Clinical Trial: Methods & Design

Autonomic Regulation Therapy for the Improvement of Left Ventricular Function and Heart Failure Symptoms: The ANTHEM-HF Study

LORENZO DICARLO, MD,1 IMAD LIBBUS, PhD,1 BADRI AMURTHUR, MS, MBA,1 BRUCE H. KENKNIGHT, PhD,1 AND INDER S. ANAND, MD, FRCP, DPhil (Oxon)2

Houston, Texas; and Minneapolis, Minnesota

ABSTRACT

Background: Outcomes of heart failure (HF) have improved dramatically with the use of blockers of the sympathetic and renin-angiotensin-aldosterone systems, as well as with more prevalent use of implantable cardiac defibrillators and cardiac resynchronization therapy. Despite these interventions, however, the overall prognosis of HF patients remains poor. Recently, stimulation of the right cervical vagus nerve in patients with symptomatic heart failure has been evaluated. Results suggest that vagal nerve stimulation provides sustained improvement in left ventricular (LV) function and symptoms associated with HF. However, much remains to be learned about the risks and benefits of therapies that alter autonomic regulatory function for the treatment of heart failure.

Methods: The Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure (ANTHEM-HF) study has been designed to address several key clinical questions about the role of autonomic regulation therapy (ART) in patients with LV dysfunction and chronic symptomatic heart failure.

Conclusions: ANTHEM-HF should provide additional and valuable information regarding the safety and the relationship between the site and intensity of ART and its salutary effects on HF. (J Cardiac Fail 2013;19:655–660)

Key Words: Vagus nerve, neural stimulation, autonomic balance.

The pathophysiology of HF is characterized by hemodynamic abnormalities1 that result in neurohormonal activation2 and autonomic imbalance with increase in sympathetic activity and withdrawal of vagal activity.3 The spectacular success in reducing HF morbidity and mortality by inhibiting certain neurohormones with β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and aldosterone receptor blockers underscores the important role played by neurohormonal activation during the progression of HF.4–8 However, despite these advances in the use of neurohormonal blockade and more recently the use of implantable cardioverter-defibrillator9 and cardiac resynchronization therapy (CRT) devices10 in the management of patients with HF, the overall prognosis of these patients remains poor.11 Therefore, development of novel therapeutic approaches for the treatment of HF remains crucial.

An approach that could further advance the neurohormonal and autonomic imbalance hypothesis in HF is the improvement of autonomic regulatory function by vagal nerve stimulation (VNS). Reduced vagal activity is associated with increased mortality in patients with HF,3,12 and a number of investigators have shown that restoration of autonomic regulatory function by VNS improves survival in animal models of HF. Li et al13 randomized myocardial infarction (MI)—induced HF rats to vagal or sham stimulation...
14 days after MI. The vagus nerve was stimulated for 10 s/min with an intensity adjusted to reduce heart rate by 5%–8% (20–30 beats/min in rats). Compared with sham stimulation, VNS was associated with a significant improvement in left ventricular (LV) hemodynamics and remodeling as well as reduced neurohormonal activation. This was associated with a significant decrease in mortality in the VNS rats at 140 days, from 50% to 14% compared with sham-stimulated rats.\(^\text{13}\) In the canine model of microembolization-induced heart failure, VNS significantly improved LV structure and function compared with sham-operated animals, independently from the use of \(\beta\)-blockers and additive to the effects of \(\beta\)-blockade.\(^\text{14}\) Similar beneficial effects of VNS on LV remodeling were reported also in the canine pacing model of HF.\(^\text{15}\) Dogs randomized to pacing alone continued to increase their LV dimensions, whereas those randomized to pacing and VNS had a significant attenuation of LV remodeling. Interestingly, these effects were seen in the absence of any heart rate lowering effect of VNS, because both groups were subjected to the same constant ventricular pacing.\(^\text{15}\) These data suggest that the beneficial effects of VNS could be seen independently from HR lowering.

More recently, a multicenter open-label phase II safety and feasibility study was reported with the use of right cervical VNS synchronized to the cardiac cycle (Cardiofit System; BioControl Medical, Yehud, Israel).\(^\text{16}\) The study occurred in 32 New York Heart Association (NYHA) functional class II–IV patients, aged 56 ± 11 years, with LV ejection fraction (LVEF) 23 ± 8%. VNS was titrated to a maximum stimulation amplitude of 5.5 mA, an HR reduction of 5–10 beats/min, or the development of intolerable side effects. After 6 months, VNS was associated with a significant improvement in NYHA functional class, quality of life, 6-minute walk distance, LVEF, and LV systolic volumes. These improvements were maintained at 1 year. However, beneficial effects of VNS were accompanied by serious adverse events in 41% of the patients, including 3 deaths and 2 device-related adverse events. Less serious but nonetheless bothersome adverse effects included cough, dysphonia, and pain related to stimulation of the right cervical vagus nerve.

