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The Autonomic Nervous System and Ventricular Arrhythmias in Myocardial Infarction and Heart Failure

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Abstract

Ventricular arrhythmias (VA) can range in presentation from asymptomatic to cardiac arrest and sudden cardiac death (SCD). Sustained ventricular tachycardia/ventricular fibrillation (VT/VF) are a common cause of SCD, accounting for up to 48% of cases in a recent prospective study of out-of-hospital sudden cardiac arrests.¹ The incidence of VT associated with myocardial infarction (MI) ranges between 3.2% and 5.7%, and in association with left ventricular dysfunction.^{2,3,4} These studies highlight a particularly arrhythmogenic cardiac syncytia in the setting of coronary syndromes and heart failure. In this review, we outline the components of the cardiac autonomic nervous system (ANS) that play an important role in normal cardiac electrophysiology and function. In addition, changes that occur in the setting of cardiac disease including adverse neural remodeling and neurohormonal activation, which significantly contribute to propensity for VT/VF are discussed.

Keywords

sympathetic; ventricular arrhythmia; vagus; heart failure; autonomic

ANATOMY AND PHYSIOLOGY OF THE AUTONOMIC NERVOUS SYSTEM

The cardiac autonomic nervous system controls every aspect of cardiac function and is often divided into two separate arms, the sympathetic and parasympathetic nervous system. These branches, when activated, tend to have opposite effects on cardiac electrophysiology. While a “traditional view” of the autonomic nervous system focuses on these opposing branches, our current understanding has evolved to include interactions between these two arms as well as integration and processing of data at multiple levels of control. Myocardial innervation is conserved to a significant degree across different species.^{5–7} This inter-species similarity allows for extrapolation of data from animal studies that have shaped the current understanding of the autonomic nervous system in humans.

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Cardiac autonomic neural processing occurs at several levels: the intrinsic cardiac and extracardiac ganglia, spinal cord, and the brain.⁶ The extracardiac ganglia include the extracardiac intrathoracic ganglia (sympathetic ganglia of the sympathetic chain) and extrathoracic dorsal root and the nodose/vagal ganglia. While the dorsal root and vagal ganglia consist of afferent sensory neurons, the stellate ganglia may contain interneurons responsible for processing of information from the heart as well as inputs from the spinal cord and brainstem. The sympathetic and parasympathetic nervous systems interact at each level, including at the intrinsic cardiac ganglia, stellate ganglia, spinal cord, brainstem, as well as the higher centers of the brain to fine-tune autonomic control. Finally, sympathetic and parasympathetic neurotransmitters and neuropeptides interact at the level of the nerve-myocyte interface. Both of these arms of the ANS feed back onto receptors located on their own axons and on synapses of the opposite arm of the nervous system to alter subsequent neurotransmitter/neuropeptide release profiles. However, specific details of many of these interactions remain to be elucidated.

It's important to note that the cardiopulmonary nerves to the heart carry both efferent and afferent nerve fibers. While efferent nerve fibers are responsible for neurotransmission from the nervous system to the heart, afferent fibers transmit signals up the neuraxis from the heart.

Parasympathetic and Sympathetic Efferent Innervation

Preganglionic neurons of the parasympathetic nervous system originate in the left and right nucleus ambiguus and dorsal motor nucleus in the medulla oblongata and project their axons to the heart via the vagal trunk.^{8,9} These axons further subdivide into intrathoracic cardiopulmonary branches, that terminate on the post-ganglionic neurons of the intrinsic cardiac ganglia and release acetylcholine. Acetylcholine acts on nicotinic acetylcholine receptors on the efferent postganglionic intrinsic cardiac neurons,¹⁰ which receive inputs from both left and right vagal trunks. Anatomic dissection in canines demonstrated that the neurons originating in a ganglionated plexus next to the right pulmonary veno-atrial junction terminate in the sinoatrial (SA) node while those located predominantly in the region adjacent to the inferior vena cava-inferior atrial junction influence the atrioventricular (AV) node.¹¹ However, the exact regions of innervation for each of the intrinsic cardiac ganglia and the information that is exchanged between these ganglia remains to be determined. Axons of post-ganglionic parasympathetic neurons innervate the atria and ventricles and can alter activation, electrical conduction, and effective refractoriness of atrial, nodal, and ventricular myocytes via muscarinic acetylcholine receptors on myocytes.

