Title

Device-Based Autonomic Modulation in Arrhythmia Patients: the Role of Vagal Nerve Stimulation

Journal

Current Treatment Options in Cardiovascular Medicine, 17(5)

ISSN

1092-8464

Authors

Huang, William A
Shivkumar, Kalyanam
Vaseghi, Marmar

Publication Date

2015-05-01

DOI

10.1007/s11936-015-0379-9

Peer reviewed

Published in final edited form as:

Curr Treat Options Cardiovasc Med. 2015 May ; 17(5): 379. doi:10.1007/s11936-015-0379-9.

Device-Based Autonomic Modulation in Arrhythmia Patients: the Role of Vagal Nerve Stimulation

William A. Huang, MD, **Kalyanam Shivkumar, MD, PhD**, and **Marmar Vaseghi, MD***

Opinion statement

Vagal nerve stimulation (VNS) has shown promise as an adjunctive therapy for management of cardiac arrhythmias by targeting the cardiac parasympathetic nervous system. VNS has been evaluated in the setting of ischemia-driven ventricular arrhythmias and atrial arrhythmias, as well as a treatment option for heart failure. As better understanding of the complexities of the cardiac autonomic nervous system is obtained, vagal nerve stimulation will likely become a powerful tool in the current cardiovascular therapeutic armamentarium.

Keywords

Vagal; Vagus; Tachycardia; Fibrillation; Arrhythmia; Parasympathetic

Introduction

The cardiac autonomic nervous system represents an important therapeutic target for modulation of atrial and ventricular arrhythmias. Current therapies involving blockade of the sympathetic nervous system including beta-blockers, angiotensin-converting enzyme inhibitors, and aldosterone antagonists have been the cornerstones for the treatment of arrhythmias and heart failure. However, there is growing attention and need for therapies targeting the parasympathetic nervous system to compliment and augment our current approach. Parasympathetic imbalance, as manifested by abnormal heart rate variability and decreased baroreceptor sensitivity, is a well-established manifestation of heart failure and increases the risk of sudden cardiac death [1–6]. Furthermore, an increase in parasympathetic tone portends a greater likelihood of survival in the setting of ischemia [7]. Vagal nerve stimulation (VNS) represents a potential approach to increase parasympathetic efferent outflow and compensate for the parasympathetic dysfunction that increases the risk of arrhythmias [8].

***Address**. UCLA Cardiac Arrhythmia Center, University of California, 100 Medical Plaza, Suite 660, Los Angeles, CA 90095, USA, mvaseghi@mednet.ucla.edu.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Dr. William A. Huang, Dr. Kalyanam Shivkumar, and Dr. Marmar Vaseghi each declare no potential conflicts of interest.

Anatomy and physiology of vagal nerve stimulation

The vagosympathetic trunk synapses in the nucleus tractus solitarius and contains efferent fibers originating in the nucleus ambiguus and dorsal motor nucleus of the brainstem [9] and, therefore, contains both efferent and afferent neural fibers (Fig. 1). Visceral efferent fibers synapse near target organs, whereas afferent fibers traveling through the vagus via the bipolar neurons of the nodose ganglia (inferior vagal ganglion) carry information to the brainstem and higher centers. Within the vagosympathetic trunk, there is a predominance of parasympathetic neural fibers, although sympathetic nerve fibers also exist [10, 11]. The cardiomotor preganglionic parasympathetic nerve fibers converge and synapse within the intrinsic cardiac nervous system ganglia, lying on the dorsal and ventral fat pads on the basal aspect of the heart. The intrinsic cardiac nervous system forms a complex neural network that responds to and maintains fine control of cardiac function [12, 13]. The postganglionic parasympathetic fibers from the ganglia within these fat pads then innervate the sinoatrial and atrioventricular nodes as well as the atrial and the ventricular myocardia [14].

It is important to note that VNS can have different effects depending on the parameters and level of stimulation used. High-level stimulation, particularly at frequencies >20 Hz, significantly reduces heart rate (>60 %) and increases AV nodal conduction time [15]. At these high stimulation thresholds, VNS can induce asystole and complete heart block [16]. With medium-level stimulation, mild reductions in heart rate (10–50 %) and prolongation in AV nodal conduction time are observed. Low-level vagal nerve stimulation is defined as combination of intensity and frequency which has no effect on heart rate or AV conduction. With high- or medium-level VNS, atrial effective refractory period is shortened while with low-intensity stimulation, the atrial effective refractory period prolongs [17]. There is a threshold effect for voltage and pulse duration [18]. Increasing frequencies up to 17 Hz causes progressive sinus bradycardia while stimulation at 20–40 Hz (with voltage and pulse width held constant) can lead to prolonged pauses with junctional or ventricular escape beats. Therefore, there is an optimal range of frequencies and output to achieve the desired rhythm and degree of bradycardia [18].

Neural modulation of ventricular arrhythmias with VNS

VNS has multiple electrophysiological effects on the ventricular myocardium. VNS lengthens the ventricular effective refractory period [19–23] and attenuates the shortening effects of stellate stimulation on refractory period as measured using VF intervals [24]. Right and left VNS have similar efferent electrophysiological effects on ventricular activation recovery intervals (ARI), a surrogate of action potential duration. Stimulation of both vagi increases ARI on all regions of the epicardium, though greater prolongation on the endocardium compared to the epicardium is observed [20]. The effects of VNS on ventricular arrhythmias have been studied in the setting of myocardial ischemia, both in normal and previously infarcted hearts. In various animal models of rats, cats, rabbits, and canines, VNS has been shown to reduce the incidence of ventricular fibrillation (VF) and increase VF threshold [19, 25–35, 36•, 37•, 38] whereas vagotomy decreased VFT [39]. In a canine model of coronary artery ligation, high-intensity VNS decreased the time to spontaneous VF in the setting of ischemia compared to controls without VNS [25]. In rats 3

months after myocardial infarction, premature ventricular contractions (PVCs) were significantly decreased with low-medium-intensity VNS when the heart rate was suppressed by 20–30 beats per minute (~10 %) [40]. Interestingly, the effects were noted 1–2 days after initiation of intermittent VNS and lingered for several days after cessation of VNS therapy, suggesting a remodeling process or memory that modulates the effects on ventricular ectopy over time [40]. VNS at an intensity to lower heart rate in a canine ischemia model to 60–100 bpm was shown to improve survival and reduce the time to spontaneous VF [27]. In rabbits in whom ventricular arrhythmias are induced by sympathetic activation via stimulation of the ansae subclaviae or by QT prolongation using intravenous cesium chloride, medium-intensity VNS preferentially reduced polymorphic ventricular tachycardia (VT) rather than monomorphic VT [30, 41]. VNS has also been shown to reduce the restitution slope to <1 [19, 35], thereby protecting against malignant arrhythmias [42].

Bradycardia is one mechanism behind the protection conferred by VNS. In the setting of acute cardiac ischemia, reducing heart rate can improve the supply-demand mismatch and thereby reduce electrical vulnerability to malignant arrhythmias. Pacing the atria [32] and ventricles [31, 43] at fixed rates, while performing VNS attenuates its protective effects in this setting. The traditional interpretation of this pacing effect was that the heart rate reduction itself is protective; however, there are new studies to suggest that pacing itself can be pro-arrhythmic by increasing sympathetic tone [44, 45] and by altering the neural activation patterns in the intrinsic cardiac ganglia [46].

Another mechanism behind the anti-arrhythmic effects of VNS may involve preservation of electrotonic coupling and thereby electrical stabilization of the myocardium. Reduction of electrotonic coupling has been linked to arrhythmogenesis in ischemia [47]. VNS preserves electrotonic coupling during ischemia along with reducing ST segment elevations and dispersion of repolarization [47]. Interestingly, in the same study, pacing attenuated the protective effects of VNS whereas bilateral stellectomy did not, further supporting the notion that VNS mediates its effects by direct innervation of the heart rather than by causing reflex activation of afferent fibers in the central nervous system. A summary of the mechanisms behind the beneficial effects of VNS is shown in Table 1.

