

Vagus nerve stimulation: An evolving adjunctive treatment for cardiac disease

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ABSTRACT

The vagus nerve is a major component of the autonomic nervous system and plays a critical role in many body functions including for example, speech, swallowing, heart rate and respiratory control, gastric secretion, and intestinal motility. Vagus nerve stimulation (VNS) refers to any technique that stimulates the vagus nerve, with electrical stimulation being the most important. Implantable devices for VNS are approved therapy for refractory epilepsy and for treatment-resistant depression. In the case of heart disease applications, implantable VNS has been shown to be beneficial for treating heart failure in both preclinical and clinical studies. Adverse effects of implantable VNS therapy systems are generally associated with the implantation procedure or continuous on-off stimulation. The most serious implantation-associated adverse effect is infection. The effectiveness of non-invasive transcutaneous VNS for epilepsy, depression, primary headaches, heart failure, and other conditions remains under investigation. VNS merits further study for its potentially favorable effects on cardiovascular disease, especially heart failure. (*Anatol J Cardiol* 2016; 16: 804-10)

Keywords: atrial fibrillation, heart failure, vagus nerve stimulation, ventricular arrhythmia

Introduction

The sympathetic and parasympathetic components of the autonomic nervous system (ANS) regulate the physiological function of a wide range of organs, glands, and involuntary muscles; conversely, the ANS may also contribute importantly to both the development and treatment of disease process in these very same organ systems. By way of example, in cardiovascular medicine, autonomic neural influences play a crucial role in determining the clinical features and severity of a wide range of conditions including hypertension, ischemic arrhythmia, heart failure, and reflex syncope (1). Further, drugs with predominant impact on autonomic function (e.g., beta- and alpha-adrenergic blockers, most antiarrhythmic agents, and angiotensin receptor blockers) are the foundation for treatment of many of these abnormalities. Additionally, apart from drugs, recently there has been increased interest in electrical ANS stimulation for treatment of certain of these disease states. In this regard, the role of direct neural stimulation for therapeutic application may be dated to initial attempts to stimulate the carotid sinus for amelioration of severe angina pectoris (1, 2). However, as more effective medical and surgical techniques were introduced, the carotid sinus electrical stimula-

tion approach largely vanished. On the other hand, indirect electrical stimulation of the heart, and inevitably its peripheral nerves, has been the subject of a number of clinical trials targeting treatment of certain reflex syncopal disorders, particularly carotid sinus syndrome and vasovagal syncope (1, 3). While these latter clinical trials have met with variable success, they have spurred a resurgence of research designed to identify the potential clinical utility of modifying ANS activity by direct electrical stimulation.

Perhaps the ANS region that offers the greatest current interest for direct electrical stimulation is that of the complex neural networks residing on the posterior aspect of the heart (particularly the atria) (1, 4). These neural complexes communicate with the central nervous system via neural connections traveling predominantly along the great vessels of the thorax. In a recent review we summarized the body of research examining these complex networks and their probable contributions to cardiac arrhythmias, including potentially life-threatening channelopathies (4). In terms of current therapeutics, stimulation of certain aspects of these neural networks, particularly the regions adjacent to the pulmonary veins, plays a role in certain atrial fibrillation ablation strategies. In essence, induction of bradycardia by atrial stimulation in the vicinity of the neural network of inter-

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est is used to confirm proximity for purposes of radio-frequency modification of efferent ANS inputs to the heart, which most likely also alter afferent signals to the mid-brain (5, 6). Although the ganglionic ablation strategy for atrial fibrillation ablation remains controversial, the concept of direct ANS stimulation to identify a ganglionic target continues to be employed in many clinical electrophysiological laboratories for difficult cases (6).

