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Cardiac innervation and the autonomic nervous system in SCD

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Summary

Neural remodeling in the autonomic nervous system contributes significantly to sudden cardiac death. The fabric of cardiac excitability and propagation are controlled by autonomic innervation. Heart disease predisposes to malignant ventricular arrhythmias by causing neural remodeling at the level of the myocardium, the intrinsic cardiac ganglia, extra-cardiac intrathoracic sympathetic ganglia, extra-thoracic ganglia, spinal cord, and the brainstem, as well as the higher centers and the cortex. Therapeutic strategies at each of these levels aim to restore the balance between the sympathetic and parasympathetic branches. Understanding this complex neural network will provide further important therapeutic insights into the treatment of sudden cardiac death.

Keywords

autonomic; innervation; sympathetic; parasympathetic; sudden death; ventricular tachycardia; ventricular fibrillation

Introduction

The autonomic nervous system controls every aspect of cardiac physiology. Autonomic imbalances, whether from central nervous system disorders such as in epilepsy[1] or cardiac pathological remodeling of the peripheral nervous system, can cause significant atrial and

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ventricular tachy- and brady-arrhythmias. In this chapter, the role of the autonomic nervous system in sudden cardiac death will be reviewed with a particular focus on the levels at which neuromodulatory therapies may have proven benefit.

Anatomy

The autonomic nervous system consists of sympathetic and parasympathetic branches. Neural processing occurs at several levels, figure 1. The intrinsic cardiac ganglia reside on the epicardium and receive post-ganglionic sympathetic and pre-ganglionic parasympathetic connections. In the thorax, the extra-cardiac but intrathoracic ganglia such as the stellate ganglia, the middle cervical ganglia, and the thoracic ganglia of T2–T4 also process neural information, controlling sympathetic outflow to the heart. Finally, sympathetic afferent information passes through the dorsal root ganglia and reaches the spinal cord where additional neural processing can take place. Some of this information is then sent to the brainstem and higher centers. At each level, afferent neurotransmission feeds back information to neurons that in turn affect efferent control of the heart, completing an independent neural circuit that modulates cardiac function. In addition, direct vagal afferent fibers originate from the myocardium and synapse via pseudo-unipolar neurons of the nodose ganglia in the nucleus tractus solitarius of the brainstem. Finally, although sympathetic efferent fibers originate in the thoracic ganglia and parasympathetic preganglionic fibers travel in the vagal trunk, it is important to note that there is significant intermixing of these fibers in the thorax so that most nerves reaching the heart in the mediastinum have mixed (sympathetic and parasympathetic) fibers.[2,3]

Sympathetic Efferent Neurotransmission

The journey of cardiac sympathetic preganglionic fibers originates in the central nervous system (CNS) primarily in the brainstem with modulation by higher centers such as the subthalamic and periaqueductal grey as well as rostral ventrolateral medulla.[4] These preganglionic fibers leave the spinal cord at the level of T1 to T4 and synapse in the right and left stellate ganglia, T2–T4 thoracic, and middle cervical ganglia. Postganglionic fibers then originate from these ganglia and travel along epicardial vascular structures as dictated by embryological growth cues of endothelin-1 and nerve growth factor (NGF) released by vascular smooth muscle cells, particularly along coronary veins and then arteries.[5,6] Therefore, sympathetic innervation is particularly dense around the sinus node and coronary sinus, with decreasing in density from the base of the ventricle to the apex.[7] In addition, these fibers provide input to the numerous ganglionated subplexuses interspersed throughout bilateral atria and ventricles.[4,8] The majority of post-ganglionic sympathetic fibers, however, synapse directly onto the myocardium. The major neurotransmitter of the sympathetic nervous system, is norepinephrine, which stimulates myocardial beta receptors. Roles for additional neurotransmitters such as neuropeptide Y are currently under investigation.[9]

Parasympathetic Efferent Neurotransmission

Preganglionic cardiac parasympathetic efferent fibers begin in the nucleus ambiguus and dorsal motor nucleus of the brainstem and travel in the vago-sympathetic trunk bilaterally.[10] These preganglionic fibers synapse within the intrinsic cardiac ganglia residing in fat pads

on the heart.[11] Postganglionic neurons then provide direct innervation to the sinus node, atrioventricular node, and bilateral atria and ventricles.[12–15] Acetylcholine is the major neurotransmitter of the heart, stimulating muscarinic (predominantly M2 and M3) receptors on the myocytes. However, important co-transmitters are released with vagal nerve stimulation including nitric oxide and vasoactive intestinal peptide. Of note, although the vagal trunk consists of primarily efferent parasympathetic nerve fibers, evidence for dopaminergic fibers within the trunk also exists.[16,17] The role of these dopaminergic fibers remains to be elucidated. Importantly, the majority of the fibers of the vagal trunk are afferent (>80%).[18] The vagal nerve has the added complexity of providing dual autonomic and bidirectional flow of information via multiple neurotransmitter messengers.