The utility of VNS in the setting of chronic myocardial infarction is currently unknown. There is limited literature examining the effects of low-to-medium-intensity VNS on the mature post-infarct scar. In one study, high-intensity VNS caused VT in setting of significant bradycardia that degenerated into VF [22]. Preliminary data suggest, however, that low- to medium-level VNS may reduce ventricular arrhythmias. In a chronic porcine infarct model, VNS at moderate levels (10 Hz, 1 ms) decreased global dispersion of repolarization and VT inducibility [48].

At the synaptic level, multiple messengers transduce the effects of VNS. Muscarinic receptors activated by acetylcholine have a clear role in reducing ventricular arrhythmias, which is reversed with atropine [49]. There are five types of cardiac muscarinic receptors [50], and the M3 receptor subtype along with the nicotinic receptor alpha-7nAChR play a dominant role in mediating the cardiac protective effects of acetylcholine [51]. Nitric oxide has also been shown to mediate some of the effects of VNS on the VF threshold and action

potential restitution slope, but not on effective refractory period prolongation [19]. Nitric oxide is increased with VNS and works independently of muscarinic receptor activation [36•].

Gap junction downregulation has been implicated in the genesis of arrhythmias with connexin-43 activity levels (regulated by phosphorylation) being closely linked to the pathogenesis of arrhythmias [52]. In an ischemia-induced VF rat model, connexin-43 phosphorylation is reduced with ischemia and preserved with VNS [34]. Inhibition of connexin-43 with carbenoxolone negates both connexin-43 phosphorylation and the protection from VF by VNS [37•]. Furthermore, aging is associated with reduced connexin-43 expression and aged rats demonstrate a decrease in the protective effects of VNS on ischemia-induced VF [37•].

Finally, VNS can cause remodeling of the stellate ganglia neurons. In dogs subjected to low-level left vagal stimulation for 1 week, left stellate ganglion neurons demonstrated increased expression of a small conductance calcium-activated potassium channel, SK2. SK channels are responsible for the slow afterhyperpolarization, hyperpolarizing neurons and decreasing neuronal firing. This data suggests that VNS can lead to beneficial remodeling of the sympathetic nervous system [53].

Not all neurotransmitters released with VNS, however, are protective. When cholinergic effects on heart rate (HR) suppression are eliminated with atropine, VNS causes a surprising increase in HR, primarily through the release of vasoactive intestinal peptide (VIP) [36•, 47, 54]. Additionally, VIP does not seem to protect against ventricular arrhythmias and does not affect VF threshold or ventricular effective refractory period [36•]. Given that the vagal trunk contains a variety of nerve fibers and VNS releases a number of neurotransmitters, characterization of the neurotransmitters and their effects is important prior to its utilization for therapeutic purposes.

The anti-arrhythmic benefits of VNS appear to be dependent on stimulation parameters as well as whether continuous (which often leads to more bradycardia) or intermittent stimulation is utilized (Table 2). Although VNS reduces ischemia-induced VF and VT, stimulation of the vagosympathetic trunk at high frequencies (>20 Hz) and at intensities that cause severe bradycardia or asystole can induce bigeminy [55–58] and monomorphic VT [15, 30, 55]. With high-intensity VNS in the setting of acute and chronic ischemia, monomorphic VT can be induced, which can degenerate into VF [22]. The genesis of the PVCs induced by high-intensity VNS has been attributed to sinus arrest and/or AV nodal blockade which unmasks the underlying ventricular automaticity [18]. This phenomenon is eliminated when ventricle is paced faster than underlying ventricular escape rate [59]. The unmasking phenomenon of PVCs also carries over to VT [30, 55, 57]. Scherf et al. in 1962 [55] showed that occurrence of ventricular couplets with VNS was more frequent when the sinus rhythm rate was lowered from 175 beats perminute (bpm) to less than 100 bpm in a canine model. Therefore, the pro-arrhythmic effects of VNS appear to occur when high-level stimulation unmasks the underlying ventricular automaticity due to suppression of supraventricular pacemakers, and there also exists either the simultaneous presence of the substrate for reentry, such as ischemia [59], concurrent sympathetic nerve stimulation [30],

or local sodium chloride injections [55]. Manning and colleagues, in normal cat hearts, induced a series of ventricular ectopic beats or idioventricular rhythm with medium stimulation intensity of 10 Hz (3–8 V, 2 ms) [57], in the setting of simultaneous right stellate ganglion stimulation. Therefore, the majority of arrhythmias observed in this setting are idioventricular rhythms, rather than ventricular tachycardia. An additional hypothesis for the etiology of the observed ventricular automaticity is the possibility that high-intensity VNS can activate afferent fibers, causing a reflex sympathetic response, or may be stimulating the intrinsic sympathetic fibers within the vagal trunk. Indeed, in a rabbit ischemia model where intermittent VNS leads to a reduction in infarct size, continuous VNS for 10 min increased infarct size, while bilateral vagotomy or beta-blockers abolished this deleterious effect. Of note, the continuous stimulation also leads to significant bradycardia and an increase in loading conditions and wall stretch of the atria, which likely activated the reflex sympathetic nervous system [60•]. Thus, the majority of studies show protection against malignant ventricular arrhythmias at low- to moderate-level intermittent VNS, with the goal of modest to minimal lowering of heart rate at lower frequencies to prevent afferent fiber stimulation.

Certain populations of patients with predispositions to ventricular arrhythmias are unlikely to benefit from VNS. Early repolarization syndrome [61], Brugada [62], LQT3 [63], and some subgroups of idiopathic VT [64] are known to have parasympathetic triggers, and VNS in these settings is likely to be proarrhythmic. Furthermore, a case report of VNS implantation to treat electrical storm exacerbating ventricular arrhythmias in an ischemic cardiomyopathy patient has been reported [65]. These studies demonstrate the importance of identifying the correct patient population and appropriate stimulation thresholds and frequencies prior to consideration of VNS for prevention of VT/VF.

Modification of atrial arrhythmias

Acetylcholine challenge has been known to facilitate triggering of atrial fibrillation (AF) [67], and the combination of parasympathetic and sympathetic activation is thought to play an important role in the genesis of AF. In particular, with medium- to high-level stimulation, VNS can induce AF [66, 68, 69]. In a canine pacing-induced AF model, VNS became pro-arrhythmic at intensities that decreased heart rate more than 40% [70]. High-intensity VNS reduces atrial effective refractory period (AERP) [68, 71], may preferentially affect right AERP more than left [72], increases AERP dispersion [68, 73, 74], causes a heterogeneity in atrial conduction leading to wave front breaks [75, 76], reduces AF threshold, and prolongs duration of AF [77]. The pro-arrhythmic effects of VNS that lead to AF have been shown to be mediated by acetylcholine activation of nicotinic receptors [71] and VIP [77].

More recently, low-level VNS has been shown to have anti-arrhythmic properties, particularly with regard to AF. Typical stimulation frequencies used for low intensity were <20 Hz with energies of 1–5 V and the goal of avoiding bradycardia. AF or atrial tachycardia in the setting of rapid burst atrial pacing of ambulatory dogs was reduced with low-level VNS [78]. In normal canine hearts, AF duration induced by direct topical application of acetylcholine to the right atrial appendage or extra-stimulus atrial pacing was reduced with low-level VNS [79]. In the setting of electrical stimulation of anterior right and superior left ganglionated plexi, low-level VNS reduced AF inducibility with extra-stimulus

atrial pacing [80]. Low-level VNS increased AF threshold in response to high-frequency stimulation near the pulmonary veins and atrial appendages during the atrial refractory period and blunted the chronotropic response to right stellate ganglion and superior left ganglionated plexi stimulation [81, 82]. Finally, low-level right VNS decreased AF duration in a rabbit model of obstructive sleep apnea [83•].