That open-label study suggested that chronic VNS could provide favorable long-term beneficial effects on LV function that might translate into improved outcomes in patients with HF. However, the study also raised several questions that need to be addressed:

1) Does stimulation of the left vagus have similar effects on LV remodeling?
2) Are the beneficial effects of VNS independent of its HR-lowering effects and additive to effects of \(\beta\)-blockers?
3) Could lower-amplitude VNS have the same beneficial effect on LV remodeling while minimizing side effects?
4) Does VNS that is not synchronized to the cardiac cycle have the same beneficial effect on LV remodeling while eliminating acute and chronic risks associated with endocardial lead implantation?
5) Are the therapeutic effects of VNS dependent on the etiology of LV dysfunction?

The Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure (ANTHEM-HF) study has been designed to address some of these key questions.

### Study Hypotheses

ANTHEM-HF is a feasibility study to demonstrate safety and to investigate several key methodologic questions regarding ART for the treatment of patients with chronic symptomatic heart failure and reduced left ventricular ejection fraction. The study will collect exploratory data to test the following hypotheses:

1) Left or right VNS provides similar salutary effects on LV remodeling in patients with HF.
2) The beneficial effects of VNS are independent from its rate-lowering effects and additive to the effects of \(\beta\)-blockade.
3) Lower-amplitude VNS improves LV function and HF symptoms with an acceptable risk (risk-to-benefit ratio).
4) The beneficial effects of VNS can be achieved without synchronization to the cardiac cycle, obviating the need for endocardial right ventricular sensing.
5) VNS has similar beneficial benefit effects in patients with ischemic and nonischemic cardiomyopathy.

### Methods

#### Study Design

ANTHEM-HF is an open-label multicenter study designed to test the safety and feasibility of VNS in patients with chronic HF.

#### Device Description

The Cyberonics VNS Therapy System (Implantable Pulse Generator model 103, lead model 304) will be used in this study. This is the same system that is commercially available in the United States and Europe for the treatment of epilepsy and depression. The system consists of an implantable pulse generator, a bipolar helical cuff lead, and an external programming system (Figs. 1 and 2). The implantable pulse generator is capable of delivering low-current electrical pulses with adjustable parameters to stimulate the cervical vagus nerve. The bipolar stimulation lead has 3 self-sizing helical cuffs, 2 of which contain stimulation electrodes and 1 serving as an anchor to stabilize the lead and reduce issues associated with cyclic stress and strain. VNS parameters can be remotely programmed with the use of an external programming system consisting of a model 201 programming wand and version 8 software running on a model 250 handheld computer with Windows Mobile (2003
2nd edition) operating system (Fig. 2). The programming wand communicates with the pulse generator via telemetry, thereby enabling functional assessments (device diagnostics), noninvasive programming, and data retrieval.

Device Implantation Procedure

Patients will be implanted with a VNS Therapy System subcutaneously. Following the commercial implantation procedure, the lead will be placed on the left or right cervical vagus nerve in the neck, and the lead body will be tunneled from the neck incision site to the pulse generator in the chest pocket. The lead will be placed with distal electrode positioned distal to the patient’s head (anchor tether proximal to the head), which is the opposite of the commercial implant configuration for epilepsy and depression.

Study Objectives

The primary safety objective is the incidence of procedure and device-related complications. The primary efficacy objective of the study is to evaluate the effects of chronic VNS on the echocardiographic changes in LV end-systolic volume (LVESV) and LVEF. Several other exploratory echocardiographic measurements will also be made. The secondary objectives are changes in NYHA functional class, Minnesota Living With Heart Failure quality of life score, 6-minute walk distance, and NYHA functional class at the end of 6 months of VNS. Several other measurements, such as neurohormones, heart rate variability, baroreceptor sensitivity slope, and health care utilization, will also be made as exploratory analyses.

Study Population

A maximum of 60 subjects with NYHA functional class II—III heart failure, aged ≥18 years, are eligible for enrollment and randomization. At the time of enrollment into the study, subjects will have been prescribed to optimal oral pharmacologic management with stable β-blocker therapy for HF (as indicated and tolerated) for ≥3 months, and all other oral pharmacologic therapy for HF (as indicated and tolerated) for ≥1 month. Key inclusion criteria include a LVEF ≤40%; LV end-diastolic diameter ≥50 mm and <80 mm; QRS width ≤150 ms; physically capable of performing 6-minute walk test (6MWT) with a baseline 6MWT distance of 150—425 meters, being limited by HF symptoms.