In normal hearts, parasympathetic activation results in negative chronotropy, inotropy, and dromotropy of the ventricles.^{12–15} It decreases rate of diastolic depolarization which decreases discharge of the SA node and slows AV nodal conduction to decrease heart rate. Finally, vagal stimulation prolongs action potential duration and effective refractory period in the ventricles,^{12,13,16} which can be anti-arrhythmic.

Preganglionic cardiac efferent neurons of the sympathetic nervous system (SNS) originate in the intermediolateral cell column of the spinal cord and project via C7-T4 rami onto the extracardiac sympathetic ganglia neurons, including middle cervical, stellate, and T1-T4

thoracic ganglia of the sympathetic chain. Preganglionic to post-ganglionic neurotransmission occurs via nicotinic acetylcholine receptors. Axons from postganglionic efferent neurons synapse on the atrial and ventricular myocardium, releasing primarily norepinephrine along with other sympathetic neuropeptides. There may also be neurons in the intrinsic cardiac ganglia that receive sympathetic inputs. Sympathetic myocardial innervation is most dense in the atria, while ventricular sympathetic innervation is most dense at the base of the heart.¹⁷ Beyond the thoracic ganglia, the brainstem and higher brain centers can also control sympathetic outflow. For example, the nucleus of the solitary tract (NTS) in the medulla oblongata serves as a crucial junction in both afferent and efferent signaling. The NTS sends projections to the caudal ventrolateral medulla which in turn, via projections to the rostral ventrolateral medulla, can control sympathetic output to intermediolateral spinal cord and the heart.^{18,19} Direct stimulation of the RVLM produces elevations in sympathetic activity, resulting in hypertension, tachycardia, and increase in catecholamine levels.¹⁹ In addition, there is new functional evidence in humans that other midbrain circuits, particularly the subthalamic nucleus²⁰ and periaqueductal grey,²¹ also contribute to modulation of sympathetic outflow. Systemically, neurohormonal activation due to sympathetic stimulation leads to release of epinephrine, and to a lesser extent, norepinephrine from the adrenal medulla and activates the renin-angiotensin-aldosterone system in the kidneys.

In the normal heart, sympathetic stimulation results in increases in positive chronotropy, ionotropy, and dromotropy. Sympathetic catecholamines increase rate of spontaneous diastolic depolarization due to funny channels (I_f), which accounts for automaticity of SA and AV nodes, and increase the chances that I_f channels open, increasing the slope of phase 4 in the SA node, leading to increases in heart rate. Contractility is increased in myocytes due to beta-adrenergic receptor activation which leads to increased influx of calcium into myocytes. Finally, sympathetic stimulation acts on both atrial and ventricular myocytes to activate other channels, including the inward sodium current, delayed rectifier potassium current, chloride current, and pacemaker current.²² Stimulation of the middle cervical as well as the right and left stellate ganglia decreases action potential duration and refractory period in the ventricles, increases dispersion of repolarization,^{23–25} and promotes AV nodal conduction.²⁶ Notably, sympathetic stimulation increases T-peak to T-end interval on the surface ECG, a marker for SCD.²³ Both stellate ganglia provide innervation to the ventricular myocardium.^{25,27}

Afferent Innervation

Afferent fibers transmit information from the heart to the neurons of the intrinsic cardiac nervous system (ICN), the sympathetic ganglia in the sympathetic chain, and via the dorsal root ganglia and nodose ganglia to the spinal cord and brainstem, respectively. Afferent information is processed at multiple levels throughout the ANS and subsequently affects efferent output to the heart.^{28–30} Therefore, afferent innervation is relatively distinct from efferent innervation but uses the same “highways” for neurotransmission. Cardiovascular reflexes are also modulated via arterial chemoreceptors and mechanoreceptors, including baroreceptors, which can alter sympathetic and parasympathetic output by sensing pressure changes via neurons of the nodose and petrosal ganglion.^{31–33}