With regard to its mechanisms, low-level VNS has opposite effects on atrial myocardium compared to high- and medium-level stimulation. In addition to increasing AF threshold, it has been shown to increase AERP and reduce AERP dispersion [80] and AF duration [79]. Low-level VNS reduces left stellate ganglion nerve activity and, in fact, has been shown to cause beneficial remodeling in the stellate ganglia with an increase in non-tyrosine hydroxylase- and choline acetyltransferase-positive neurons [78]. As mentioned above, an additional potential mechanism for the anti-arrhythmic properties attributed to low-level VNS is the upregulation of small conductance calcium-activated potassium channel type 2 among stellate ganglion neurons, which reduces the overall activity of these neurons [53]. Although topical application of acetylcholine to atrial tissue induces AF, downstream cell signaling mediators of acetylcholine such as nitric oxide and PI3K have anti-arrhythmic properties [17]. Vasostatin-1 may also be one of the mediators of the beneficial effects of low-level VNS. Injection of vasostatin-1 into the autonomic ganglia demonstrates similar anti-arrhythmic effects as low-level VNS, reducing AF inducibility and leading to the release of nitric oxide and PI3K [79], although immunohistochemical data regarding the presence of vasostatin-1 in cardiac autonomic ganglia is lacking. The mechanisms behind the protective effects of VNS on atrial arrhythmias are summarized in Table 1.

It should be noted, however, that certain subgroups of patients with vagally mediated AF may not benefit from low-level VNS. Vagally mediated AF is a well-described entity in which patients experience paroxysmal AF that primarily occurs at night, at rest, or with digestion or swallowing. These patients do not respond to treatments with digoxin, beta-blockers, or verapamil and have been successfully treated with fixed atrial pacing [84]. There is no data that VNS would be of any benefit in these patients.

Improvement in heart failure as an additional mechanism for the beneficial effects of VNS on arrhythmias

The hemodynamic response to VNS tends to be one of decreased inotropy and chronotropy without a significant change in diastolic function. A decrease in LV systolic pressure [85, 86] and load-independent parameter of end-systolic elastance [87, 88] is observed. Much of the negative inotropic effects can be overcome by holding the heart rate constant with pacing [85, 89–91]. However, there also exist interspecies variations. In rats, an unexpected increase in inotropic response to medium-intensity bilateral VNS (10 Hz, 10 V, 3 ms) is observed, which may be due to the paucity vagal innervation in the rat ventricle [89]. Furthermore, positive inotropic effects of VNS on the right ventricle (RV) have been demonstrated in the setting of muscarinic and sympathetic blockade. VIP has been implicated as the molecular mediator of this effect [92].

In a variety of animal models of heart failure, VNS improves cardiac function and even survival. In a canine heart failure model, VNS combined with beta-blockers was superior to beta-blockers alone in improving left ventricular ejection fraction (LVEF) [93]. In a canine pacing-induced heart failure model, chronic intermittent VNS with the goal of decreasing heart rate by 20 bpm improved left ventricular (LV) end-diastolic and end-systolic volumes, LVEF, heart rate variability, and baroreflex sensitivity [94]. Similar improvements in LVEF and LV end-systolic volume were shown in an infarct heart failure canine model with low-level VNS [95]. VNS attenuates much of the detrimental effects of ischemia. Low-medium VNS reduces infarct size [96–98], lowers LVEDP, raises dp/dt, reduces biventricular weight, decreases LV dilation and wall thinning, and improves survival rate [99]. Intermittent VNS compared to continuous VNS [98] and initiating VNS during ischemia as opposed to after ischemia [97] seems to increase these beneficial effects. It is important to understand, however, that variability in stimulation parameters and interspecies differences may lead to unexpected outcomes, particularly during continuous stimulation with significant bradycardia, which can lead to reflex sympathetic activation or activating sympathetic efferents via activation of vagal afferent fibers [60•].

The mechanisms of the effects of VNS on cardiac function are still under investigation. Calcium influx is reduced when VNS is performed in the setting of sympathetic stimulation, but not when VNS is performed alone [85]. Modulation of sympathetic function via presynaptic inhibition of norepinephrine release has also been shown [100]. The anti-inflammatory effects, described below, also play an important role in reducing infarct size and improving cardiac function. Finally, VNS causes vasodilation, an effect mediated by acetylcholine and nitric oxide, as well as VIP [101–103]. VNS increases coronary blood flow in situ in normal canine hearts, an effect that is reduced by infusion of a VIP receptor antagonist [(4Cl-$_{D}$-Phe^{6}, Leu^{17})VIP]. VIP is released at 10–20-Hz stimulation frequencies in the coronary vasculature and throughout the myocardium [102] and is a potent vasodilator (greater than adenosine or nitroprusside) [104]. It interacts with VIP receptors (VPAC1 and VPAC2), activates the adenylyl cyclase signaling cascade, leading to vasodilation and increase in inotropy and chronotropy. The vasodilatory effects could mediate the reduction in infarct size observed when applied simultaneously with ischemia due to coronary occlusion in a porcine model [97, 98]. Of note, in normal canine hearts, VIP released by VNS in the setting of muscarinic and beta receptor blockade augments right ventricular contraction, relaxation, and heart rate [92].

Heart failure is known to affect the levels of the three isoforms of nitric oxide synthase: endothelin nitric oxide (eNOS), inducible nitric oxide (iNOS), and neuronal nitric oxide (nNOS). eNOS is significantly decreased in heart failure [93, 105, 106]. iNOS has an important role in generating oxidative radicals, bradyarrhythmias, and fibrosis and is increased in heart failure [93, 107]. nNOS has also been shown to be elevated in heart failure [93, 108]. The effects of VNS on the various isoforms of nitric oxide were demonstrated by Hamann and colleagues who showed that 6 months of low-level VNS in a chronic infarct heart failure model leads to an increase in eNOS, decrease in nNOS, and normalization of nNOS levels [95].

Currently, there are three large human clinical trials assessing the effect of VNS as a treatment option for heart failure. A pilot study in 2008 showed improvement in New York Heart Association (NYHA) class heart failure (HF), Minnesota quality of life, and LV end-systolic volume [109]. ANTHEM-HF, a nonblinded study which includes adults with NYHA functional class II–III, LVEF <40 %, LV end-diastolic diameter between 50 and 80 mm, QRS <150 ms, on optimal medical therapy for 3 months, showed improvements in LVEF (4.5 %), LV end-systolic volume (−4.1 mL), LV end-systolic dimension (−1.7 mm),HR variability, 6 min walk test, and NYHA class in 77% of patients. No notable difference between right and left sided vagal stimulation has been observed in this trial, similar to that seen in translational studies [110]. NECTAR-HF is an ongoing randomized blinded study that enrolled adults with LVEF <=35 %, NYHA class II–III, and on optimal medical therapy for at least 1 month. The 6-month results showed an improvement in heart failure score and an increase in heart rate variability. However, there was no significant difference in LVEF, LV dimensions, or peak VO_2 (oxygen consumption rate) [111]. INOVATE-HF is another ongoing clinical trial to assess long-term outcomes of VNS in patients with LVEF <40 %, NYHA class III QRS <120 ms, and LV end-diastolic dimension of 50–80 mm [112].

Anti-inflammatory effects of VNS

Low- to medium-intensity VNS has significant anti-inflammatory effects that may also explain much of its benefit. In a canine pacing-induced heart failure model, the rise in plasma norepinephrine, angiotensin II, and CRP levels were attenuated with medium-intensity VNS [94]. In a post-infarct porcine model, low-medium-intensity VNS reduced production of mitochondrial reactive oxygen species and release of cytochrome-c [97, 98]. While continuous VNS increased inflammatory markers in a rabbit model of ischemia, potentially by activating the reflex sympathetic nervous system, intermittent VNS and decentralization of vagus eliminated these deleterious effects [60•]. Similar beneficial effects of intermittent VNS compared to continuous VNS have been observed in an ischemic porcine model where low-level left VNS attenuated ventricular dysfunction through prevention of mitochondrial dysfunction [98]. Oxidative stress is also modified by VNS. In a mouse chronic heart failure model 28 days post-infarct, medium-intensity VNS reduced the production of radical oxygen species [113, 114].

The effects of VNS on TNF-alpha are controversial and may be species dependent. TNF-alpha has historically been considered a harmful inflammatory mediator. Its levels are variably affected by VNS depending on the species. Studies in rats [51, 115] and rabbits [96] with medium-level VNS have shown TNF-alpha levels increase with ischemia, an effect that is attenuated with VNS. TNF-alpha is also reduced by low VNS in a canine microembolization heart failure model [95], in endotoxin-exposed rats [116], and in heatstroke-exposed rats [117]. These anti-inflammatory effects are in alignment with the known anti-inflammatory effects of acetylcholine, which inhibits the synthesis of TNF-alpha in the liver and spleen as well as the heart [118]. On the other hand, TNF-alpha has pleiotropic effects and can function as a protective inflammatory molecule mediating ischemic preconditioning and prevention of heart failure in mice [119]. In contrast to other studies, an increase in TNF-alpha level was observed in a mice model of acute ischemia,

though VNS in this study was still protective [119]. These differences may be explained by the effects of VNS on TNF receptors, rather than TNF levels. VNS in this study simultaneously increased protective TNFR2 and downregulated the destructive TNFR1, which imparted an overall protective effect to TNF-alpha, and attenuated infarct size [119].