Neural Afferent Neurotransmission

Afferent nerve fibers provide critical feedback from the myocardium and can be mechanosensory, chemosensory, or both.[4] Chemosensory neurons respond to a variety of stimuli including hydrogen ions, potassium, bradykinin, oxygen radicals, adenosine, adenosine triphosphate and arachidonic acid metabolites. These nerve fibers send information to the intrinsic cardiac ganglia, the intrathoracic ganglia, the dorsal root ganglia of the spinal cord, and via the nodose ganglia (the inferior ganglia of the vagosympathetic trunk) to the brainstem. Afferents arising from renal parenchyma and renal pelvis travel via the dorsal root ganglia of the spinal cord and can also modulate sympathetic outflow.[19] Of note, aortic and carotid body mechanosensory and chemosensory afferents appear to travel via the vagal trunk to the brain.[20,21]

Neural Circuits

Local circuit neurons in the intrathoracic and intracardiac ganglia serve as processors of afferent information. They provide local reflex arcs back to the heart through efferent nerves, fine tuning cardiac function on a beat by beat basis.[4,22,23] Orthotopic heart transplantation serves as a prime example of independent regulation with intact but isolated intracardiac ganglia.[24] Transection of the spinal cord at T1–T4 in a porcine model demonstrates the ability of the remaining neuronal networks to regulate cardiac function, independently of the central nervous system.[25] In addition to local information processing that occurs at the intrinsic cardiac ganglia, the local circuit neurons within these ganglia serve as important peripheral stations for processing neural information, receiving input both from the central nervous system (sympathetic and parasympathetic) and the myocardium.[26]

Autonomic Nervous System and Cardiac Pathophysiology

Response to Sympathetic Activation

Norepinephrine stimulation of beta adrenergic receptors causes downstream modulation of ion channels and calcium release, which culminates in increases in inotropy, chronotropy, lusitropy, and dromotropy in normal hearts. However, in the setting of structural heart disease, the electrophysiological effects of sympathetic activation predispose to sudden death.[27] The calcium loading effects on the sarcoplasmic reticulum can create delayed after depolarizations that can initiate ventricular arrhythmias.[28] Action potential duration (APD) is shortened in areas of dense sympathetic innervation, and due to the heterogeneity of

sympathetic innervation, APD dispersion increases. In ischemic cardiomyopathy, direct and indirect sympathetic activation with isoproterenol and nitroprusside in humans[29] and electrical stimulation of the stellate ganglia in porcine hearts has been shown to significantly increase dispersion of repolarization.[30] T-peak to T-end interval, a marker of sudden cardiac death, correlates with dispersion of repolarization and is significantly increased with stellate ganglion stimulation in these studies. Of note, T peak to T-end interval is not increased with uniform norepinephrine infusion in normal hearts, highlighting the nonuniform distribution of direct nerve activation.[31] The dispersion of repolarization sets the stage for functional blocks and promotes a substrate for reentrant arrhythmias. In addition, sympathetic stimulation in animal models has been shown to increase electrical restitution and electrical alternans, and decrease ventricular effective refractory period (ERP) and ventricular fibrillation threshold (VFT).[32] Furthermore, the co-transmitters released with sympathetic stimulation, namely neuropeptide Y, has been shown to reduce vagal release of acetylcholine and increase VF inducibility by acting directly on the myocardial Y1 receptor.[9] Other indirect effects of sympathetic activation include a neurally induced pro-inflammatory state which confers negative remodeling of the myocardium.[33] The sympathetic activation that occurs with cardiac disease along with structural changes such as connexin-43 down regulation and lateralization,[34,35] act in concert to cause malignant ventricular arrhythmias that result in sudden death, figure 2.

Parasympathetic Activation

The primary method of increasing parasympathetic tone has been via stimulation of the vagal trunk. Vagal nerve stimulation has been shown to reduce slope of APD restitution, lengthen ventricular ERP, and raise VFT in various animal models including rats, rabbits, pigs, cats and dogs.[36–38] Furthermore, direct right and left vagal nerve stimulation or indirect stimulation via phenylephrine infusion increases epicardial and endocardial ventricular APD, and ERP.[39] Unlike right and left thoracic ganglia stimulation, lateral differences are not evident when stimulating the vagal nerves.[37] The neurotransmitter conferring these beneficial effects include acetylcholine, which interacts with beneficial receptor subtypes which include muscarinic receptor subtype 3 and nicotinic receptor α7nAChR.[40] Nitric oxide release due to vagal nerve stimulation also protects against ventricular arrhythmias.[41] Connexin-43, a gap junction protein that is decreased in myocardial infarction (MI), is preserved in the setting of vagal nerve stimulation.[42] Other beneficial effects of parasympathetic activation include improvement of heart failure in animal models,[43] coronary vasodilation,[44–46] decrease in reactive oxygen radicals,[47] and reduction of inflammation.[48] Therefore, through a number of mechanisms, increasing parasympathetic tone protects against ventricular arrhythmias.

