Kember G, Armour JA, Zamir M. Neural control hierarchy of the heart has not evolved to deal with myocardial ischemia. Physiol Genomics. 2013;45:638–644. doi: 10.1152/physiolgenomics.00027.2013.
10. Zucker IH, Patel KP, Schultz HD. Neurohumoral stimulation. Heart Fail Clin. 2012;8:87–99. doi: 10.1016/j.hfc.2011.08.007.
11. Oppenheimer SM, Cechetto DF. Cardiac chronotropic organization of the rat in vivo. Brain Res. 1990;533:66–72.
12. Child N, Hanson B, Bishop M, Rinaldi CA, Bostock J, Western D, Cooklin M, O’Neil M, Wright M, Razavi R, Gill J, Taggart P. Effect of mental challenge induced by movie clips on action potential duration in normal human subjects independent of heart rate. Circ Arrhythm Electrophysiol. 2014;7:518–523. doi: 10.1161/CIRCEP.113.000909.
13. Gray MA, Taggart P, Sutton PM, Groves D, Holdright DR, Bradbury D, Brull D, Critchley HD. A cortical potential reflecting cardiac function. Proc Natl Acad Sci U S A. 2007;104:6818–6823. doi: 10.1073/pnas.0609509104.
ratory function. J Am Coll Cardiol. 2013;62:2422–2430. doi: 10.1016/j.jacc.2013.03.011.

Leenen FH. Brain mechanisms contributing to sympathetic hyperactivity and heart failure. Circ Res. 2007;101:221–223. doi: 10.1161/CIRCRESAHA.107.158261.

Laufer H. Novel mechanisms of sympathetic regulation in chronic heart failure. Hypertension. 2006;48:1005–1011. doi: 10.1161/HYPV000246614.72131.25.

Hirooka Y. Brain perivascular macrophages and central sympathetic activation after myocardial infarction: heart and brain interaction. Hypertension. 2005;55:610–611. doi: 10.1161/HYPERTENSIONAHA.109.145128.

Dawson TA, Li D, Woodward T, Barber Z, Wang L, Paterson DJ. Cardiac cholinergic NO-cGMP signaling following acute myocardial infarction and nNOS gene transfer. Am J Physiol Heart Circ Physiol. 2008;295:H990–H4998. doi: 10.1152/ajpheart.00492.2008.

Sobotka PA, Krum H, Böhm M, Francis DP, Schlaich MP. The role of renal denervation in the treatment of heart failure. Curr Cardiol Rep. 2012;14:285–292. doi: 10.1007/s11886-012-0258-x.

Calaresu FR, Ciriello J. Renal afferent nerves affect discharge rate of medullary and hypothalamic single units in the cat. J Auton Nerv Syst. 1981;31:31–220.

Ciriello J, Calaresu FR. Central projections of afferent renal fibers in the rat: an anterograde transport study of horseradish peroxidase. J Auton Nerv Syst. 1983;8:273–285.

Cechetto DF. Cortical control of the autonomic nervous system. Exp Physiol. 2014;99:326–331. doi: 10.1113/expphysiol.2013.075192.

Rippel MK, Zarins D, Barman NC, Wu A, Duncan KL, Zarins CK. Cather-based renal sympathetic denervation: chronic preclinical evidence for renal artery safety. Clin Res Cardiol. 2011;10:1095–1101. doi: 10.1007/00392-011-0346-8.

Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambir S, Abraham WT, Eister M. Cather-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet. 2009;373:1275–1281. doi: 10.1016/S0140-6736(09)60656-3.

Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmiede RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (the symplicity htn-2 trial): A randomised controlled trial. Lancet. 2010;376:1903–1909.

Krum H, Schlaich MP, Sobotka PA, Böhm M, Mahfoud F, Rocha-Singh K, Katholi E, MD. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the SYMPATHT trial. Lancet. 2014;383:622–629. doi: 10.1016/ S0140-6736(13)62192-3.

Vogel B, Kirchberger M, Zeier M, Stoll F, Meder B, Sauer D, Andrassy M, Mueller OJ, Hardt S, Schwenger V, Strothmeyer A, Katus HA, Blessing E. Renal sympathetic denervation therapy in the real world: results from the Heidelberg registry. Clin Res Cardiol. 2014;103:117–124. doi: 10.1007/ s00392-013-0627-y.

Bhatt DL, Kandzari DE, O’Neill WW, D’Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Lauer M, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL; SYMPATHT-3 Investigators. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370:1393–1401. doi: 10.1056/NEJMoa1402620.