VNS also affects levels of interleukins (IL). Pro-inflammatory IL-6 is reduced with low-level VNS in canine heart failure model [95], medium-level VNS in rat ischemia model [115], medium-level VNS in dog ischemia model [120], and in a rat heatstroke model [117]. Pro-inflammatory IL-1 and lipopolysaccharide-inducible CXC chemokine (LIX, IL-8 analogue in rats) were attenuated in the presence of medium-intensity VNS in ischemic rat models [51, 115, 121]. Anti-inflammatory IL-4 is increased in a post-infarct porcine model with low- to medium-intensity VNS [97].

Other inflammatory markers are generally reduced across various studies. A decrease in neutrophil count, MMP-8, and MMP-9 is observed with medium-level VNS in rabbits undergoing coronary occlusion [96]. Monocyte chemoattractant protein (MCP)-1 is increased with ischemia, and the increase is attenuated in the presence of medium-intensity VNS in an ischemic rat model [121]. Thus, the current studies support an anti-inflammatory role for low- to medium-intensity intermittent VNS.

Conclusions

VNS has shown promise in reducing malignant ventricular arrhythmias, particularly in the setting of ischemia, as well as atrial arrhythmias, particularly AF. The improvement in heart failure and the anti-inflammatory and vasodilatory properties of VNS provide additional anti-arrhythmic benefit. Given the complexity of the cardiac autonomic nervous system, including the presence of both afferent and efferent as well as parasympathetic and sympathetic fibers in the vagosympathetic trunk, it is critical to carefully elucidate the mechanisms of VNS and the parameters of stimulation to ensure that vagal nerve stimulators achieve the desired therapeutic effect.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

1. Farrell TG, Bashir Y, Cripps T, et al. Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. J Am Coll Cardiol. 1991; 18:687–697. [PubMed: 1822090]
2. Farrell TG, Paul V, Cripps TR, et al. Baroreflex sensitivity and electrophysiological correlates in patients after acute myocardial infarction. Circulation. 1991; 83:945–952. [PubMed: 1999042]
3. Hull SS Jr, Evans AR, Vanoli E, et al. Heart rate variability before and after myocardial infarction in conscious dogs at high and low risk of sudden death. J Am Coll Cardiol. 1990; 16:978–985. [PubMed: 2212380]
4. Kleiger RE, Miller JP, Bigger JT Jr, et al. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol. 1987; 59:256–262. [PubMed: 3812275]
5. La Rovere MT, Bigger JT Jr, Marcus FI, et al. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and

Reflexes After Myocardial Infarction) Investigators. Lancet. 1998; 351:478–484. [PubMed: 9482439]

6. Vanoli E, Schwartz PJ. Sympathetic–parasympathetic interaction and sudden death. Basic Res Cardiol. 1990; 85(Suppl 1):305–321. [PubMed: 2091609]
7. Schwartz PJ, Billman GE, Stone HL. Autonomic mechanisms in ventricular fibrillation induced by myocardial ischemia during exercise in dogs with healed myocardial infarction. An experimental preparation for sudden cardiac death. Circulation. 1984; 69:790–800. [PubMed: 6697463]
8. Vaseghi M, Shivkumar K. The role of autonomic nervous system in sudden cardiac death. Prog Cardiovasc Dis. 2008; 50:404–419. [PubMed: 18474284]
9. Waxman, SG. Clinical neuroanatomy. 27e ed. Mc-Graw Hill Medical; 2013.
10. Randall WC, Priola DV, Pace JB. Responses of individual cardiac chambers to stimulation of the cervical vagosympathetic trunk in atropinized dogs. Circ Res. 1967; 20:534–544. [PubMed: 6057686]
11. Seki A, Green HR, Lee TD, et al. Sympathetic nerve fibers in human cervical and thoracic vagus nerves. Heart Rhythm. 2014; 11:1411–1417. [PubMed: 24768897]
12. Armour JA. The little brain on the heart. Cleve Clin J Med. 2007; 74(Suppl 1):S48–S51. [PubMed: 17455544]
13. Armour JA, Murphy DA, Yuan BX, et al. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. Anat Rec. 1997; 247:289–298. [PubMed: 9026008]
14. Shen MJ, Zipes DP. Role of the autonomic nervous system in modulating cardiac arrhythmias. Circ Res. 2014; 114:1004–1021. [PubMed: 24625726]
15. Takahashi N, Zipes DP. Vagal modulation of adrenergic effects on canine sinus and atrioventricular nodes. Am J Physiol. 1983; 244:H775–H781. [PubMed: 6859280]
16. Naggar I, Nakase K, Lazar J, et al. Vagal control of cardiac electrical activity and wall motion during ventricular fibrillation in large animals. Auton Neurosci. 2014; 183:12–22. [PubMed: 24530112]
17. Stavrakis S, Scherlag BJ, Fan Y, et al. Inhibition of atrial fibrillation by low-level vagus nerve stimulation: the role of the nitric oxide signaling pathway. J Interv Card Electrophysiol. 2013; 36:199–208. [PubMed: 23179922]
18. Peiss CN, Spurgeon HA. Origin of initial escape beat during graded vagal stimulation. J Electrocardiol. 1975; 8:25–29. [PubMed: 1110335]
19. Brack KE, Patel VH, Coote JH, et al. Nitric oxide mediates the vagal protective effect on ventricular fibrillation via effects on action potential duration restitution in the rabbit heart. J Physiol. 2007; 583:695–704. [PubMed: 17627986]
20. Martins JB, Zipes DP. Effects of sympathetic and vagal nerves on recovery properties of the endocardium and epicardium of the canine left ventricle. Circ Res. 1980; 46:100–110. [PubMed: 7349909]
21. Martins JB, Zipes DP, Lund DD. Distribution of local repolarization changes produced by efferent vagal stimulation in the canine ventricles. J Am Coll Cardiol. 1983; 2:1191–1199. [PubMed: 6630790]
22. Scherlag BJ, Kabell G, Harrison L, et al. Mechanisms of bradycardia-induced ventricular arrhythmias in myocardial ischemia and infarction. Circulation. 1982; 65:1429–1434. [PubMed: 7074798]
23. Yamakawa K, So EL, Rajendran PS, et al. Electrophysiological effects of right and left vagal nerve stimulation on the ventricular myocardium. Am J Physiol Heart Circ Physiol. 2014; 307:H722–H731. [PubMed: 25015962]
24. Opthof T, Dekker LR, Coronel R, et al. Interaction of sympathetic and parasympathetic nervous system on ventricular refractoriness assessed by local fibrillation intervals in the canine heart. Cardiovasc Res. 1993; 27:753–759. [PubMed: 8348575]
25. Scherlag BJ, Helfant RH, Haft JI, et al. Electrophysiology underlying ventricular arrhythmias due to coronary ligation. Am J Physiol. 1970; 219:1665–1671. [PubMed: 5312495]
26. Kent KM, Smith ER, Redwood DR, et al. Electrical stability of acutely ischemic myocardium: influences of heart rate and vagal stimulation. Circulation. 1973; 47:291–298. [PubMed: 4684930]