Neural Remodeling in the Setting of Myocardial Infarction

Denervation

Myocardial infarction can cause local denervation of sympathetic fibers and create electrical heterogeneity of the myocardium.[49] Local denervation of infarcted regions exhibit a blunted ability to shorten ARI with stellate stimulation, contributing to ARI dispersion.[30]

Denervation of myocardium increases beta adrenergic sensitivity, calcium mishandling, and APD dispersion.[50,51]

Sympathetic denervation can be imaged with radioactive analogues of norepinephrine, namely 131I-meta-iodo-benzyguanidine using single photon emission computerized tomography or 11C-hydroxyephedrine using positron emission tomography (PET). Greater degree of denervation on these imaging modalities predicts sudden cardiac death risk better than infarct size or ejection fraction (EF).[52,53] Furthermore, the denervation patterns seen on PET imaging correspond well with late gadolinium enhancement scar regions seen on magnetic resonance imaging[54] and the heterogeneity of innervation at the border zones correlate with increased ventricular arrhythmia inducibility.[55]

The re-innervation process is shaped by chemoattractants and chemorepellents with NGF playing a key role as a chemoattractant. In a heart failure rat model, myocardial NGF levels decrease in response to norepinephrine stimulation.[56] The reduced NGF levels decrease sympathetic innervation density in the myocardium, thus attenuating the synaptic input and equilibrating the myocardial exposure to higher sympathetic tone. Afferent innervation is also controlled by NGF. In a streptozosin induced diabetic mice model, diabetes decreased NGF production and afferent signaling in the dorsal root ganglia. This cardiac sensory neuropathy predisposes to sudden death by means of clinically silent ischemia.[57] Other neurotrophic factors such as Sema3a acts as a chemorepellent and thereby prevents innervation. Clinically, polymorphisms in the SEMA3A gene have been linked to unexplained cardiac arrest.[58] Sema3a overexpression in left stellate ganglion of ischemic rats has shown to reduce nerve sprouting, attenuate the dephosphorylation of connexin 43, and reduce ventricular arrhythmia inducibility.[59] Similarly, Sema3a overexpression in the infarct border zones of rats reduces sympathetic innervation and VT inducibility.[60] The mechanism behind the persistent post-infarction sympathetic denervation has been attributed to the chemorepellent effect of chondroitin sulfate proteoglycans (present in scar) binding with neuronal protein tyrosine phosphatase receptor σ, which is a key regulator of axonal growth depending on its ligand.[61] When this paired binding is prevented with intracellular sigma peptide, sympathetic innervation is restored and arrhythmia susceptibility is reduced.[51] In summary, pathologic patterns of denervation predispose to sudden death by creating proarrhythmic substrate. Understanding this pathophysiology has led to a few promising therapeutic molecular targets that focus on modulating re-innervation at the level of myocardium.

Hyperinnervation

Axonal damage and denervation is followed by attempts at reinnervation by the cardiac peripheral nerves. However, this process appears to be very heterogeneous. Reinnervation is observed in localized regions along border zones of infarcts and appears to proceed in a heterogeneous fashion likely determined by the underlying molecular milieu driving the innervation process. This heterogeneous hyperinnervation increases the dispersion of repolarization and provides the substrate for ventricular arrhythmias.[62] In explanted human hearts with history of ventricular tachycardia, evidence of myocardial hyperinnervation at border zones of scar regions has been observed.[63] In addition, following myocardial

infarction, infusing NGF into the stellate ganglia to promote sympathetic nerve sprouting increases the incidence of ventricular arrhythmias and sudden cardiac death in canine hearts.[64] Restoring appropriate re-innervation of the scar has been shown to decrease arrhythmias in a mouse model of myocardial infarction.[51] Therefore, agents that promote homogeneous reinnervation may serve as an important cornerstone in autonomic clinical therapeutics.

Neural Remodeling of the Cardiac and Extra-cardiac Ganglia

In addition to neural remodeling at the level of the myocardium, ischemic and non-ischemic cardiomyopathy are associated with remodeling of the extra-cardiac (stellate) ganglia. Human stellate ganglia from patients with structural heart disease have been shown to contain enlarged neurons,[65] and in a porcine infarct model, stellate ganglia contain less non-sympathetic neural populations, and more pro-arrhythmic neuropeptide Y activity.[66] In a canine infarct model, an increase in synaptic density of stellate ganglion neurons has been observed by measuring growth-associated protein 43 and synaptophysin.[67] Similar increases in sympathetic remodeling of stellate ganglia has been seen in patients with heart failure.[65] In a porcine infarct model, the degree of neural remodeling including increased neuronal size and neuronal nitric oxide synthase (nNOS) activity has been shown in the dorsal root, stellate, right atrial, and ventral interventricular ganglionated plexi.[68] Furthermore, the ability of neurons within the intrinsic cardiac ganglia to respond to various stimuli, such as preload reduction, is altered in the setting of myocardial infarction.[26] Extracardiac ganglia remodeling plays an important role in modulating ventricular arrhythmias. Refer to figure 3 for flow chart representing the different effects of infarcted myocardium on remodeling the afferent and efferent limbs of the sympathetic nervous system.

Neuraxial Modulation to Reduce Risk of SCD

Modulation of the Sympathetic Nervous System

Except for a few disorders such as LQT3 or Brugada, reducing the sympathetic activity is expected to reduce ventricular arrhythmias and sudden cardiac death in setting of structural heart disease.