Key exclusion criteria include:

- Heart failure due to congenital heart disease; mitral or aortic valve disease; or hypertrophic obstructive cardiomyopathy or infiltrative cardiomyopathy;
- Medical conditions including vasovagal syncope or vasodepressor syncope; congenital or acquired long QT syndrome; recurrent nerve paralysis; carotid or vertebral vascular malformation; carotid murmur, vascular bruit, or carotid artery lesion; severe vertebral cervical disease or limited neck mobility; childbearing potential, pregnancy, or breast-feeding; presence of autonomic or sensory neuropathy of any cause; diabetes mellitus with measured hemoglobin A1c > 8.0% in the past 60 days; untreated hypothyroidism or hyperthyroidism; or anticipated life expectancy of <12 months;
• History of unstable angina, myocardial infarction, cerebral vascular accident, or transient ischemic attack within the past 90 days; refractory hypotension; asthma, severe chronic obstructive pulmonary disease; severe restrictive lung disease or oxygen dependence; peptic ulcer disease or upper gastrointestinal bleeding within the past 180 days;
• A treatment history of cardiac transplantation, coronary artery bypass surgery (CABG), valve replacement or repair, aortic surgery, or percutaneous coronary intervention (PCI) within the past 90 days; CRT; subcutaneous thoracic implantation of semi/permanent devices, such as vascular catheters; radiother-apy for thyroid disease/cancer; previous neck surgery and resultant scar formation that would interfere with the ability to implant the study system; tracheotomy; hospitalization or need for intravenous HF therapy within the past 30 days; sleep apnea or sleep-disordered breathing therapies to maintain airway patency with or without oxygen supplementation; renal dialysis; use of investigational therapy within the past 90 days; vagotomy; previous or existing VNS treatment; inability to tolerate the anesthesia required for VNS Therapy System implantation;
• Anticipated intervention during the course of the study such as cardiac surgery, cardiac transplantation, pacing, or CRT implantation; or shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy.

Study Treatment

Currently, 10 sites are participating in the study; however, additional sites may be added. Subjects who provide informed consent are randomized to thoracic subcutaneous VNS Therapy System implantation for either right or left cervical VNS. After a 2-week post-implant recovery period, the device is activated. Vagal nerve stimulation begins at an output current amplitude of 0.25 mA, pulse frequency of 10 Hz, pulse width of 130 μs, and duty cycle of 17.5% (14 s on/66 s off). Over the 10-week titration period, stimulation parameters are adjusted in a stepwise fashion under continuous ECG monitoring during weekly sessions to a pulse width of 250 μs, a pulse frequency of 10 Hz, and an output current amplitude of 1.5 - 3.0 mA, limited by acute expression of VNS-related side effects such as activation of the expiratory reflex (mild cough) or heart rate response (> 4 bpm). Once the titration period is complete, VNS therapy is sustained for 26 weeks. Subjects will have 2 follow-up visits, at 13 and 26 weeks after titration.

Subjects are instructed regarding potential adverse device-related effects and are provided a magnet to inhibit pulse generator stimulation in the event of any uncomfortable device-related effects. Should subjects perform this intervention, they are instructed to contact the site investigator, who will assess whether an adverse device-related effect has occurred and whether the programmed settings should be changed.

Study Measurements

At each follow-up visit, the following assessments are made: device system diagnostics and change in device parameters settings if necessary; measurement of LVESD and LVE SV; LVEF; NYHA functional class; 6MWT; quality of life assessment with the Minnesota Living With Heart Failure Questionnaire; heart rate variability; baroreflex sensitivity slope (optional); B-type natriuretic peptide (BNP), N-terminal pro-BNP, glomerular filtration rate, norepinephrine, angiotensin II, and C-reactive protein; health care utilization; and adverse events.

Study Analysis

All transthoracic echo recordings and blood samples are sent to a designated core laboratory facility for analysis. All adverse events will be adjudicated by an independent clinical events committee, who will determine whether events are device related or not device related.

In addition to testing the primary and secondary objectives of the study, exploratory analyses will also be performed to evaluate the safety and efficacy of VNS therapy based on a patient’s baseline LVEF, baseline heart rate, heart rate lowering, and stimulation intensity. These analyses will be used to generate hypotheses for future studies.

Study Risks and Mitigations

VNS is known to affect the sinoatrial and atrioventricular nodes. Although there is a risk that VNS during this study could cause bradycardia and/or asystole, significant bradycardia has not been observed clinically in HF patients using stimulation intensities greater than those used in this study.8 The Cyberonics VNS Therapy System has been used to treat > 100,000 patients worldwide with left VNS for epilepsy and depression. A reversible bradycardia occurred in only 0.1% of patients. In this study, the intensity of VNS is programmed to levels below the threshold for symptomatic bradycardia.