Apart from targeting ganglionic plexus (GP), there are various elements of the ANS that may be amenable to functional modification by direct electrical stimulation. In this context, the vagus nerve (10th cranial nerve) has the virtue of being readily accessible (vagus nerve stimulation, VNS). The vagus is principally a mixed parasympathetic nerve, containing both afferent and efferent sensory fibers. Vagal nerve activity plays a prominent role in heart rate and respiratory control, gastric secretion, and intestinal motility. In addition, vagus nerve connections modulate the function of higher brain centers, forming the basis for its potential use in many clinical disorders (1, 3, 4). For instance, the vagus nerve plays a key role in blood pressure (BP) control. Further, in conjunction with sympathetic "withdrawal" in reflex vasodepressor syncope, increased parasympathetic activity largely traveling in the vagus nerve can act to substantially reduce BP. This latter attribute was investigated in our laboratory and we demonstrated that enhanced vagal activity triggered indirectly by carotid sinus stimulation acted to reduce systemic BP even in the setting of sympathetic blockade and absence of cardiac slowing (7). This and other similar observations provide a reasonable basis for assessing the potential for direct vagal stimulation to contribute to BP control in difficult to treat patients, and by virtue of afterload reduction, to possibly play a role in treatment of both low cardiac output states, and diminishing arrhythmia susceptibility in systolic heart failure (8).

Apart from its potential value for cardiovascular disease, electrical stimulation of the vagus (either directly or indirectly) has proved useful in treatment of a number of other medical conditions. In this regard, electrical VNS has US Food and Drug Administration (FDA) approval for management of epilepsy and depression. In addition, VNS is being studied for possible benefits in headache, gastric motility disorders, and asthma (9). This article focuses primarily on development of clinical VNS for cardiac applications, including consideration of VNS device types (invasive or noninvasive), and potential adverse effects.

Development of clinical VNS

VNS and epilepsy

In the late 19th century, VNS was first used to treat epilepsy by American neurologist James Corning, but the method was associated with excessive adverse effects (e.g., bradycardia, syncope) and was abandoned (10). More recently the concept has been resurrected and is used clinically.

VNS effectiveness in epilepsy was demonstrated with early animal studies (11, 12). Subsequently, clinical studies of implant-

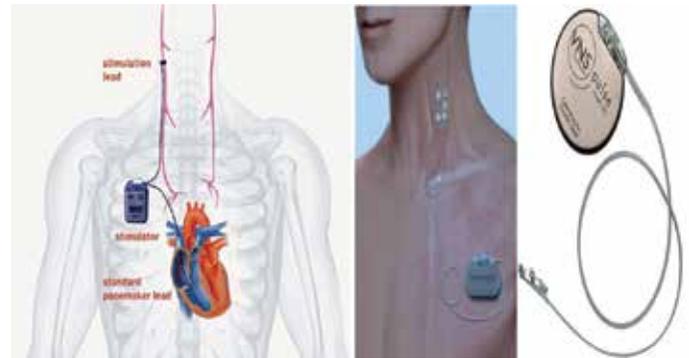


Figure 1. Implantable vagus nerve stimulation therapy system (Cardiofit™, BioControl-Medical, Yehud, Israel; Pulse Model 102 Generator, Cyberonics, Inc., Houston, TX, USA.)

able VNS Therapy System® (Cyberonics, Inc., Houston, TX, USA, Fig.1) in patients with refractory epilepsy, showed a seizure reduction of $\geq 50\%$ in 24.5% to 46.6% of patients (13). The VNS Therapy System® was approved for the treatment of medically refractory epilepsy in Europe in 1994 and in the USA and Canada in 1997. As of August 2014, over 100,000 VNS devices had been implanted in more than 75,000 patients worldwide (14).

The mechanism(s) of VNS benefit for epilepsy prevention remains largely unknown. However, in this regard, we have recently reported that ictal asystole may be a model for improving understanding of 1 set of cortical sites that may trigger both vagal bradycardia and vasodepression mimicking a reflex faint. In essence, focal epilepsy arising in the right or left insular cortex has been associated with both a drop in BP and at times bradycardia, and thereby may reflect 1 cortical region in which electrical stimulation may modify susceptibility to epilepsy, as well as beneficially reduce BP when desired (15, 16).

VNS and depression

VNS has also found a role in the management of treatment-resistant depression (TRD). Several observations led to consideration of this application, including in particular improvement of mood and cognition in epilepsy patients after initiation of VNS therapy, and usage of several anticonvulsant medications as mood stabilizers and antidepressants in bipolar disorder.

Brain regions that are critical to mood regulation (orbital cortex, limbic system) are targets for VNS. Rush et al. (17) designed a study to investigate effect of VNS on TRD. In short-term VNS therapy for TRD, there was no statistical difference between VNS therapy "on" versus VNS "off," in terms of the 24-item Hamilton Depression Rating Scale (HRSD24) response. However, the study was extended to 1 year in 205 patients, and findings indicated that the HRSD24 score improved significantly in VNS therapy group ($p < 0.001$) (18). Based on these observations, VNS therapy was approved by FDA for TRD patients ≥ 18 years old (19).