Chemical Blockade—The pharmacologic cornerstones of cardioprotective heart failure therapy in the past two decades block sympathetic activation with the use of beta blockers,[69] angiotensin converting enzyme inhibitors (ACEI),[70] angiotensin receptor blockers (ARB),[71] and aldosterone antagonists.[72] Beta adrenergic receptor blockade has long term improvement in heart failure and mortality.[73] ACEI and ARB effectively block the effect of angiotensin II, which is known to increase central nervous system sympathetic outflow and impair the baroreceptor pathways that restrain sympathetic outflow at the nucleus tractus solitarius.[74] Aldosterone antagonists have been shown to decrease myocardial norepinephrine content and increase VFT.[75] Statins, in addition to its cornerstone role in ischemic heart disease,[76] have been also implicated in reducing sympathetic outflow.[77] In the critical care setting of electrical storm, sedation and general anesthesia can reduce sympathetic activity and control ventricular arrhythmias.[78]

Cardiac Resynchronization Therapy—Cardiac resynchronization therapy (CRT) with biventricular pacing has been another cornerstone of heart failure therapy that modulates the autonomic nervous system. Using PET imaging, homogeneous sympathetic innervation has been shown to be increased in the myocardium of CRT responders.[79] In addition, while heart failure increases muscarinic receptor subtype 2 and its Gαi counterpart, CRT upregulates known protective muscarinic receptor subtype 3.[80]

Thoracic Epidural Anesthesia—Reduction of sympathetic outflow from the spinal cord can be accomplished by injecting anesthetic agents into the thoracic epidural space. Reducing ventricular fibrillation with thoracic epidural anesthesia (TEA) has been demonstrated in an ischemic rat model.[81] The initial human case report showed a dramatic reduction of a patient's electrical storm corresponding with the initiation of bupivacaine in the T1–T2 epidural space.[82] A subsequent case series of 8 patients who underwent TEA showed no adverse procedural outcomes and 6 patients showed a significant decrease (> 80%) in VT burden.[83] For patients in whom the procedure is not contraindicated due to anticoagulation, TEA offers the advantages of emergency bedside initiation with minimal effects on hemodynamic parameters,[84] while bridging towards a more definitive therapy. In addition, there has been reported success with intrathecal clonidine in reducing ischemia induced ventricular arrhythmias in a postinfarct canine model.[85]

Spinal Cord Stimulation—Spinal cord stimulation (SCS) has been approved in the United States for chronic pain and intractable angina.[86] Similar to TEA, SCS acts in the epidural space of T1–T4, but the nerves are modulated by electrical impulses rather than chemical deactivation. SCS modulates the autonomic innervation of the heart by reducing stellate ganglia activity,[87] increasing vagal tone,[88] altering intrinsic cardiac neuron activity,[89] and modifying sympathetic nerve sprouting in the myocardium.[90] In a post-infarct canine heart model with superimposed pacing induced heart failure, SCS reduced ischemia driven VF from 59 to 23%.[91] Furthermore, intermittent chronic SCS in a similar model lowered VF due to ischemia and improved the EF compared to carvedilol, demonstrating benefit beyond conventional heart failure medical therapy.[92] Similar reductions in ventricular ectopy were observed in an ischemic porcine model where SCS decreased dispersion of repolarization.[93] An initial case series of SCS in patients with heart failure showed benefit. SCS reduced VT/VF burden by at least 75% over 4 months with a 2 month midpoint cross over design.[94] However, SCS has shown mixed results in human clinical trials of heart failure. Thoracic Spinal Cord Stimulation for Heart Failure as a Restorative Treatment (SCS-HEART) study showed safety and efficacy in New York Heart Association (NYHA) class III patients with EF 25–30%.[95] Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Systolic Heart Failure (DEFEAT-HF) study evaluated NYHA class III patients with EF ≤35% and showed no improvement in EF.[96] It is possible that the discrepant SCS clinical results of VT/VF versus HF can be explained by differences of how SCS was applied including duration and frequency of stimulation.

Cardiac Sympathetic Denervation/Decentralization—Cardiac sympathetic denervation (CSD) can be achieved with surgical removal of stellate and T1 to T4 ganglia via video assisted thoracoscopic surgery.[78] Although this surgery does not interrupt all the

thoracic sympathetic pathways to the heart, as the upper half of the stellate and the middle cervical ganglia remain intact, it has shown benefit in a variety of clinical settings. In a case series of 22 patients with long QT, catecholaminergic polymorphic VT, and idiopathic VT, 73% had a marked reduction in VT burden with 55% having complete cessation at median follow up of 28 months with left CSD.[97] In the setting for VT storm and structural heart disease in 9 patients, 3 had complete cessation of VT and 2 had partial response.[83] The beneficial effects of bilateral CSD was reported in case series of 41 patients, 17 of whom underwent unilateral and 27 of whom underwent bilateral.[98] Although both left and bilateral CSD significantly reduced burden of ICD shocks in the year after the procedure compared to the 6 months prior, patients with bilateral CSD had a significantly greater ICD shock free survival at one year. Therefore, for control of ventricular arrhythmias refractory to standard medial therapy, bilateral CSD serves as a promising therapeutic strategy. Risks of the procedure are less than 5% and include mild ptosis, pneumothorax or hemothorax, and occasionally, vasopressor support after the procedure. Long term side-effects include a change in sweating pattern and sensation in approximately 10–15% of patients as well as neuropathic pain, which generally resolves within 6 months after the procedure.[98]