Intrinsic Cardiac Nervous System

The intrinsic cardiac nervous system consists of nine main ganglionated plexi located in epicardial fat pads,³⁴ consisting of between 700–1500 epicardial ganglia.³⁵ These ganglia form a complex neural network involving afferent neurons, interneurons, and cholinergic and adrenergic efferent neurons.³⁴ This network of ganglia processes signals at the level of the heart, receiving and integrating inputs from the thoracic sympathetic postganglionic and vagal preganglionic fibers. In this regard, they control both cardiocentric local reflexes, coordinating cardiac function, and are modulated by information received from the brainstem and spinal cord.^{35–37}

PATHOPHYSIOLOGY OF VENTRICULAR ARRHYTHMIAS IN HEART DISEASE

With the exception of cardiac channelopathies, where specific mutations predispose to occurrence of VT/VF, ventricular arrhythmias occur in the setting of myocardial injury or scar due to MI, nonischemic cardiomyopathy, and adult congenital heart disease. The presence of myocardial scar and fibrosis contributes to neural remodeling, which predisposes to VT/VF.³⁸

VA in the Setting of Myocardial Infarction

The role of the autonomic nervous system, and more specifically, sympathetic nervous system in occurrence of VT/VF is well-established. Myocardial injury and infarction lead to cardiac sympathetic afferent activation, which in turn increases cardiac sympathetic outflow to the heart via the stellate, middle cervical, and thoracic sympathetic ganglia, figure 1. Whole ganglion recordings in canines found that spontaneous sympathetic nerve discharge from LSG immediately preceded VF and SCD.³⁹ The effects of sympathetic stimulation are amplified and the threshold for VF is further reduced in the setting of acute ischemia. Studies in cats and canine models of ischemia revealed that sympathetic stimulation creates both the electrophysiological substrate and the trigger for VT/VF by reducing action potential duration, increasing dispersion of repolarization, and causing early after depolarizations (EADs) and delayed after depolarizations (DADs), table 1.^{40–42} Action potential shortening and increased dispersion of repolarization (as also evidenced by increased T-peak to T-end interval) have been demonstrated in chronic porcine infarct models as well, in response to sympathetic nerve stimulation.^{43,44}

Inflammation and ischemia also injure axons of the autonomic nerves, resulting in denervation. Ischemia and myocardial injury are followed by scar formation. Studies in canine models of MI and humans undergoing catheter ablation for recurrent VA demonstrate that denervation is observed within the infarcted myocardium as well as nearby viable myocardium.^{45,46} As a result, over time, denervation super-sensitivity develops, so that infusion of catecholamines results in even greater shortening and heterogeneity of action potential duration at denervated sites, resulting in increased dispersion of repolarization.^{46,47} Combined with heterogeneous electrical activation and refractoriness observed with sympathetic nerve stimulation,⁴⁸ denervation super-sensitivity further contributes to

development of VA in the setting of MI. Increased areas of denervation are associated with increased ICD therapies and VT in patients with ischemic cardiomyopathy.⁴⁹

Sympathetic axonal damage that results from the acute injury is followed by the attempt of peripheral neurons to regrow neurites. The autonomic ganglia have the capability to grow axons as long as their cell bodies remain intact. However, this process, which results in localized nerve sprouts at border-zones of infarcts,^{50,51} is incomplete, likely as a consequence of the proteoglycans produced within the scar that prevents normal reinnervation of these regions.⁵² Localized nerve sprouting potentially further exacerbates the heterogeneity in activation and repolarization during sympathetic activation and leads to VT/ VF and SCD. Nerve sprouts have also been observed in explanted human hearts of patients undergoing transplantation. Compared to patients with similar structural heart disease but no history of VA, patients with history of VA were found to have augmented sympathetic nerve sprouting at the border zones of scars.⁵¹ Nestin-expressing neural stem cells have been found in myocardial scars, suggesting recruitment of stem cells may contribute to nerve sprouting in regions of infarct.⁵³