VNS and heart disease

As noted earlier, neural stimulation for amelioration of cardiovascular disease has been the subject of study for many

years. Early interest focused on carotid sinus stimulation for intractable angina and later for treatment of hypertension (2). These applications are summarized further below, but were based on the already well-known propensity for carotid sinus massage to decrease heart rate and BP. More recently, direct VNS has begun to be of special interest as an adjuvant therapy in heart failure patients.

Carotid sinus nerve stimulation (CsNS) for angina pectoris and hypertension

Stimulation of baroreceptors in the carotid sinuses and aortic arch results in reflex systemic arterial and splanchnic bed dilation, and reduction of both heart rate and myocardial contractility (20). The heart rate and contractility changes occur as a consequence of reduction in the frequency of sympathetic efferent impulses to sinus node and ventricular muscle, and an increase in the frequency of vagal impulses (21).

In the mid-20th century CsNS gained interest as a potential means for alleviating drug-refractory angina pectoris, by decreasing myocardial oxygen consumption (i.e., decreased heart rate and contractility) at a time when it was not possible to improve myocardial blood supply (1, 22). Braunwald et al. (23), in a landmark report, showed that carotid nerve stimulation decreased angina episodes and increased exercise tolerance in 15 of 22 patients who had stable coronary artery disease. However, CsNS never became a mainstream therapy for angina pectoris due to advances in both pharmacological and coronary reperfusion strategies.

CsNS has also been investigated for systemic hypertension for more than 40 years. An implantable CsNS therapy system (Barostim neo™ System, CVRx Inc., Minneapolis, MN, USA, Fig. 2) has CE (Conformité Européene) mark in Europe for the treatment of hypertension patients. This device is currently under clinical evaluation in the USA and Canada for the treatment of high blood pressure and heart failure (24).

VNS for heart failure

That autonomic disturbances contribute importantly to the progression of heart failure is now widely recognized (1, 22). In this context, autonomic imbalance characterized by vagal withdrawal and increased sympathetic activity has been shown to play a major role in the worsening of both heart failure and its prognosis. Specifically, while sympathetic pre-dominance may be beneficial in acute cardiac events to maintain cardiac output, chronically excessive sympathetic activity is detrimental, contributing to adverse cellular calcium loading, left ventricular (LV) remodeling, myocyte apoptosis, fibrosis, and electrical instability.

Clinical evidence from the Autonomic Tone and Reflexes after Myocardial Infarction study (25) and the Cardiac Insufficiency Bisoprolol Study II (26) indicates that diminished cardiac vagal activity and increased heart rate predict a high mortality rate in congestive heart failure. Therefore, modulation of the ANS (neuromodulation) with the aim of restoring a more normal



Figure 2. Carotid sinus nerve stimulation therapy system (Barostim neo™ System, CVRx Inc., Minneapolis, MN, USA)

autonomic balance is gaining increasing interest as a potential therapy for patients with heart failure. In this regard, it is hypothesized that electrical stimulation of the vagus nerve may help to normalize parasympathetic activation of cardiac control reflexes and inhibit sympathetic hyperactivation (1, 27).

In preclinical studies, VNS has demonstrated improved cardiac electrical and mechanical function. For instance, Li et al. (28) showed improvement in hemodynamics, LV remodeling and reduced neurohormonal activation with VNS in a rat infarct model with heart failure. Study results showed a reduction in mortality rate at 140 days (50% in the sham model and 14% with VNS stimulation) (28).

An initial clinical study for heart failure included patients with New York Heart Association (NYHA) class II-III heart failure and LV ejection fraction (LVEF) <35%. This report demonstrated improvement of LV end-systolic volume (LVESV), NYHA classification, and quality of life (29). A subsequent report on patients with reduced EF and NYHA classes II-IV showed improvement in LVEF, cardiac volume, and 6-minute walk test at 6 months, which was maintained at 1 year (30).

The Increase of Vagal Tone in Heart Failure (INOVATE-HF) trial (Cardiofit™ VNS therapy system; BioControl Medical, Yehud, Israel, Fig. 1) is similarly assessing VNS in heart failure and has just recently achieved target of 650 patients. Findings are expected in December 2016.