Emerging frontiers in animal models include molecular modification of the stellate ganglia. Delivering nNOS to hypertensive rats to can improve impaired vagal tone[99] and attenuate hyperactive sympathetic tone.[100] Another therapeutic avenue includes reducing stellate activity with low level vagal nerve stimulation. By upregulating a hyperpolarizing small conductance calcium activated potassium channel SK2 in dogs, neuronal firing of the sympathetic branch is effectively reduced with vagal nerve stimulation.[101] The ability to translate nonsurgical methods to modify stellate activity can potentially provide the benefits without the complications of surgical CSD.

Renal Sympathetic Denervation—Renal afferent nerve fibers that modulate the sympathetic outflow can be reduced by catheter ablation of these fibers in the renal arteries, a procedure known as renal artery denervation (RDN). The first successful report of RDN for arrhythmias showed dramatic reductions of VT/VF burden for 2 patients with VT storm.[102] Similar benefit was seen in a refractory VT patient during the post revascularization recovery after a ST elevation MI[103] and another who failed endocardial and epicardial ablation.[104] A case series of 4 patients with cardiomyopathy undergoing RDN showed safety and efficacy with reduction of VT burden from 11 VT episodes in the month preceding procedure to 0.3 per month following the procedure.[105] A subsequent case series of 10 patients with cardiomyopathies showed a dramatic reduction with 28.5 device shocks in the preceding 6 months and 0 shocks after renal denervation.[106] However, although RDN has shown anti-arrhythmic benefit in case series of patients with refractory ventricular arrhythmias and structural heart disease, the inability to reach a prespecified clinical outcome in the SIMPLICITY-HTN3 trial[107] has highlighted the challenges of identifying precise targets and end-points of ablation within the renal arteries.[78,108] There is much anticipation of the results from the current ongoing trials evaluating the efficacy of RDN to reduce ventricular arrhythmias, including RESCUE[109] and RESET-VT.[110]

Modulation of the Parasympathetic Nervous System

Vagal Nerve Stimulation—Augmenting the protective effects of parasympathetic nervous system for controlling ventricular arrhythmias has been accomplished with vagal nerve stimulation (VNS) in animal models. Vagal nerve stimulators are implanted surgically akin to an implantable pacemaker with stimulation leads attached to the cervical the vagal trunk, adapted from FDA approved treatment for epilepsy and depression.[111,112] Side effects from the procedure include infection, dysphagia, hoarseness, cough, and pain.[86] A reduction in sudden cardiac death from ventricular arrhythmias has been demonstrated with vagal stimulation in a healed infarct canine model subjected to repeat ischemia.[113] First human cardiac application was described in 8 patients for the indication of heart failure using CardioFit stimulators.[114] Subsequent human trials for heart failure have shown mixed results. ANTHEM-HF, a nonblinded trial for NYHA II–III patients with EF <40%, showed improvements in NYHA class and EF.[115] NECTAR-HF was a randomized blinded study, which showed no improvements with VNS with respect to objective parameters, such as EF, but improved clinical parameters such as NYHA class.[116] INOVATE-HF was a randomized study that further showed no benefit of mortality or worsening HF in NYHA III patients with EF ≤40%.[117] In many ways, vagal nerve stimulation trials for heart failure share parallel lessons to the negative trials of spinal cord stimulation. As mentioned above, the vagosympathetic trunk contains both parasympathetic and sympathetic as well as afferent and efferent nerves. Different stimulation parameters can differentially engage these fibers[118] and the effects of VNS is significantly increased when the vagosympathetic trunk is transected in animal studies,[119,120] demonstrating the powerful effects of afferent fiber activation on efferent effects. In addition, a case of a patient experiencing an increase in ventricular arrhythmias after VNS has been reported.[38] Therefore, the stimulation parameters used can significantly affect the outcomes of VNS and may account for the mixed human clinical trial results. With better characterization of the optimal dose of stimulation, VNS remains a promising option to apply to reduce VT/VF.

Tragus Nerve Stimulation—A less invasive method of stimulating the parasympathetic nervous system has been performed using tragus nerve stimulation.[86] A flat electrical clip is applied to the tragus, the anterior protuberance of the outer ear, and electrical stimulation is applied to the auricular branch of the vagal nerve. Much of the data on tragus nerve stimulation has focused on its beneficial effects for atrial fibrillation and atrial arrhythmias.[121] In addition, chronic tragus nerve stimulation in a canine model of healed myocardial infarction demonstrated improved left ventricular remodeling.[122] A randomized trial of 40 patients demonstrated that tragus nerve stimulation suppressed pacing-induced atrial fibrillation, increased cycle length of atrial fibrillation, and decreased inflammatory cytokines.[123] TREAT-AF trial will study the effects in a larger population.[124] It is possible that the anti-inflammatory and cardiac remodeling effect of tragus nerve stimulation could prove useful in treatment of heart failure and ventricular arrhythmias.