The neural remodeling that accompanies myocardial injury affects intrinsic cardiac neurons, resulting in both structural and functional changes in these ganglia.⁵⁴ In addition, in canine and porcine models of chronic MI nerve density and neuronal size are increased in bilateral stellate ganglia and phenotypical changes in neuropeptides and neurotransmitters are observed, including an increase in neuropeptide Y, irrespective of site of MI.^{55,56} Likewise, stellate ganglia from humans with cardiomyopathy and refractory VAs exhibits excessive inflammation, oxidative stress, a shift in neurochemical profile and satellite glial cell activation when compared to controls, demonstrating ongoing pathologic remodeling within the extracardiac sympathetic pathways.⁵⁷ Finally, histological changes, including changes in neuropeptide levels, have been noted in the nodose ganglion as well as other sensory ganglia.⁵⁸

In the setting of heterogeneity in sympathetic innervation and pathological neural remodeling that accompanies a heterogeneous myocardial substrate, effects of sympathetic activation are further amplified leading to greater heterogeneity in APDs and areas of functional conduction block and promoting reentry, figure 2.^{25,59}

In addition to sympathoexcitation, after MI and myocardial injury, parasympathetic dysfunction occurs, further predisposing to VT/VF.^{60,61} The mechanisms behind this dysfunction, which persist long after the acute event, remain to be elucidated. It is known that parasympathetic afferent neurotransmission from aortic and carotid baroreceptors are reduced, figure 1, potentially due to decreased blood pressure and cardiac output. This in turn seems to decrease central parasympathetic drive, figure 1. The role of cardiac afferent neurotransmission in parasympathetic function is still under investigation.⁵⁸ Inhibition of acetylcholine release may also occur at the nerve-myocyte interface by the high levels of norepinephrine,⁶² as well as sympathetic neuropeptides such as neuropeptide Y,^{63–65} though this area remains in need of further investigation.

VA in Heart failure

Significant myocardial scar formation leads to heart failure, characterized by a reduced cardiac output and increased myocardial stretch. In addition to the cardiac and extracardiac neural remodeling mentioned above, these changes further cause activation of sympathetic afferent fibers, which effectively increase sympathetic efferent outflow, and potentially reduce parasympathetic afferent neurotransmission from the carotid and aortic baroreceptors, decreasing vagal tone, figure 1. This chronic sympathetic activation is supported by studies showing increased cardiac norepinephrine spillover in cardiac veins in heart failure.^{66,67} There is also indirect evidence for parasympathetic tone withdrawal and dysfunction, as manifested by abnormal heart rate variability and baroreflex sensitivity. Abnormalities in these variables do portend a significantly increased risk of SCD.^{68,69} As with after MI, many of the mechanisms that lead to parasympathetic dysfunction in heart failure still remain to be elucidated, but may be related to afferent signaling or increased sympathetic neurotransmitter or co-transmitters reducing acetylcholine release at the nerve-myocyte interface.

In addition to pathological neural remodeling associated with myocardial scar formation described above, decreased cardiac output and blood pressure in heart failure are sensed by the afferent sympathetic nerve fibers of the kidneys, leading to persistent neurohormonal activation, including activation of the renin-angiotensin-aldosterone system (RAAS), figure 1. There is a significant positive relationship between mortality and levels of angiotensin II, aldosterone, and circulating catecholamines.⁷⁰ Studies in animal models have found a direct relationship between increased angiotensin converting enzyme activity in the ventricles and degree of ventricular dilatation.⁷¹ Aldosterone has direct proinflammatory effects and leads to interstitial and perivascular fibrosis as well as hypertrophy, figure 2.⁷² The chronic upsurge in RAAS activity leads to fibrosis and alterations in gap junction,⁷³ which, within the context of elevated catecholamine levels and altered conduction, exacerbates dispersion of repolarization and electromechanical feedback, figure 2. Finally, release of angiotensin II directly promotes ventricular arrhythmias not only due to loss of urinary potassium and magnesium, but also by directly increasing catecholamine release from nerve endings, including release of norepinephrine, by activation of prejunctional angiotensin II receptors.^{74,75}

EFFECTS OF NEUROMODULATION ON VENTRICULAR ARRHYTHMIAS

Various approaches for neuromodulation have been investigated to prevent or treat VT/VF in heart disease. In addition to pharmacological blockade with beta-adrenergic receptor blockers, angiotensin blockers and aldosterone antagonists, ongoing efforts are investigating methods that stimulate parasympathetic pathways (vagal nerve stimulation, low-level baroreceptor stimulation and spinal cord stimulation) and interrupt sympathetic outflow to the heart (left or bilateral stellate ganglion denervation and renal sympathetic denervation)