27. Myers RW, Pearlman AS, Hyman RM, et al. Beneficial effects of vagal stimulation and bradycardia during experimental acute myocardial ischemia. Circulation. 1974; 49:943–947. [PubMed: 4828616]
28. Kolman BS, Verrier RL, Lown B. The effect of vagus nerve stimulation upon vulnerability of the canine ventricle: role of sympathetic-parasympathetic interactions. Circulation. 1975; 52:578–585. [PubMed: 239801]
29. Yoon MS, Han J, Tse WW, et al. Effects of vagal stimulation, atropine, and propranolol on fibrillation threshold of normal and ischemic ventricles. Am Heart J. 1977; 93:60–65. [PubMed: 831412]
30. Takahashi N, Ito M, Iwao T, et al. Vagal modulation of ventricular tachyarrhythmias induced by left ansae subclaviae stimulation in rabbits. Jpn Heart J. 1998; 39:503–511. [PubMed: 9810300]
31. Zuanetti G, De Ferrari GM, Priori SG, et al. Protective effect of vagal stimulation on reperfusion arrhythmias in cats. Circ Res. 1987; 61:429–435. [PubMed: 3621502]
32. Vanoli E, De Ferrari GM, Stramba-Badiale M, et al. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. Circ Res. 1991; 68:1471–1481. [PubMed: 2019002]
33. Rosenshtraukh L, Danilo P, Anyukhovsky EP, et al. Mechanisms for vagal modulation of ventricular repolarization and of coronary occlusion-induced lethal arrhythmias in cats. Circ Res. 1994; 75:722–732. [PubMed: 7923618]
34. Ando M, Katare RG, Kakinuma Y, et al. Efferent vagal nerve stimulation protects heart against ischemia-induced arrhythmias by preserving connexin43 protein. Circulation. 2005; 112:164–170. [PubMed: 15998674]
35. Ng GA, Brack KE, Patel VH, et al. Autonomic modulation of electrical restitution, alternans and ventricular fibrillation initiation in the isolated heart. Cardiovasc Res. 2007; 73:750–760. [PubMed: 17217937]
36. Brack KE, Coote JH, Ng GA. Vagus nerve stimulation protects against ventricular fibrillation independent of muscarinic receptor activation. Cardiovasc Res. 2011; 91:437–446. [PubMed: 21576131] This paper highlights the potential role of NO released with VNS in reducing ventricular arrhythmias.
37. Wu W, Lu Z. Loss of anti-arrhythmic effect of vagal nerve stimulation on ischemia-induced ventricular tachyarrhythmia in aged rats. Tohoku J Exp Med. 2011; 223:27–33. [PubMed: 21187697] This paper exemplifies that VNS reduces VF and mechanisms include connexin-43 regulation.
38. Matta RJ, Verrier RL, Lown B. Repetitive extrasystole as an index of vulnerability to ventricular fibrillation. Am J Physiol. 1976; 230:1469–1473. [PubMed: 59552]
39. Brooks WW, Verrier RL, Lown B. Influence of vagal tone on stellectomy-induced changes in ventricular electrical stability. Am J Physiol. 1978; 234:H503–H507. [PubMed: 645915]
40. Zheng C, Li M, Inagaki M, et al. Vagal stimulation markedly suppresses arrhythmias in conscious rats with chronic heart failure after myocardial infarction. Conf Proc IEEE Eng Med Biol Soc. 2005; 7:7072–7075. [PubMed: 17281904]
41. Takahashi N, Ito M, Ishida S, et al. Effects of vagal stimulation on cesium-induced early afterdepolarizations and ventricular arrhythmias in rabbits. Circulation. 1992; 86:1987–1992. [PubMed: 1451270]
42. Weiss JN, Karma A, Shiferaw Y, et al. From pulsus to pulseless: the saga of cardiac alternans. Circ Res. 2006; 98:1244–1253. [PubMed: 16728670]
43. James R, Arnold J, Allen JD, et al. The effects of heart rate, myocardial ischemia and vagal stimulation on the threshold for ventricular fibrillation. Circulation. 1977; 55:311–317. [PubMed: 832347]
44. Herre JM, Thames MD. Responses of sympathetic nerves to programmed ventricular stimulation. J Am Coll Cardiol. 1987; 9:147–153. [PubMed: 2432106]
45. Smith ML, Hamdan MH, Wasmund SL, et al. High-frequency ventricular ectopy can increase sympathetic neural activity in humans. Heart Rhythm. 2010; 7:497–503. [PubMed: 20184979]
46. Rajendran PS, Vaseghi M, Armour JA, et al. Abstract 12655: cardiac pacing alters neural information processing in the intrinsic cardiac nervous system. Circ J. 2014; 130:A12655.

47. Del Rio CL, Dawson TA, Clymer BD, et al. Effects of acute vagal nerve stimulation on the early passive electrical changes induced by myocardial ischaemia in dogs: heart rate-mediated attenuation. Exp Physiol. 2008; 93:931–944. [PubMed: 18376003]
48. Vaseghi M, Yagishita D, Yamakawa K, et al. Abstract 16272: intermittent vagal nerve stimulation reduces VT inducibility and dispersion of repolarization in a chronic infarct model. Circ J. 2013; 128:A16272.
49. Waxman MB, Sharma AD, Asta J, et al. The protective effect of vagus nerve stimulation on catecholamine-halothane-induced ventricular fibrillation in dogs. Can J Physiol Pharmacol. 1989; 67:801–809. [PubMed: 2766111]
50. Harvey RD. Muscarinic receptor agonists and antagonists: effects on cardiovascular function. Handb Exp Pharmacol. 2012:299–316. [PubMed: 22222704]
51. Zhao M, He X, Bi XY, et al. Vagal stimulation triggers peripheral vascular protection through the cholinergic anti-inflammatory pathway in a rat model of myocardial ischemia/reperfusion. Basic Res Cardiol. 2013; 108:345. [PubMed: 23519622]
52. Remo BF, Giovannone S, Fishman GI. Connexin43 cardiac gap junction remodeling: lessons from genetically engineered murine models. J Membr Biol. 2012; 245:275–281. [PubMed: 22722763]
53. Shen MJ, Hao-Che C, Park HW, et al. Low-level vagus nerve stimulation upregulates small conductance calcium-activated potassium channels in the stellate ganglion. Heart Rhythm. 2013; 10:910–915. [PubMed: 23357541]
54. Hill MR, Wallick DW, Mongeon LR, et al. Vasoactive intestinal polypeptide antagonists attenuate vagally induced tachycardia in the anesthetized dog. Am J Physiol. 1995; 269:H1467–H1472. [PubMed: 7485582]
55. Scherf D, Blumenfeld S, Yildiz M. Experimental study on ventricular extrasystoles provoked by vagal stimulation. Am Heart J. 1961; 62:670–675. [PubMed: 14498267]
56. Takato T, Ashida T, Seko Y, et al. Ventricular tachyarrhythmia-related basal cardiomyopathy in rabbits with vagal stimulation—a novel experimental model for inverted Takotsubo-like cardiomyopathy. J Cardiol. 2010; 56:85–90. [PubMed: 20409691]
57. Manning JW, Cotten MDV. Mechanism of cardiac arrhythmias induced by diencephalic stimulation. Am J Physiol. 1962; 203:1120–1124.
58. Ashida T, Ono C, Sugiyama T, et al. Mitral valve hemorrhage and mitral annulus shrinkage in rabbits with transient ventricular bigeminies induced by vagal stimulation. J Heart Valve Dis. 2004; 13:779–783. [PubMed: 15473479]
59. Kerzner J, Wolf M, Kosowsky BD, et al. Ventricular ectopic rhythms following vagal stimulation in dogs with acute myocardial infarction. Circulation. 1973; 47:44–50. [PubMed: 4405614]
60. Buchholz B, Donato M, Perez V, et al. Changes in the loading conditions induced by vagal stimulation modify the myocardial infarct size through sympathetic-parasympathetic interactions. Pflugers Arch. 2014 This paper highlights sympathetic and parasympathetic interactions that can occur, particularly in the setting of continuous vagal nerve stimulation where bradycardia and changes in loading conditions can cause sympathetic activation.
61. Koncz I, Gurabi Z, Patocskai B, et al. Mechanisms underlying the development of the electrocardiographic and arrhythmic manifestations of early repolarization syndrome. J Mol Cell Cardiol. 2014; 68:20–28. [PubMed: 24378566]
62. Antzelevitch C. Brugada syndrome. Pacing Clin Electrophysiol. 2006; 29:1130–1159. [PubMed: 17038146]
63. Flaim SN, McCulloch AD. Acetylcholine-induced shortening of the epicardial action potential duration may increase repolarization gradients and LQT3 arrhythmic risk. J Electrocardiol. 2007; 40:S66–S69. [PubMed: 17993332]
64. Kasanuki H, Ohnishi S, Ohtuka M, et al. Idiopathic ventricular fibrillation induced with vagal activity in patients without obvious heart disease. Circulation. 1997; 95:2277–2285. [PubMed: 9142005]
65. Shalaby AA, El-Saed A, Nemec J, Moossy JJ, Balzer JR. Exacerbation of electrical storm subsequent to implantation of a right vagal stimulator. Clin Aut Res. 2007; 17:385–390.