Baroreceptor Activation Therapy—Baroreflex sensitivity is significantly reduced in setting of the heart failure and patients with decreased baroreflex sensitivity have an increased risk of SCD.[125,126] Baroreceptor activation therapy (BAT) via electrical stimulation of the carotid bodies augments vagal tone[127] and decreases sympathetic outflow.

[128] At the intrathoracic level, BAT attenuated left stellate ganglia electrical activity (amplitude and frequency) in setting of canine ischemia.[129] At the level of the intrinsic cardiac ganglia, BAT reduced anterior right ganglionated plexus electrical amplitude and frequency, decreased ability of the superior left ganglionated plexus to reduce sinus slowing, and reduced AF in dogs.[130] In canine models of ischemic cardiomyopathy, BAT has decreased ventricular arrhythmias, decreased slope of APD restitution, and lengthened ventricular ERP.[129,131,132] BAT has also been shown to decrease ischemia driven inflammation, oxidative stress, and apoptosis and improve connexin-43 levels. Current human data has focused on the use of BAT for treatment of hypertension and heart failure.[133] A phase III trial of the Rheos BAT system which stimulates bilateral carotid bodies for resistant hypertension has shown mixed results, failing to achieve prespecified endpoints but able to improve proportion of patients with SBP < 140 mmHg. The primary risk with this procedure was cranial nerve injury resulting in dysphonia, dysphagia, and localized numbness in 4.8% of patients.[134] Phase II trial results for resistant hypertension using Barostim, a smaller device with unilateral stimulation of the right carotid body, has shown similar reductions in blood pressure without significant cranial nerve injury.[135] Barostim in heart failure patients with NYHA III and EF ≤35%, showed improvements in NYHA class, 6 minute walk, and quality of life scores.[136] Although BAT has not been used for treatment of ventricular arrhythmias, its potential promise for treatment of heart failure could lead to a reduction in ventricular arrhythmias. Refer to figure 4 for summary of neuraxial modulation targets and their relationship to the levels of cardiac innervation. The level of evidence of translating these various modalities from benchside to bedside are summarized in figure 5.

Conclusion

Autonomic cardiac innervation plays a significant role in sudden cardiac death, modulating the fabric of cardiac excitability and propagation. Significant neural remodeling in the setting of heart disease predisposes to malignant ventricular arrhythmias by causing alterations at the level of the myocardium, the intrinsic cardiac ganglia, extra-cardiac intrathoracic sympathetic ganglia, extra-thoracic ganglia, spinal cord, and the brainstem, as well as the higher centers and the cortex. Therapeutic strategies at each of these levels have been used to restore the balance between the sympathetic and parasympathetic branches of the autonomic nervous system. Detailed characterization of this complex neural network will provide further important therapeutic insights into the treatment of sudden cardiac death.

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Key Points

1. Cardiac neural control occurs at multiple levels, and each level has the capability to receive afferent neurotransmission and control efferent outflow to the heart.
2. Sympathetic nervous system activation in myocardial infarction increases VT/VF by providing both of the ingredients required for arrhythmogenesis: increased myocardial excitability and heterogeneous repolarization predisposing to reentry.
3. Myocardial infarction remodels the sympathetic nervous system such that sympathetic activity is amplified, promoting VT/VF.
4. Strategies for neuraxial modulation have aimed at decreasing sympathetic activity and augmenting parasympathetic tone, at various levels of cardiac neural control.
5. Autonomic modulation has progressed from basic science to animal studies and human studies, though in clinical trials, some therapies have had mixed results.

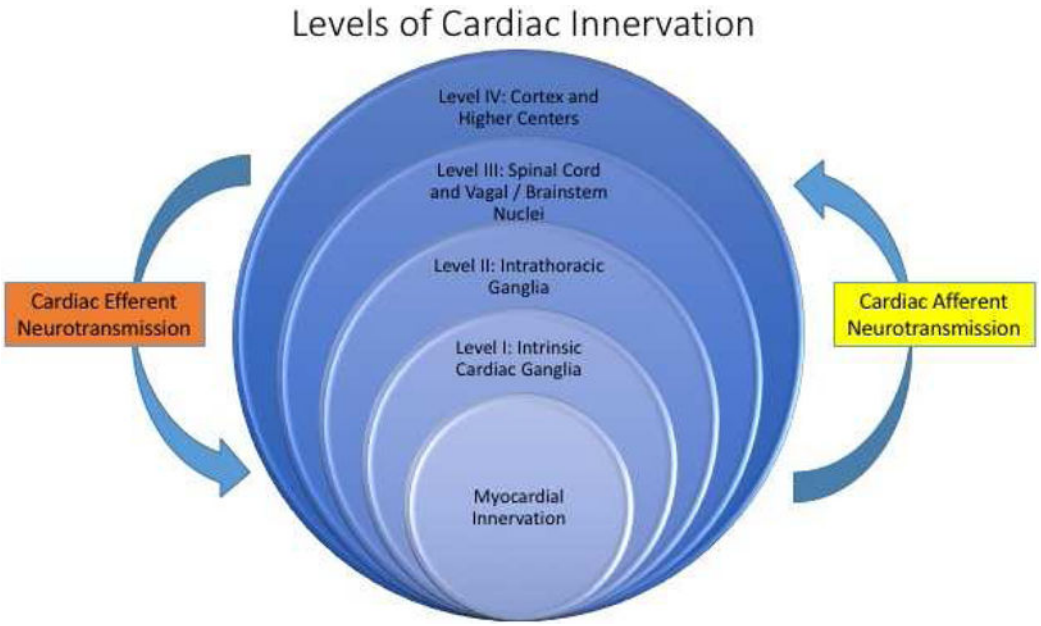

Figure 1.

