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 sudden cardiac death. This system also plays a major role in the pathophysiology and progression of heart disease, including heart failure and arrhythmias leading to sudden cardiac death. Transdifferentiation of neurons in heart failure, functional denervation, cardiac and extracardiac neural remodeling has also been identified and characterized during the progression of disease. Recent advances in understanding the cellular and molecular processes governing innervation and the functional control of the myocardium in health and disease provide a rational mechanistic basis for the development of neuraxial therapies for preventing sudden cardiac death and other arrhythmias. Advances in cellular, molecular, and bioengineering realms have underscored the emergence of this area as an important avenue of scientific inquiry and therapeutic intervention. (Circ Res. 2015;116:2005-2019. DOI: 10.1161/CIRCRESAHA.116.304679.)

Key Words: arrhythmias, cardiac autonomic nervous system death, sudden cardiac physiopathology
arrhythmias and sudden death.1,2 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 (eg, 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.4,5 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.

![Cardiac neurotransmission](http://circres.ahajournals.org/)

**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 al22 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 al23 demonstrated that a polymorphism of SEMA3A (I334V) diminishes the cardiac sympathetic innervation gradient and partially contributes to the pathogenesis of SCD 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 al30 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.31 In addition, Cao et al32 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 al32 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.33
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 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. Baroreceptor activation has been thought to confer benefits in prevention of SCD which is prevalent in patients with HF. The HOPE4HF (Health Outcomes Prospective Evaluation for Heart Failure With EF ≥40%) trial showed that carotid chemoreceptor ablation reduces cardiorepiratory 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 vanilloid 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...
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 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.

Crosstalk Between Cardiomyocyte and Cardiac Sympathetic Nerves Mediated by Humoral Factors

The pathology of HF involves various abnormalities in sympathetic nerve terminals. During the transition to overt HF, sympathetic neural tone is upregulated, and NGF expression is elevated contributing to hyperinnervation of cardiac sympathetic nerves. However, there is a paradoxical reduction in norepinephrine synthesis concomitant with downregulation of tyrosine hydroxylase (TH), the rate-limiting enzyme in inner sympathetic nerve terminals. During the transition to overt HF, the rate-limiting enzyme in innervated neurons, norepinephrine reuptake into the sympathetic nervous system in HF remain poorly understood (Figure 5).

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. In the cardiac sympathetic nervous system in CHF, strong expression of growth-associated protein 43 and highly 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.

Crosstalk Between Cardiomyocyte and Cardiac Sympathetic Nerves Mediated by Humoral Factors

The pathology of HF involves various abnormalities in sympathetic nerve terminals. During the transition to overt HF, sympathetic neural tone is upregulated, and NGF expression is elevated contributing to hyperinnervation of cardiac sympathetic nerves. However, there is a paradoxical reduction in norepinephrine synthesis concomitant with downregulation of tyrosine hydroxylase (TH), the rate-limiting enzyme in innervated neurons, norepinephrine reuptake into the sympathetic nervous system in HF remain poorly understood (Figure 5).

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. In the cardiac sympathetic nervous system in CHF, strong expression of growth-associated protein 43 and highly 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.
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. 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. 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.

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. Indeed, in recent reported clinical trial, vagal nerve stimulation improves cardiac function and quality of life with tolerable safety profile in patients with CHF. 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.

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. Recently, Rana et al 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). 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. Dispersion of action potential duration in response to sympathetic stimulation (heterogeneity in response) is significantly increased in cardiomyopathic hearts which explains the proneness 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. 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). 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. 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. Such changes likely reflect the pathophysiological changes in response to neural

![Figure 5. Temporal changes in cardiac innervation with disease progression.](http://circres.ahajournals.org/)

Figure 5. Temporal changes in cardiac innervation with disease progression. NE indicates norepinephrine; NGF, nerve growth factor; and LIF, leukemia inhibitory factor.
transduction in the stressed heart and the removal of these structures is beneficial by interrupting efferent and afferent pathways. 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).