Brandt MC, Mahfoud F, Reda S, Schirmer SH, Erdmann E, Böhm M, Hoppe UC. Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. J Am Coll Cardiol. 2012;59:901–909. doi: 10.1016/j.jacc.2011.11.034.

Davies JE, Manisty CH, Petroczi R, Barron AJ, Unsworth B, Mayet J, Hamady M, Hughes AD, Sever PS, Sobotka PA, Francis DP. First-in-man safety evaluation of renal denervation for chronic systolic heart failure: primary outcome from REACH-Pilot study. Int J Cardiol. 2013;162:189–192. doi: 10.1016/j.ijcard.2012.09.019.

Witkowski A, Prebisz A, Florczak E, Kądziela J, Sliwiński P, Bielen P, Michałowski I, Kabat M, Warchol E, Januszewicz M, Narkiewicz K, Somers VK, Sobotka PA, Januszewicz A. Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycolic control in patients with resistant hypertension and sleep apnea. Hypertension. 2011;58:559–565. doi: 10.1161/HYPERTENSIONAHA.111.173799.

Pokushalov E, Romanov A, Corbucci G, Artymyenko S, Baranova V, Turov A, Shirokova N, Karasov A, Mittal S, Steinberg JS. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. J Am Coll Cardiol. 2012;60:1163–1170. doi: 10.1016/j.jacc.2012.05.036.

Remo BF, Preminger M, Bradfield J, Mittal S, Boyle N, Gupta A, Shvikumar K, Steinberg JS, Dickfeld T. Safety and efficacy of renal denervation as a novel treatment of ventricular tachycardia storm in patients with cardiomyopathy. Heart Rhythm. 2014;11:541–546. doi: 10.1016/j.hrthm.2013.12.038.

Ukema C, Bauer A, Mahfoud F, Schreieck J, Neuberger HR, Eick C, Sobotka PA, Gavaz M, Böhm M. Renal sympathetic denervation for
Chapter 7: Integration of Vagal and Sympathetic Nervous System in Cardiac Arrhythmias

The role of the calcineurin-NFAT pathway in cardiac ventricular arrhythmias.

K, Rassaf T, Kelm M, Schauerte P. Regulation of nerve growth factor in the heart: the role of the calcineurin-NFAT pathway. J Neurochem. 2012;120:239–247. doi: 10.1111/j.1471-4159.2011.07539.x.

Regulation of nerve growth factor in the heart: the role of the calcineurin-NFAT pathway.

K, Rassaf T, Kelm M, Schauerte P. Regulation of nerve growth factor in the heart: the role of the calcineurin-NFAT pathway. J Neurochem. 2012;120:239–247. doi: 10.1111/j.1471-4159.2011.07539.x.

Regulation of nerve growth factor in the heart: the role of the calcineurin-NFAT pathway.

K, Rassaf T, Kelm M, Schauerte P. Regulation of nerve growth factor in the heart: the role of the calcineurin-NFAT pathway. J Neurochem. 2012;120:239–247. doi: 10.1111/j.1471-4159.2011.07539.x.

Regulation of nerve growth factor in the heart: the role of the calcineurin-NFAT pathway.

K, Rassaf T, Kelm M, Schauerte P. Regulation of nerve growth factor in the heart: the role of the calcineurin-NFAT pathway. J Neurochem. 2012;120:239–247. doi: 10.1111/j.1471-4159.2011.07539.x.

Regulation of nerve growth factor in the heart: the role of the calcineurin-NFAT pathway.

K, Rassaf T, Kelm M, Schauerte P. Regulation of nerve growth factor in the heart: the role of the calcineurin-NFAT pathway. J Neurochem. 2012;120:239–247. doi: 10.1111/j.1471-4159.2011.07539.x.

Regulation of nerve growth factor in the heart: the role of the calcineurin-NFAT pathway.

K, Rassaf T, Kelm M, Schauerte P. Regulation of nerve growth factor in the heart: the role of the calcineurin-NFAT pathway. J Neurochem. 2012;120:239–247. doi: 10.1111/j.1471-4159.2011.07539.x.
Heart Rhythm
P, Amin R, Somers VK. Gene-specific paradoxical QT responses during rapid eye movement sleep in women with congenital long QT syndrome. J Am Coll Cardiol. 2010;55:2355–2365. doi: 10.1016/j.jacc.2010.01.041.