66. Katsouras G, Sakabe M, Comtois P, et al. Differences in atrial fibrillation properties under vagal nerve stimulation versus atrial tachycardia remodeling. Heart Rhythm. 2009; 6:1465–1472. [PubMed: 19968926]
67. Burn JH, Williams EM, Walker JM. The effects of acetylcholine in the heart-lung preparation including the production of auricular fibrillation. J Physiol. 1955; 128:277–293. [PubMed: 14392608]
68. Wang Z, Page P, Nattel S. Mechanism of flecainide's antiarrhythmic action in experimental atrial fibrillation. Circ Res. 1992; 71:271–287. [PubMed: 1628386]
69. Goldberger AL, Pavelec RS. Vagally-mediated atrial fibrillation in dogs: conversion with bretylium tosylate. Int J Cardiol. 1986; 13:47–55. [PubMed: 3771001]
70. Zhang Y, Ilsar I, Sabbah HN, et al. Relationship between right cervical vagus nerve stimulation and atrial fibrillation inducibility: therapeutic intensities do not increase arrhythmogenesis. Heart Rhythm. 2009; 6:244–250. [PubMed: 19187919]
71. Schauerte P, Scherlag BJ, Pitha J, et al. Catheter ablation of cardiac autonomic nerves for prevention of vagal atrial fibrillation. Circulation. 2000; 102:2774–2780. [PubMed: 11094046]
72. Furukawa T, Hirao K, Horikawa-Tanami T, et al. Influence of autonomic stimulation on the genesis of atrial fibrillation in remodeled canine atria not the same as in normal atria. Circ J. 2009; 73:468–475. [PubMed: 19151502]
73. Alessi R, Nusynowitz M, Abildskov JA, et al. Nonuniform distribution of vagal effects on the atrial refractory period. Am J Physiol. 1958; 194:406–410. [PubMed: 13559489]
74. Liu L, Nattel S. Differing sympathetic and vagal effects on atrial fibrillation in dogs: role of refractoriness heterogeneity. Am J Physiol. 1997; 273:H805–H816. [PubMed: 9277498]
75. Page PL, Hassanalizadeh H, Cardinal R. Transitions among atrial fibrillation, atrial flutter, and sinus rhythm during procainamide infusion and vagal stimulation in dogs with sterile pericarditis. Can J Physiol Pharmacol. 1991; 69:15–24. [PubMed: 2036596]
76. Ninomiya I. Direct evidence of nonuniform distribution of vagal effects on dog atria. Circ Res. 1966; 19:576–583. [PubMed: 5925156]
77. Liu Y, Scherlag BJ, Fan Y, et al. Inducibility of atrial fibrillation after GP ablations and "autonomic blockade": evidence for the pathophysiological role of the nonadrenergic and noncholinergic neurotransmitters. J Cardiovasc Electrophysiol. 2013; 24:188–195. [PubMed: 23066921]
78. Shen MJ, Shinohara T, Park HW, et al. Continuous low-level vagus nerve stimulation reduces stellate ganglion nerve activity and paroxysmal atrial tachyarrhythmias in ambulatory canines. Circulation. 2011; 123:2204–2212. [PubMed: 21555706]
79. Stavrakis S, Scherlag BJ, Fan Y, et al. Antiarrhythmic effects of vasostatin-1 in a canine model of atrial fibrillation. J Cardiovasc Electrophysiol. 2012; 23:771–777. [PubMed: 22487376]
80. Yu L, Scherlag BJ, Li S, et al. Low-level vagosympathetic nerve stimulation inhibits atrial fibrillation inducibility: direct evidence by neural recordings from intrinsic cardiac ganglia. J Cardiovasc Electrophysiol. 2011; 22:455–463. [PubMed: 20946225]
81. Li S, Scherlag BJ, Yu L, et al. Low-level vagosympathetic stimulation: a paradox and potential new modality for the treatment of focal atrial fibrillation. Circ Arrhythm Electrophysiol. 2009; 2:645–651. [PubMed: 19948505]
82. Sha Y, Scherlag BJ, Yu L, et al. Low-level right vagal stimulation: anticholinergic and antiadrenergic effects. J Cardiovasc Electrophysiol. 2011; 22:1147–1153. [PubMed: 21489033]
83. Gao M, Zhang L, Scherlag BJ, et al. Low-level vagosympathetic trunk stimulation inhibits atrial fibrillation in a rabbit model of obstructive sleep apnea. Heart Rhythm. 2014 In Press. This experimental canine model of atrial fibrillation highlights the role of low level VNS in protecting against atrial arrhythmias and demonstrates a mechanism for its beneficial effects via modulating stellate ganglion nerve activity.
84. Coumel P, Friocourt P, Mugica J, et al. Long-term prevention of vagal atrial arrhythmias by atrial pacing at 90/minute: experience with 6 cases. Pacing Clin Electrophysiol. 1983; 6:552–560. [PubMed: 6191292]
85. Brack KE, Coote JH, Ng GA. Vagus nerve stimulation inhibits the increase in Ca2+ transient and left ventricular force caused by sympathetic nerve stimulation but has no direct effects alone—

epicardial Ca2+ fluorescence studies using fura-2 AM in the isolated innervated beating rabbit heart. Exp Physiol. 2010; 95:80–92. [PubMed: 19700520]

86. Ng GA, Brack KE, Coote JH. Effects of direct sympathetic and vagus nerve stimulation on the physiology of the whole heart—a novel model of isolated Langendorff perfused rabbit heart with intact dual autonomic innervation. Exp Physiol. 2001; 86:319–329. [PubMed: 11471534]
87. Lewis ME, Al-Khalidi AH, Bonser RS, et al. Vagus nerve stimulation decreases left ventricular contractility in vivo in the human and pig heart. J Physiol. 2001; 534:547–552. [PubMed: 11454971]
88. Nakayama Y, Miyano H, Shishido T, et al. Heart rate-independent vagal effect on end-systolic elastance of the canine left ventricle under various levels of sympathetic tone. Circulation. 2001; 104:2277–2279. [PubMed: 11696465]
89. Takahashi H, Maehara K, Onuki N, et al. Decreased contractility of the left ventricle is induced by the neurotransmitter acetylcholine, but not by vagal stimulation in rats. Jpn Heart J. 2003; 44:257–270. [PubMed: 12718487]
90. Brack KE, Coote JH, Ng GA. The effect of direct autonomic nerve stimulation on left ventricular force in the isolated innervated Langendorff perfused rabbit heart. Auton Neurosci. 2006; 124:69–80. [PubMed: 16455307]
91. Matsuura W, Sugimachi M, Kawada T, et al. Vagal stimulation decreases left ventricular contractility mainly through negative chronotropic effect. Am J Physiol. 1997; 273:H534–H539. [PubMed: 9277466]
92. Henning RJ, Feliciano L, Coers CM. Vagal nerve stimulation increases right ventricular contraction and relaxation and heart rate. Cardiovasc Res. 1996; 32:846–853. [PubMed: 8944815]
93. Sabbah HN. Electrical vagus nerve stimulation for the treatment of chronic heart failure. Cleve Clin J Med. 2011; 78(Suppl 1):S24–S29. [PubMed: 21972326]
94. Zhang Y, Popovic ZB, Bibevski S, et al. Chronic vagus nerve stimulation improves autonomic control and attenuates systemic inflammation and heart failure progression in a canine high-rate pacing model. Circ Heart Fail. 2009; 2:692–699. [PubMed: 19919995]
95. Hamann JJ, Ruble SB, Stolen C, et al. Vagus nerve stimulation improves left ventricular function in a canine model of chronic heart failure. Eur J Heart Fail. 2013; 15:1319–1326. [PubMed: 23883651]
96. Uemura K, Zheng C, Li M, et al. Early short-term vagal nerve stimulation attenuates cardiac remodeling after reperfused myocardial infarction. J Card Fail. 2010; 16:689–699. [PubMed: 20670848]
97. Shinlapawittayatorn K, Chinda K, Palee S, et al. Vagus nerve stimulation initiated late during ischemia, but not reperfusion, exerts cardioprotection via amelioration of cardiac mitochondrial dysfunction. Heart Rhythm. 2014
98. Shinlapawittayatorn K, Chinda K, Palee S, et al. Low-amplitude, left vagus nerve stimulation significantly attenuates ventricular dysfunction and infarct size through prevention of mitochondrial dysfunction during acute ischemia-reperfusion injury. Heart Rhythm. 2013; 10:1700–1707. [PubMed: 23933295]
99. Li M, Zheng C, Sato T, et al. Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats. Circulation. 2004; 109:120–124. [PubMed: 14662714]
100. Muscholl E. Peripheral muscarinic control of norepinephrine release in the cardiovascular system. Am J Physiol. 1980; 239:H713–H720. [PubMed: 7192494]
101. Feigl EO. Parasympathetic control of coronary blood flow in dogs. Circ Res. 1969; 25:509–519. [PubMed: 5351322]
102. Henning RJ, Sawmiller DR. Vasoactive intestinal peptide: cardiovascular effects. Cardiovasc Res. 2001; 49:27–37. [PubMed: 11121793]
103. Zhao G, Shen W, Xu X, et al. Selective impairment of vagally mediated, nitric oxide-dependent coronary vasodilation in conscious dogs after pacing-induced heart failure. Circulation. 1995; 91:2655–2663. [PubMed: 7743629]
104. Sawmiller DR, Henning RJ, Cuevas J, et al. Coronary vascular effects of vasoactive intestinal peptide in the isolated perfused rat heart. Neuropeptides. 2004; 38:289–297. [PubMed: 15464194]