Increasing Parasympathetic Drive

Parasympathetic activation is antiarrhythmic and vagal nerve stimulation has been shown to improve survival in animal models of cardiac ischemia, if started at the time of coronary

artery occlusion.^{76–78} Improved baroreflex sensitivity, a marker of parasympathetic function, is associated with reduced mortality in patients with MI.⁶¹ Clinical trials of vagal nerve stimulation in the setting of heart failure have resulted in mixed findings. It is important to note that effects of electrical stimulation of the vagus nerve are frequency and current dependent. A study in canines outlined the importance of stimulation parameters by evaluating heart rate responses after delivering a combination of five frequencies (2, 5, 10, 15 and 20 Hz), four pulse widths (130, 250, 500 and 750 μ s) and fourteen intensities ranging from 0.25 to 3.50 mA in 0.25 mA increments with a 17.5% duty cycle and titrations over 14 months.⁷⁹ The study found that balancing afferent and efferent fiber activation could result in a null heart rate response approaching zero. This “neural fulcrum” may be useful in guiding stimulation parameters in different disease states and in finding a therapeutic target zone where there is optimal reduction of VAs with limited adverse effects. Also notable is that high intensity VNS can lead to heart block and emergence of idiopathic ventricular arrhythmias.^{79,80} Higher frequencies at lower currents can activate selective afferent fibers and lead to a tachycardia response.^{13,79} Therefore, when using electrical stimulation of the vagus to increase parasympathetic outflow, parameters must be carefully chosen.

In this regard, in the chronic MI porcine model, vagal nerve stimulation (10 Hz, 1ms, 15 seconds “on”, 15 seconds “off”) at just above the neural fulcrum increased action potential duration and refractory period, reduced dispersion of repolarization along border zone regions,⁸¹ and decreased VT/VF inducibility, benefits that were observed even after cardiac sympathetic denervation.⁸² In addition, parasympathetic activation leads to release of nitric oxide,⁸³ reduces VF threshold,⁸⁴ and reduces cardiac oxygen demand, further improving cardiac function, table 1.⁸⁰

Baroreceptor stimulation, also known as baroreceptor activation therapy (BAT), targets baroreceptors at the carotid sinus, and aims to increase parasympathetic afferent activity to augment vagal tone, leading to drop in blood pressure and heart rate. Since strong stimulation of baroreceptors may induce dramatic hemodynamic fluctuations and atrial arrhythmias by activating the vagal nerve, studies often use low level carotid baroreceptor stimulation (LL-CBS) where voltage is below the threshold for blood pressure and heart rate changes. In canine studies in the post-infarct period, LL-CBS resulted in changes in nerve activity and heart rate variability with protection from VAs.⁸⁵ Likewise, studies in canines with pacing-induced heart failure found that carotid baroreceptor stimulation also had effects on electrophysiologic properties and autonomic remodeling as well as ionic remodeling, with more pronounced effect when moderate-level carotid baroreceptor stimulation (ML-CBS) was used.⁸⁶ A recent study in HFrEF patients, Baroreflex Activation Therapy for Heart Failure (BEAT-HF), found that BAT using a surgically implanted stimulating electrode led to improved quality of life and functional capacity, as well as reductions in heart rate and cardiac remodeling. The level of carotid stimulation that is safe in patients and whether or not endpoints may also identify a reduction of VAs remains to be seen.