Very high-intensity VNS (10–20 mA) is also known to alter the atrial refractory period, which might promote the initiation and maintenance of atrial fibrillation (AF). In nonhuman studies, intense right VNS has been observed to induce acute AF that is usually not sustained. Although AF has been reported rarely during the acute phase of VNS in humans, a definite temporal relationship between VNS and development has not been established. In the present study, subjects are observed at weekly intervals during the titration phase of VNS therapy for any possible adverse effects, including the development of AF. If AF occurs during VNS and is considered to be due to VNS, the investigators are advised to use their clinical judgment regarding continuation of ART.

Although all previous clinical and preclinical research has suggested a beneficial effect of VNS on cardiac function and symptoms of HF, it is possible that VNS may worsen HF; and even lead to cardiac decompensation. Subjects are observed closely during the study for the development of any signs and symptoms of worsening HF. In the event of worsening HF that is considered due to VNS, the principal investigator may discontinue VNS.

All adverse events are reviewed by an independent data and safety monitoring board (DSMB) to determine if the investigational therapy poses an unacceptable risk to subject safety. The DSMB has the authority to halt the study to ensure subject safety.

Discussion

One of the hallmarks of HF is autonomic imbalance with withdrawal of parasympathetic activity and increase in sympathetic activity.17 Some of the physiologic manifestations of autonomic imbalance include a decrease in baroreflex sensitivity and reduction in heart rate variability, both of which are associated with increased mortality.13–15,18
Moreover, acute decompensated HF is preceded by withdrawal of parasympathetic activity. Thus the vagus nerve appears to play an important role in the pathogenesis of heart failure.

Cardiac efferent fibers constitute only a small portion of the vagal trunk. Under normal circumstances, efferent vagal impulses are conducted to the heart throughout the cardiac cycle and mediate parasympathetic influence on heart rate and local cardiac reflex processing via release of acetylcholine and other neurotransmitters. In addition to its effects on the sinoatrial and atrioventricular nodes, the release of acetylcholine by vagal efferents stimulates the muscarinic receptors in the myocardium. There is evidence in animals and humans that stimulation of the local muscarinic receptors in the heart inhibit norepinephrine release from adrenergic nerve terminals, and therefore muscarinic receptors in the heart appear to play an important role in the modulation of cardiac sympathetic activity in both normal and HF patients. In HF, parasympathetic ganglionic transmission is reduced, muscarinic receptor density and composition are altered, and acetylcholinesterase activity is decreased. Therefore, a reduction in parasympathetic activity, as seen in HF, would further contribute to increase norepinephrine in the heart with consequent long-term deleterious effects. Interestingly, the salutary effects of VNS on LV function and HF symptoms are not dependent on a reduction in heart rate. These data provide support for the role of other, nondromotropic, mechanisms that have been proposed for the beneficial effects of VNS seen in preclinical and clinical studies.

Studies have also shown some subtle differences in the response to right and left VNS. In addition to reducing heart rate, right cervical VNS has been shown to increase nitric oxide activity and cause vasodilation. It also increases heart rate variability, reduces systolic blood pressure, diminishes sympathetic nervous system activation of T cells, reduces reactive oxygen species, and decreases inflammation and fibrosis. Right cervical VNS also reduces renal sympathetic nervous activity, resulting in renal arterial vasodilation with a decrease in plasma renin activity and activation of the renin-angiotensin-aldosterone system.

Although the left vagal nerve may have a proportionally lower number of cardiac efferent fibers than the right vagal nerve, acetylcholine responses in cats have been observed by the separate stimulation of the right or the left cervical vagal nerves. In dogs, left cervical VNS has been observed to decrease left stellate ganglion activity, morning surge of heart rate, and pacing-induced paroxysmal atrial tachycardia while having less of an impact on heart rate than right cervical VNS. Thus, the preclinical data support left cervical VNS being safe and having salutary effects in chronic HF.

**Summary**

ANTHEM-HF is a feasibility study to investigate several key methodologic questions regarding ART for the treatment of patients with chronic symptomatic HF and reduced LVEF. The hypotheses being tested in ANTHEM-HF will provide additional and valuable information regarding the relationship between the site and intensity of VNS and its effects on HF.

**Disclosures**

Drs DiCarlo and Anand are consultants to Cyberonics. Dr Libbus, Mr Amurthur, and Dr KenKnight are employees of Cyberonics.

**References**