105. Kelly RA, Balligand JL, Smith TW. Nitric oxide and cardiac function. Circ Res. 1996; 79:363–380. [PubMed: 8781470]
106. Feng Q, Song W, Lu X, et al. Development of heart failure and congenital septal defects in mice lacking endothelial nitric oxide synthase. Circulation. 2002; 106:873–879. [PubMed: 12176963]
107. Mungrue IN, Gros R, You X, et al. Cardiomyocyte overexpression of iNOS in mice results in peroxynitrite generation, heart block, and sudden death. J Clin Invest. 2002; 109:735–743. [PubMed: 11901182]
108. Damy T, Ratajczak P, Shah AM, et al. Increased neuronal nitric oxide synthase-derived NO production in the failing human heart. Lancet. 2004; 363:1365–1367. [PubMed: 15110495]
109. Schwartz PJ, De Ferrari GM, Sanzo A, et al. Long term vagal stimulation in patients with advanced heart failure: first experience in man. Eur J Heart Fail. 2008; 10:884–891. [PubMed: 18760668]
110. Premchand RK, Sharma K, Mittal S, et al. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF Trial. J Card Fail. 2014
111. Zannad F, De Ferrari GM, Tuinenburg AE, et al. Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the neural cardiac therapy for heart failure (NECTAR-HF) randomized controlled trial. Eur Heart J. 2014
112. Hauptman PJ, Schwartz PJ, Gold MR, et al. Rationale and study design of the increase of vagal tone in heart failure study: INOVATE-HF. Am Heart J. 2012; 163:954–962. [PubMed: 22709747]
113. Tsutsumi T, Ide T, Yamato M, et al. Modulation of the myocardial redox state by vagal nerve stimulation after experimental myocardial infarction. Cardiovasc Res. 2008; 77:713–721. [PubMed: 18065771]
114. Kong SS, Liu JJ, Yu XJ, et al. Protection against ischemia-induced oxidative stress conferred by vagal stimulation in the rat heart: involvement of the AMPK-PKC pathway. Int J Mol Sci. 2012; 13:14311–14325. [PubMed: 23203066]
115. Wang Q, Cheng Y, Xue FS, et al. Postconditioning with vagal stimulation attenuates local and systemic inflammatory responses to myocardial ischemia reperfusion injury in rats. Inflamm Res. 2012; 61:1273–1282. [PubMed: 22825626]
116. Borovikova LV, Ivanova S, Zhang M, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature. 2000; 405:458–462. [PubMed: 10839541]
117. Yamakawa K, Matsumoto N, Imamura Y, et al. Electrical vagus nerve stimulation attenuates systemic inflammation and improves survival in a rat heatstroke model. PLoS One. 2013; 8:e56728. [PubMed: 23424673]
118. Tracey KJ. The inflammatory reflex. Nature. 2002; 420:853–859. [PubMed: 12490958]
119. Katare RG, Ando M, Kakinuma Y, et al. Differential regulation of TNF receptors by vagal nerve stimulation protects heart against acute ischemic injury. J Mol Cell Cardiol. 2010; 49:234–244. [PubMed: 20302876]
120. Zhang R, Wugeti N, Sun J, et al. Effects of vagus nerve stimulation via cholinergic anti-inflammatory pathway activation on myocardial ischemia/reperfusion injury in canine. Int J Clin Exp Med. 2014; 7:2615–2623. [PubMed: 25356117]
121. Calvillo L, Vanoli E, Andreoli E, et al. Vagal stimulation, through its nicotinic action, limits infarct size and the inflammatory response to myocardial ischemia and reperfusion. J Cardiovasc Pharmacol. 2011; 58:500–507. [PubMed: 21765369]
122. Imataka K, Yamaoki K, Seki A, et al. Peculiar mitral valve and papillary muscle lesions induced by vagus manipulations in rabbits. An experimental model for nonrheumatic mitral regurgitation. Jpn Heart J. 1986; 27:377–386. [PubMed: 3761568]