Spinal cord stimulation (SCS) is another method that has been tried to decrease sympathetic activation and increase vagal tone. In canine models of MI, SCS applied at 50 Hz with 200- μ s pulse width to T1-T5 spinal cord level for 1 hour was found to prolong the ventricular refractory period, attenuate LSG activity, and reduce VF/VT incidence.⁸⁷ In a porcine

ischemia-reperfusion model, SCS at similar settings was found to improve myocardial function and reduce VAs.⁸⁸ SCS has also been shown to improve left ventricular function and decrease incidence of VAs in canines with healed MI and pacing-induced HF.^{89,90} Two studies of SCS in heart failure patients performed stimulation at frequency of 50 Hz with 200- μ s pulse width for 12 hours a day at the T1-T3 level (SCS HEART) or at the T2-T4 level (DEFEAT-HF).^{91,92} However, the SCS HEART trial, which was a first in-human study, did not measure endpoints of reduced VAs. The DEFEAT-HF trial did not find significant differences of VA episodes when compared to SCS-off patient group. This may be attributed to a variety of factors, including differences in mode of stimulation or delivery. Further studies are warranted to investigate this neuromodulation technique specifically for treatment of VAs in humans.

Blockade of Sympathetic Neurotransmission

Blockade of sympathetic outflow from the stellate and cardiac sympathetic ganglia has traditionally been achieved through several methods ranging from the surgical approach with cardiac sympathetic denervation (CSD) in humans to less-invasive blockade with anesthetics, and kilohertz (kHz) frequency block tried in animal models. Techniques for modulation at this level of the ANS with electromagnetic fields (EMF) and optogenetics have also been tried but remain experimental. A canine study found reduced incidence of ischemic-induced VAs when low-frequency EMF was applied to the LSG area at 1 Hz, with 8 seconds “on”, 10 seconds “off” and intensity at about 90% of motor threshold.⁹³ A similar finding was found using optogenetic techniques, which combines optical stimulation and genetic modification of target cells, to suppress genetically modified LSG neuronal activity in canines.⁹⁴ In the clinic setting, bilateral CSD has been successful in prevention of HF-associated VT or VF storms and may have more prolonged and durable effect on VA suppression when compared to LSG denervation alone.⁹⁵ In a study of 121 patients from 5 international sites with structural heart disease and recurrent VT, CSD decreased sustained VT and ICD shock recurrence and approximately one-third of patients no longer took antiarrhythmic medications on follow up.⁹⁶ The observed benefit in these high-risk patients supports the need for prospective randomized clinical trials to better characterize the impact of this therapy.

Ablation along the renal arteries affects both renal sympathetic afferent and efferent fibers, that in turn seem to downregulate efferent sympathetic output to the heart and decreased VA threshold.^{56,97} Renal sympathetic denervation (RSD) decreases myocardial sympathetic effectors and rates of spontaneous VAs in porcine models of ischemia.^{98–100} In a canine study of myocardial ischemia, RSD led to decreased whole-body and local tissue sympathetic activity and reversed neural remodeling in the heart and stellate ganglion.¹⁰¹ This resulted in beneficial electrophysiological changes in border zones of infarcts, culminating in decreased VAs.¹⁰¹ There have also been a few small studies in patients with refractory VAs or VT storm that showed a reduction in VAs after RSD. A study of 32 patients with refractory VAs found a significant reduction in VA burden, ICD shocks, and anti-tachycardia pacing (ATP) therapy with catheter ablation combined with adjunctive RSD when compared to catheter ablation alone, without significant differences in mortality between the two groups.¹⁰² In another study of 10 patients with cardiomyopathy who

underwent RSD as an adjunctive therapy to CSD for refractory VT, ICD therapies were significantly reduced.¹⁰³ However, careful mechanistic studies are still needed to define the role of RSD before large randomized clinical trials can be safely initiated to investigate long-term efficacy and safety profile for this intervention.

CONCLUSIONS

There is important evidence for the role of the important autonomic nervous system in occurrence of VT and VF. Sympathetic activation and parasympathetic dysfunction are important factors that increase the risk of VA and lead to sudden cardiac death in the setting of MI and heart failure. The sympathetic nervous system is vital in providing both the triggered activity (the fire) and heterogeneity in repolarization (the fuel) required for initiation and persistence of VT, while appropriate augmentation of the parasympathetic nervous system can increase refractory period and decrease dispersion of repolarization to reduce VT/VF. Therefore, neuromodulation is an obvious target for treatment of ventricular arrhythmias. However, the autonomic nervous system comprises of multiple levels of feedback loops that undergo remodeling in the setting of myocardial injury, and the cardiac autonomic nerves represent mixed nerves, containing both efferent and afferent as well as myelinated and unmyelinated fibers. The success of neuromodulatory therapies, therefore, will depend on a critical understanding of the effects of blockade or stimulation of specific ganglia and fibers. A deeper understanding of specific sympathetic and parasympathetic interactions is needed in order to tip the balance toward mitigation of electrical heterogeneity and triggered activity and reduce ventricular arrhythmias beyond current therapies.