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 arrhythmias 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. Alterations of the heart rate is easily measured clinically from ECG recordings and is used to quantify cardiac autonomic modulations 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. 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.

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.

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 primarily 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.

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. The clinical correlation of an autonomic influence was noted by Coumel et al 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. It is now generally accepted that the ANS has an important contribution to the pathogenesis of AF. 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, ablate ganglionated plexi, or the vein of Marshall. Recent studies have used an alternative neuromodulation-based strategy for control of the atrial arrhythmogenic substrate, spinal cord stimulation. 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.
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, and there is some evidence of this having relevance to humans post ablation suggesting the need for careful follow-up (Table 2).

**Ventricular Tachyarrhythmias Related to Ischemia and Infarction**

In patients with myocardial infarction, ventricular arrhythmias develop during the acute and chronic phase. In the acute
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, neuaxial 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 after depolarizations 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.

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–Nielson 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.

Table 2. Disease-Specific Treatment by Sympathetic or Parasympathetic Modulation to Prevent Sudden Cardiac Death

<table>
<thead>
<tr>
<th>Disease</th>
<th>Trigger</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular tachyarrhythmias</td>
<td>Sympathetic</td>
<td>BB, ARB, ACE-I, aspirin, RFCA, ICD, BCSD</td>
</tr>
<tr>
<td>Ischemia and myocardial infarction</td>
<td>Sympathetic</td>
<td>BB, ARB, ACE-I, aspirin, RFCA, ICD, BCSD</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCM</td>
<td>Sympathetic</td>
<td>BB, ARB, ACE-I, III, ICD, BCSD</td>
</tr>
<tr>
<td>HCM</td>
<td>Sympathetic</td>
<td>BB, Ca-B, III, ICD, BCSD</td>
</tr>
<tr>
<td>ARVC</td>
<td>Sympathetic</td>
<td>BB, ARB, ACE-I, III, ICD, BCSD</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-QT syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LQT1</td>
<td>Sympathetic</td>
<td>BB, LCSD</td>
</tr>
<tr>
<td>LQT2</td>
<td>Sympathetic</td>
<td>BB, LCSD?</td>
</tr>
<tr>
<td>LQT3</td>
<td>Parasympathetic</td>
<td>Mexiletine, pacemaker, ICD</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>Parasympathetic</td>
<td>Quinidine, isoproterenol, ICD</td>
</tr>
<tr>
<td>Idiopathic VF</td>
<td>Parasympathetic</td>
<td>BB, ICD</td>
</tr>
<tr>
<td>CPVT</td>
<td>Sympathetic</td>
<td>BB, flecaïnide, LCSD</td>
</tr>
</tbody>
</table>

1 and III indicates class I and III antiarrhythmics; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, β-blocker; BCSD, bilateral cardiac sympatheticotomy; Ca-B, calcium channel blocker; CPVT, catecholaminergic polymorphic ventricular tachycardia; ICD, implantable cardioverter defibrillator; LCSD, left cardiac sympatheticotomy; ?, the efficacy was not established; RFCA, radiofrequency catheter ablation; and VF, ventricular fibrillation.
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.

**Idiopathic VF**
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 β-blocking agents are the first line of therapy. Flecaïnide 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{131} 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 macrostructure and functional control. The importance of understanding why 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{18} 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. Neuronmodulation 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; R01 HL084261) and Dr Ardell was supported by NHLBI (R01 HL071830). Dr Ardell has grant funding from the St. Jude Medical, Glaxo Smith Klein, and Cyberonics Inc.

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

References


47. Uekana B, Bauer A, Mahfoud F, Schriech J, Neuberger HR, Eck C, Sobotka PA, Gawaz M, Böhm M. Renal sympathetic denervation for...


Reddy V. Renal sympathetic denervation to suppress ventricular tachyarhythmias (rescue-vc), nct01778377.


Cardiac Innervation and Sudden Cardiac Death
Keiichi Fukuda, Hideaki Kanazawa, Yoshiyasu Aizawa, Jeffrey L. Ardell and Kalyanam Shivkumar

doi: 10.1161/CIRCRESAHA.116.304679

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/