Neural Cardiac Therapy for Heart Failure (Precision™, Boston Scientific Corporation, St. Paul, MN, USA) was a randomized controlled trial of VNS in patients with EF <35%, increased LV end-diastolic dimensions (>55 mm), and NYHA classes III-IV, but excluding patients with cardiac resynchronization therapy devices; or QRS>130 milliseconds (31). Patients were randomized in a 2:1 fashion to VNS on or off for 6 months. The primary endpoint was improvement in LV systolic dimensions; secondary endpoints were improvement in other echocardiographic param-

eters and circulating biomarkers. The study failed to reach primary or secondary endpoints; however, it did show improvement in quality of life and NYHA classification (31).

The Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure (Cyberonics, Houston, TX, USA) study investigated VNS of right or left cervical vagus in 60 patients (32). The main inclusion criteria were EF <40%, LV end-diastolic dimensions 50–80 mm, and QRS<150 milliseconds. There was improvement in LVEF by 4.5%, but LVESV did not decrease significantly. There was again an improvement in quality of life, exercise capacity, and NYHA classification. There was no significant difference between left or right cervical vagus stimulation (32).

VNS for cardiac arrhythmias

Atrial fibrillation

As discussed earlier, supra-threshold VNS (i.e., electrical stimulation of the vagus nerve at a voltage level that slows the sinus rate or prolongs atrioventricular conduction) has been studied in other cardiac and non-cardiac diseases. Supra-threshold VNS has been used to induce and maintain atrial fibrillation (AF), and animal studies have shown that supra-threshold VNS can be utilized to induce and maintain AF in experiments. However, recent experimental and clinical studies show that low-level cervical VNS (i.e., the voltages/currents do not slow the sinus rate or prolong atrioventricular conduction) induces effects opposite to supra-threshold VNS and plays an anti-arrhythmic role in AF management. Since 2009, several studies have reported the anti-arrhythmic role of low-level cervical VNS in AF population (33–36). For example, Li et al. (33) showed that cervical low-level VNS induced a progressive increase in AF threshold at all pulmonary vein and atrial appendage sites. Yu et al. (34) also demonstrated that cervical low-level VNS inhibited AF inducibility, prevented shortening of effective refractory period (ERP) at pulmonary vein and atrial sites and increase of ERP dispersion induced by activation of atrial GP. Finally, a series of recent studies also showed that cervical low-level VNS can prevent and/or reverse atrial electrophysiological remodeling and autonomic remodeling (35, 36).

Cervical VNS is an invasive approach in which cervical surgery is needed to position vagal stimulation electrode and has adverse effects that are discussed in detail below. Recently, a noninvasive approach for VNS (nVNS), transcutaneous electrical stimulation of the auricular branch of the vagus nerve located at the tragus, has been used in some studies (Fig. 3). In these studies, it has been shown that low-level nVNS suppressed AF, reversed acute atrial electrophysiological remodeling, decreased sympathetic nerve activity and increased heart rate variability (37, 38).

Ventricular arrhythmias

As noted earlier, different levels of parasympathetic stimulation exert different anti-arrhythmic effects. Thus, it has been



Figure 3. Non-implantable vagus nerve stimulation systems: (a) NEMOS® (transcutaneous vagus nerve stimulation; Cerbomed, Erlangen, Germany), (b) gammaCore (noninvasive vagus nerve stimulation; ElectroCore, Basking Ridge, NJ, USA)

shown that parasympathetic hyperactivity induces and maintains AF, but at the same time, parasympathetic hyperactivity is protective for ventricular arrhythmias. In animal studies, cervical supra-threshold VNS suppressed the incidence of ventricular arrhythmias, especially ventricular tachycardia and ventricular fibrillation during acute myocardial ischemia and ischemia reperfusion (39, 40). Multiple mechanisms have been described to explain this anti-arrhythmic effect of VNS, such as its bradycardiac effect, anti-adrenergic effects, prevention of the loss of phosphorylated connexin 43 proteins, and inhibition of the opening of the mitochondrial permeability transition pore. The anti-arrhythmic role of atrial GP stimulation has also been investigated in several studies. In the normal heart, activation of atrial GP prolonged ventricular ERP, decreased the slope of ventricular action potential restitution curves and delayed action potential duration (41). In the ischemic heart, atrial GP activity significantly inhibited the incidence of ventricular arrhythmias during not only acute myocardial ischemia (42), but also ischemia reperfusion (43). Atrial GP stimulation also increased heart rate variability and prevented the loss of connexin 43 induced by ischemia/reperfusion (43).