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Figure 1. Autonomic efferent and afferent neurotransmission in setting of myocardial infarction and heart failure.

In the setting of MI and heart failure, parasympathetic afferent neurotransmission from the aortic and carotid baroreceptors is reduced, likely due to decrease in cardiac output, which in turn reduces central parasympathetic drive to neurons of the intrinsic cardiac ganglia. On the other hand, decreased cardiac output and blood pressure leads to activation of both cardiac sympathetic and renal sympathetic afferents, which in turn, increased cardiac sympathetic efferent outflow to the heart via the post-ganglionic sympathetic thoracic ganglia. In addition, sympathetic afferent activation leads to activation of sympathetic post-ganglionic

fibers to the kidneys, which causes the release of renin as well as increased catecholamine release via activation of the preganglionic adrenal sympathetic efferents. Catecholamine release via the adrenals is approximately 2/3 epinephrine (E) and 1/3 norepinephrine (NE). Renin in turn leads to release of aldosterone from the adrenal cortex (not shown) and hydrolyzes angiotensinogen to angiotensin I (ATI), which is cleaved in the lungs to angiotensin II (ATII). ATII causes vasoconstriction as well as fibrosis and increased release of catecholamine from sympathetic nerve endings. ++ indicates increased neurotransmission; – – indicates decreased neurotransmission.

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Figure 2.

Both cardiac and renal/adrenal autonomic dysregulation in heart failure and MI contribute to the propensity for ventricular arrhythmias. Increased dispersion of repolarization, areas of altered conduction and functional block due to heterogenous denervation and reinnervation, as well as EADs and DADs due to sympathetic activation create both the trigger and substrate for ventricular arrhythmias. In addition, anti-arrhythmic effects of parasympathetic activation are significantly reduced due to decreased central drive (as manifested by decreased baroreceptor sensitivity and heart rate variability) and peripheral inhibition of

acetylcholine release by sympathetic neurotransmitters and, possibly, neuropeptides. Contributing to the arrhythmic substrate is release of catecholamines by the adrenal gland which can further exacerbate electrical heterogeneity as well as release of aldosterone and angiotensin II, which can lead to increased fibrosis and gap junction remodeling, further disruption electrical conduction and creating the substrate for reentry. HR = heart rate; ATII = angiotensin II; ACh = acetylcholine; NE = norepinephrine

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Table 1:

Sympathetic versus parasympathetic cardiac electrophysiological effects

Cardiac Parameter	Sympathetic Activation	Parasympathetic Activation	Potential mechanisms
Chronotropy (heart rate)	↑	↓	SNS: Increased SA node phase 4 slope due increased L-type Ca and I _f currents. PSNS: Less steep phase 4 slope from increased magnitude of ligand-gated K current.
Ventricular action potential duration and refractory period	↓	↑	SNS leads to release of NE and beta-adrenergic receptors. Role of co-transmitters unknown. PNS releases ACh which inhibits NE release and may also increase APD by muscarinic receptor activation.
Automaticity	↑	↓	SNS mediated release of NE and beta-adrenergic receptor activation. Role of co-transmitters unknown. PNS releases ACh which inhibits NE release and may also increase APD by muscarinic receptor activation.
Dispersion of repolarization	↑	↓	SNS: causes heterogeneity in repolarization in infarcted hearts PNS: reduces DOR by reducing dispersion in border zone of infarcts
Afterdepolarizations (EADs and DADs)	↑	↓	SNS: causes calcium overload PNS: reduces calcium entry

SNS = sympathetic nervous system activation; PNS = parasympathetic nervous system activation, DOR = dispersion of repolarization, ACh = acetylcholine; NE = norepinephrine; EAD = early after depolarization; DAD = delayed after depolarization; APD = action potential duration