Schwartz PJ, Vanoli E, Strandm-Badiale M, De Ferrari GM, Billman GE, Foreman RD. Autonomic mechanisms and sudden death. New insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. Circulation. 1988;78:969–79.

Sakabe K, Ikeda T, Sakata T, Kawase A, Kumagai K, Tezuka N, Takami M, Nakae T, Noro M, Enjoji Y, Sugi K, Yamaguchi T. Prediction of the recurrence of ventricular tachyarrhythmias from T-wave alternans assessed on antithrombolytic pharmacotherapy: a prospective study in patients with dilated cardiomyopathy. Am J Cardiol. 2011;108:203–208.

Sakabe K, Ikeda T, Sakata T, Kawase A, Kumagai K, Tezuka N, Takami M, Nakae T, Noro M, Enjoji Y, Sugi K, Yamaguchi T. Comparison of T-wave alternans and QT interval dispersion to predict ventricular tachyarrhythmias in patients with dilated cardiomyopathy and without antithrombolytic drugs: a prospective study. Jpn Heart J. 2001;42:451–457.

The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353:9–13.

Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med. 1996;334:1349–1355. doi: 10.1061/NEJM199605334320110.

Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in congeitive heart failure (MERIT-HF). Lancet. 1999;353:201–207.

Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128:1810–1852. doi: 10.1161/CIRCULATIONAHA.113.002830.

Effets de la tachycardie et de l'arythmie dans les cardiopathies (I). Butyrate and head-to-head randomized control trial in ischemic heart disease with and without heart failure. J Am Coll Cardiol. 2012;9:1426–1433.e3. doi: 10.1016/j.hrthm.2012.04.038.

Lopshyre JC, Zhou X, Dusa C, Ueyama T, Rosenberg J, Courtney N, Ujihay M, Mullen T, Das M, Zipps DP. Spinal cord stimulation improves ventricular function and reduces ventricular arrhythmias in a canine postinfarction heart failure model. Circulation. 2009;120:286–294. doi: 10.1161/CIRCULATIONAHA.108.812412.

Shinlapawiyatatayor K, Chinda K, Palee S, Surinkaew S, Thunsiri K, Weeratereangkul P, Chattipakorn S, KenKnight BH, Chattipakorn N. Low-amplitude, left vagus nerve stimulation significantly attenuates ventricular dysfunction in patients with dilated cardiomyopathy. J Cardiovasc Electrophysiol. 2010;21:554–561. doi: 10.1111/j.1540-8167.2009.01737.x.

Southerland EM, Gibbons DD, Smith SB, Sipe RM,向往 D. American College of Cardiology Foundation/American Heart Association/APHRS expert consensus on ventricular arrhythmias. Heart Rhythm. 2014;11:e166–e196. doi: 10.1016/j.hrthm.2014.07.024.

Bernstein SA, Wong B, Vasquez C, et al. Spinal cord stimulation protects against atrial fibrillation induced by tachypacing. Heart Rhythm. 2012;9:1426–1433.e3. doi: 10.1016/j.hrthm.2012.04.038.

Cohn JN, Gibson MD, Foreman RD, Linderoth B, Lohstroh LC, Armstrong SP, Vosmer VK. Vagal therapy to modulate the autonomic nervous system to treat heart failure. Curr Cardiol Rep. 2012;14:593–600. doi: 10.1007/s11886-012-0292-8.

Ondedsted J, Lendroth B, Bergfeldt L, Ekre O, Grip L, Mannheimer C, Andréll P. 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. doi: 10.1016/j.hrthm.2011.01.029.

Southerland EM, Gibbons DD, Smith SB, Sipe RM, Gourlay D. Activated cranial cervical cord nerves affect left ventricular infarct size and the potential for sudden cardiac death. Auton Neurosci. 2012;169:34–42. doi: 10.1016/j.autneu.2012.03.003.

Jäng W. Sympathetic nervous system and inflammation: a conceptual view. Auton Neurosci. 2014;182:2–14. doi: 10.1016/j.autneu.2014.01.004. http://www.autonomicneuroscience.com/article/S1566-0702(14)00006-X/abstract.
Cardiac Innervation and Sudden Cardiac Death
Keiichi Fukuda, Hideaki Kanazawa, Yoshiyasu Aizawa, Jeffrey L. Ardell and Kalyanam Shivkumar

Circ Res. 2015;116:2005-2019
doi: 10.1161/CIRCRESAHA.116.304679

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/116/12/2005

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/