Cardiac neural control occurs at multiple levels, and each level has the capability to receive afferent neurotransmission and control efferent outflow to the heart (directly or indirectly). Level I represents the intrinsic cardiac ganglia, located in the fat pads of the epicardium. Level II includes the stellate, middle cervical, and thoracic ganglia. Level III includes the spinal cord, vagal nerve and brainstem nuclei. Level IV represents cortex and higher centers. Each level also demonstrates parallel processing of neural information.

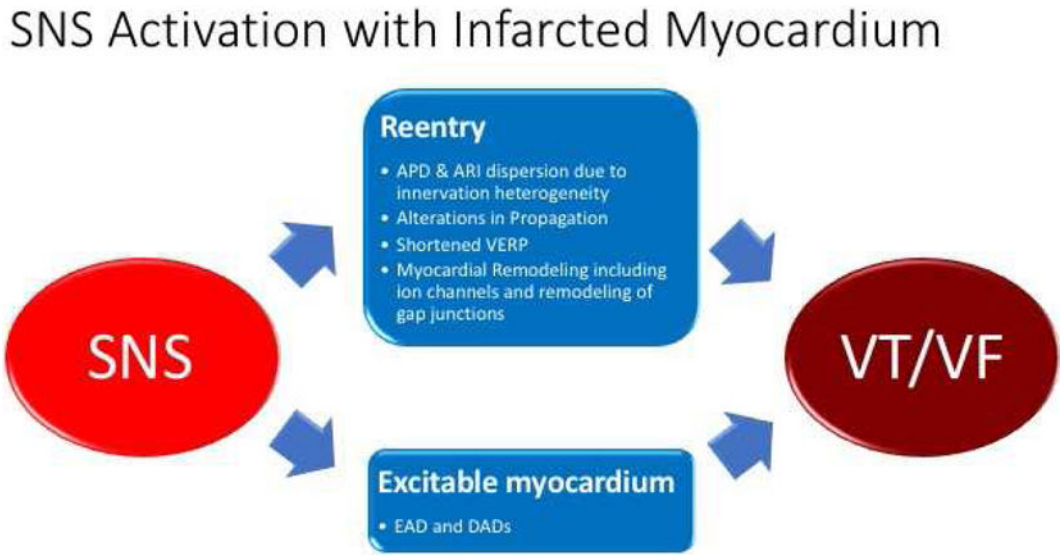

Figure 2.

Sympathetic nervous system activation in the setting of myocardial infarction increases the risk of VT/VF by modulating the two primary criteria needed for initiation of arrhythmias, including conduction velocity and repolarization. Therefore, sympathetic activation creates both more excitable myocardium by initiating EADs and DADs and creates a substrate that is more likely to promote reentry. SNS: Sympathetic Nervous System, APD: action potential duration, ARI: activation recovery interval, VERP: ventricular effective refractory period, EAD: early after depolarization, DAD: delayed after depolarization

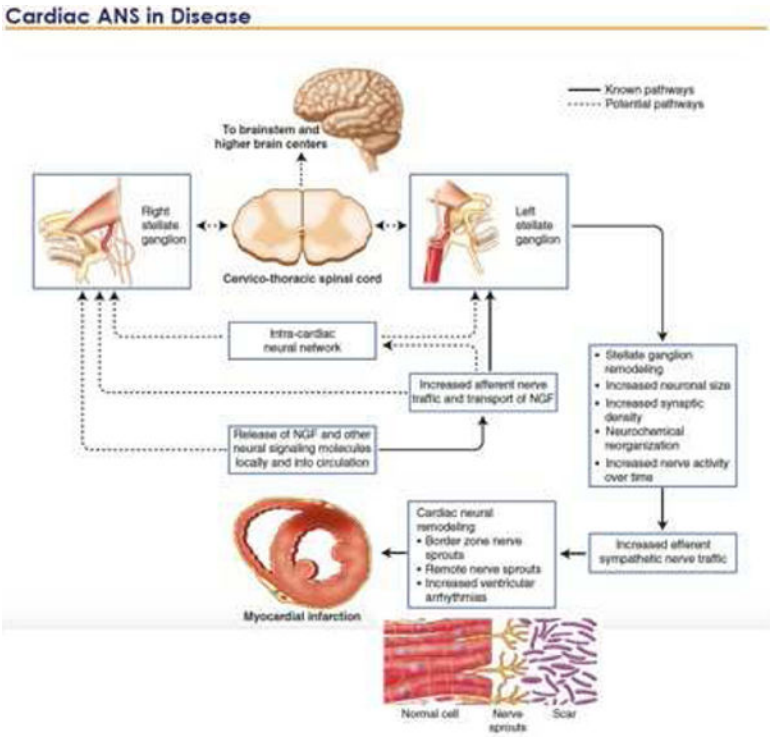

Figure 3.