VNS device types and adverse effects

Implantable VNS appears to be safe and well tolerated. The electrodes are attached to the left or right vagus nerve connected to a stimulating device implanted under the anterior chest wall (Fig. 1). Stimulation is turned on or off by a magnet. The VNS device may operate using a wide variety of stimulation parameters (output current, signal frequency, pulse width, signal on time, signal off time). Currently approved stimulation parameters are 0.25–3.5 mA (0.25 mA steps), 20–30 Hz (<10 Hz is ineffective, >50 Hz might induce nerve damage), 0.25–0.5 milliseconds pulse, signal on for 30–60 seconds, and signal off for 5 minutes. (44, 45) A rapid stimulation of signal on for 7 seconds and off for 14–21 seconds is also available (46). The optimal VNS stimulation settings, however, remain unknown.

Adverse events (AEs) with VNS are generally associated with implantation or continuous on-off stimulation. As is the case with any implanted device, infection is the most serious implantation-associated complication. Bradycardia and asystole have also been described during implantation, as has vocal cord palsy, which has been noted to persist up to 6 months, and occurrence depends on surgical skill and experience. Recently, a retrospective study (47) was published that was designed to investigate surgical and hardware-related complications of VNS implantation. Complications related to surgery occurred in 8.6% and hardware complications in 3.7%. Table 1 summarizes complication rates related to surgery and hardware. Complication rates in the first 10 years of implantation experience were compared with last 15 years implantation experience; similar surgical complication rates were found in both groups (8.9%, 9.2%) but hardware-related complication rates were less in the last 15 years experience (7.3%, 2.3%).

The most frequent stimulation-associated AEs include voice alteration, paresthesia, cough, headache, dyspnea, pharyngitis, and pain. Table 2 summarizes stimulation-associated AEs in clinical trials of the VNS Therapy System. The frequency of these AEs declines with continued treatment (48). Treatment will likely require a decrease in stimulation strength or intermittent or permanent device deactivation (9).

Table 1. Complications of implantable VNS device related to surgery and hardware (47)

Complications related to surgery	Rate (%)
Hematoma	1.9
Infection	2.6
Vocal cord palsy	1.4
Lower facial weakness	<1
Pain and sensory-related complications	1.4
Bradycardia	<1
Complications related to hardware	Rate (%)
Lead fracture/lead malfunction	3
Spontaneous VNS turn-on	<1
Lead disconnection	<1
VNS - vagus nerve stimulation	

Table 2. Stimulation-associated adverse events in clinical trials of the VNS Therapy System (48)

Adverse event	3 months (%)	12 months (%)	5 year (%)
Cough	21	15	1.5
Voice alteration	62	55	18.7
Dyspnea	16	13	2.3
Pain	17	15	4.7
Paresthesia	25	15	1.5
Headache	20	16	NA
VNS: vagus nerve stimulation			

Alternative nVNS delivery systems such as that stimulating the tragus of the ear avoid surgery-related complications and may limit AEs related to the continuous on-off stimulation cycle of implantable devices since nVNS devices can be adjusted to balance efficacy and tolerability (49, 50). Efficacy could not be compared between implantable VNS system and nVNS system at the time of this review. Randomized prospective studies are needed to compare efficacy of nVNS with implantable VNS therapy system.

Summary

Neuromodulation offers a potentially important new approach to enhance treatment of a range of cardiovascular diseases. VNS is currently the neuromodulation method that has so far received most clinical interest. Specifically, by modifying sympathetic/parasympathetic balance to the heart and other cardiovascular structures, VNS may offer an adjunct to conventional treatment strategies for a number of inadequately controlled cardiovascular conditions. At present, heart failure provides the most important potential application, but additional study is needed to ascertain whether VNS will provide substantial incremental benefit. However, other possible VNS opportunities may include ameliorating inappropriate sinus tachycardia, preventing AF and reducing propensity for sudden death in certain high-risk populations.

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