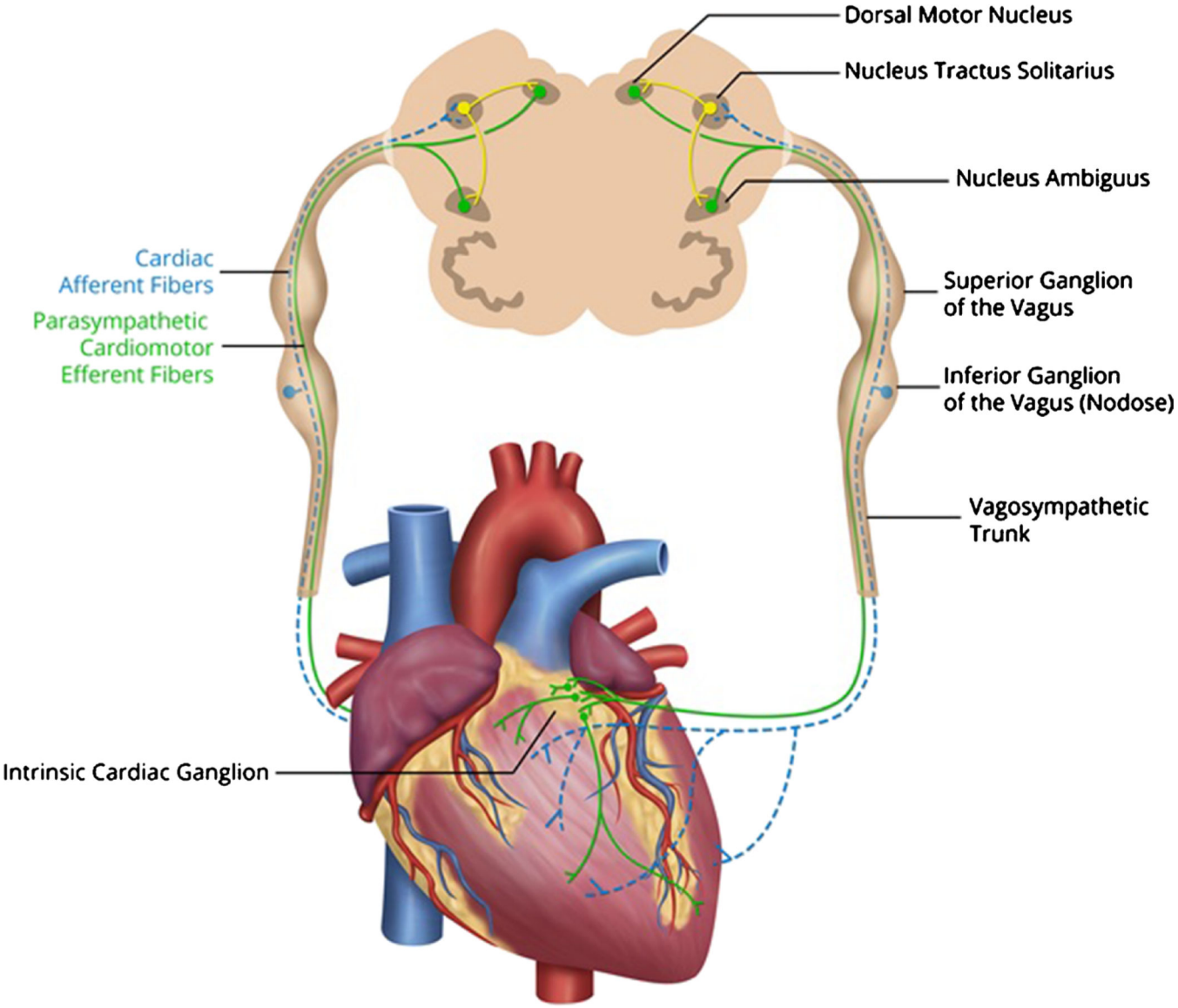

Fig. 1.

The afferent bipolar neurons that lie in the inferior vagal ganglia (nodose ganglia) are bipolar neurons that transmit signals from the myocardium to the brainstem via the vagosympathetic trunk and synapse in the nucleus tractus solitarius. The cardiomotor efferent fibers in the vagosympathetic trunk originate in the brainstem from the nucleus ambiguus and dorsal motor nucleus and are preganglionic fibers that synapse on the neurons of the intrinsic cardiac nervous system. These neurons subsequently provide postganglionic parasympathetic innervation to the *right* and *left* ventricular myocardia, *right* and *left* atria, and sinus and atrioventricular nodes.

Table 1

Anti-arrhythmic mechanisms of VNS

Mechanisms of VNS on reducing ventricular fibrillation	Mechanisms of low-level VNS on reducing atrial fibrillation
Longer VERP	Longer AERP
Higher VFT	Higher AF threshold
Restitution slope <1	Reduced AERP dispersion
Slower HR	Ganglionic plexus
ACh muscarinic receptors	Possible VASOSTATIN-1
Nitric oxide	Nitric oxide
Stellate ganglion remodeling	Stellate ganglion remodeling
CONNEXIN-43 preserved activity	

VERP ventricular effective refractory period, *VFT* ventricular fibrillation threshold, *ACh* acetylcholine, *AERP* atrial effective refractory period, *AF* atrial fibrillation

Table 2

Anti-arrhythmic and pro-arrhythmic VNS Studies of VF/VT

Reference	Animal model	Side	Vagus nerve	Frequency (Hz)	Amplitude, PW	Degree of HR reduction	Abbreviated summary of results with VNS
Anti-arrhythmic							
Ando 2005 [34]	Rats	R	Dec	10	2–6 V, 0.1 ms	10 %	Less VT/VF with ischemia, connexin-43 mediated
Brack 2007 [19]	Rabbits	R	Intact	11±2.2	8±12 V, 0.2 ms	20 %	Higher VFT, reduce APD restitution, isolated normal heart
Brack 2011 [36•]	Rabbits	L	Intact	11±2.4	10±2.2 V, 2 ms	40 %	Less VF, NO mediated, isolated normal heart
Brooks 1978 [39]	Dogs	R/L	Dec	40	5–15 V, 5 ms	100 %	Higher repetitive extrasystole threshold and overdrive pacing at 214 bpm during VNS
Del Rio 2008 [47]	Dogs	B	Intact	10	10 V, 1 ms	50–70 %	Preserves electrotonic coupling during ischemia
James 1977 [43]	Dogs	R	Dec	N/R	5–12 V, 1 ms	0–75 %	Graded VNS increased VFT during ischemia
Kent 1973 [26]	Dogs	B	Intact	10–40	To goal HR, 0.3 ms	60–70 %	Higher VFT during ischemia with VNS
Kolman 1975 [28]	Dogs	B	Dec	40	6–10 V, 0.5 ms	100 %	Higher VFT and VNS during stellate stimulation, overdrive pacing performed at 180–250 bpm
Matta 1976 [38]	Dogs	B	Dec	40	5–15 V, 5 ms	100 %	Higher VFT/RET with VNS and pacing at 214 bpm
Myers 1974 [27]	Dogs	B	Intact/Dec	20–60	1.5–6 V, 0.3 ms	20–75 %	Graded VNS improved survival during ischemia
Ng 2007 [35]	Rabbits	L	Intact	7.9±0.4	1–20 V, 2 ms	20 %	Higher VFT/ERP in isolated normal heart
Rosenshtraukh 1994 [33]	Cats	B	Dec	1–5	5–10 V, 2 ms	50 %	Less VF with VNS during ischemia
Scherlag 1970 [25]	Dogs	R/L	Dec	25	9–15 V, 2–4 ms	100 %	VNS cardioverted PMVT during ischemia
Takahashi 1992 [41]	Rabbits	R	Intact	50	To goal HR, 2 ms	67 %	Less PMVT, more MMVT with VNS with Ce-induced arrhythmias
Takahashi 1998 [30]	Rabbits	L	Dec	50	1–10 mA, 3.0 ms	67 %	Less PMVT, more MMVT with VNS during sympathetic stimulation
Vanoli 1991 [32]	Dogs	R	Intact	3–8	1–3 mA, 3.0 ms	<25 %	Less VF with ischemia in post-infarct canines
Waxman 1989 [49]	Dogs	B	Dec	20	Titrated to goal HR, 2 ms	80 %	VNS raises NE and Epi doses needed to cause VF, negated by atropine
Wu 2011 [37•]	Rats	R	Intact	5	1–6 V, 2 ms	10 %	Less VF with ischemia, connexin-43 mediated
Yoon 1977 [29]	Dogs	B	Dec	10–20	5–8 V, 0.2 ms	IR	Higher VFT in normal hearts, no effect in ischemia
Zheng 2005 [40]	Rats	R	Intact	20	0.1–0.13 mA, 0.2 ms	20–30 %	Less PVCs with VNS post-infarct
Zuanetti 1987 [31]	Cats	B	Dec	10–15	4–10 V, 0.4 ms	60 %	Less VF with VNS during ischemia, attenuated with pacing
Pro-arrhythmic							
Imataka 1986 [122]	Rabbits	R/L	Intact	50	0.3–0.8 V, 1 ms	Severe bradycardia	Transient bigeminy/trigeminy, papillary muscle damage in normal hearts
Kerzner 1973 [59]	Dogs	R/L	Intact/Dec	10–60	5–40 V, 0.5–5 ms	100 %	Salvos of idioventricular rhythm with VNS during ischemia, suppressed with overdrive pacing
Manning 1962 [57]	Cats	R	Dec	10	3–8 V, 2 ms	50 %	More VT/VF with VNS and concurrent RSG stimulation

Curr Treat Options Cardiovasc Med. Author manuscript; available in PMC 2015 November 28.

Reference	Animal model	Side	Vagus nerve	Frequency (Hz)	Amplitude, PW	Degree of HR reduction	Abbreviated summary of results with VNS
Scherf 1961 [55]	Dogs	R	Intact	N/R	N/R	JR	More PVCs with ventricular injection of 20–30 % NaCl
Scherlag 1982 [22]	Dogs	R/L	Intact	20 Hz	10–20 V, 0.5 ms	75–100 %	VNS during ischemia increased PVC/VT in setting of significant bradycardia
Takato 2010 [56]	Rabbits	R	Intact	50 Hz	0.1–1 V, 1 ms	40 %	Bigeminy and papillary/basal muscle damage in normal hearts

Dec decentralized, *Hz* hertz, *V* volt, *ms* millisecond, *VFT* ventricular fibrillation threshold, *PMVT* polymorphic VT, *MMVT* monomorphic VT, *PVC* premature ventricular contraction, *N/R* not reported, *Ce* cesium, *IR* idioventricular rhythm