Effects of myocardial infarction on the cardiac sympathetic system. Infarcted myocardium stimulates release of signaling molecules including NGF that promote remodeling of the afferent and efferent nervous system such that sympathetic nervous activity is amplified. Remodeling of the nervous system occurs at all levels, including the intrinsic cardiac ganglia, the thoracic ganglia, and the higher centers. This along with denervation and nerve sprouting at the myocardial level further amplify the substrate heterogeneity and ultimately increases risk of VT and VF. Adapted from Dilsizian V. *Atlas of cardiac innervation.* New York, NY: Springer Science+Business Media; 2016 (with permission).

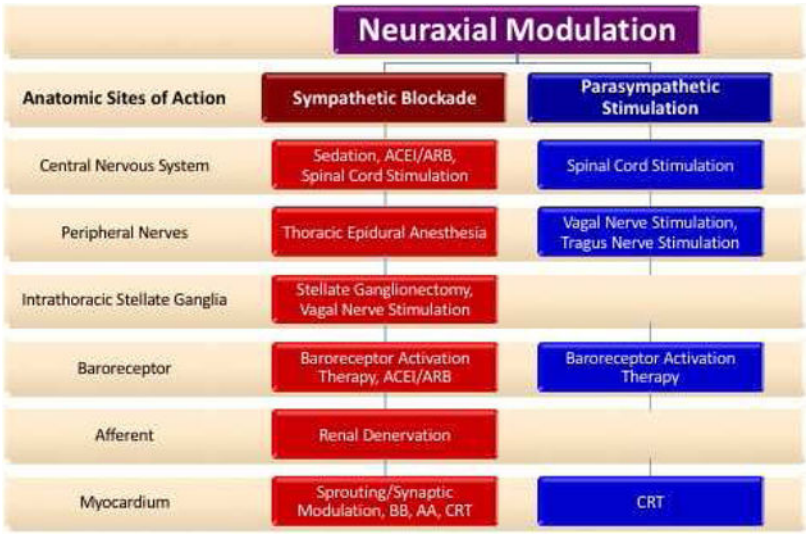

Figure 4.

Neuraxial modulation can be targeted at multiple levels of the cardiac autonomic nervous system, from the central nervous system to neuro-myocardial junction. Therapeutic goals generally include decreasing sympathetic activity and augmenting parasympathetic activity. BB: Beta blocker, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, AA: aldosterone antagonist, CRT: cardiac resynchronization therapy

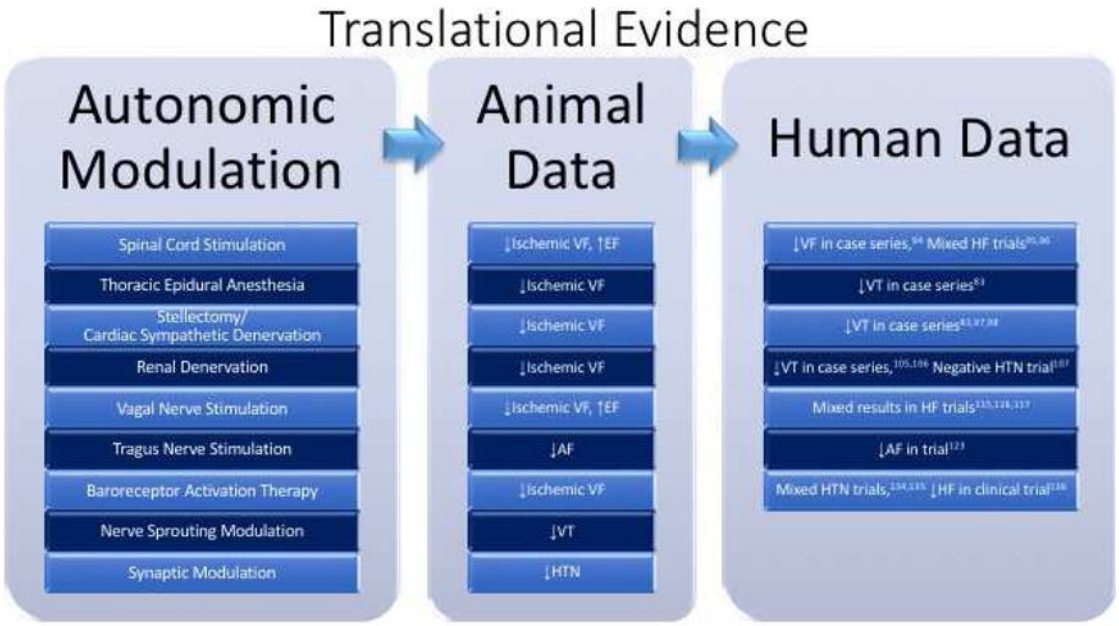

Figure 5.

Autonomic modulation therapies have translated from basic research to animal studies and human studies, though in clinical trials, some therapies have had mixed results. VF: ventricular fibrillation, EF: ejection fraction, HF: heart failure, HTN: hypertension, AF: atrial fibrillation