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Autonomic Regulation Therapy via Left or Right Cervical Vagus Nerve Stimulation in Patients With Chronic Heart Failure: Results of the ANTHEM-HF Trial

RAJENDRA K. PREMCHAND, MD,[1] KAMAL SHARMA, MD,[2] SANJAY MITTAL, MD,[3] RUFINO MONTEIRO, MD,[4] SATYAJIT DIXIT, MD,[2] IMAD LIBBUS, PhD,[5] LORENZO A. DICARLO, MD,[6] JEFFREY L. ARDELL, PhD,[7] THOMAS S. RECTOR, PharmD, PhD,[8] BADRI AMURTHUR, MS,[5] BRUCE H. KENKNIGHT, PhD,[5] AND INDER S. ANAND, MD, DPhil (Oxon), FRCP[8]

Secunderabad, Ahmedabad, Haryana and Goa, India; Houston, Texas; San Francisco and Los Angeles, California; and Minneapolis, Minnesota

ABSTRACT

Objective: ANTHEM-HF evaluated a novel autonomic regulation therapy (ART) via either left or right vagus nerve stimulation (VNS) in patients with heart failure (HF) and reduced ejection fraction (HFrEF).

Methods and Results: Sixty subjects (New York Heart Association [NYHA] functional class II−III, left ventricular ejection fraction (LVEF) ≤40%, left ventricular end-diastolic diameter ≥50 mm to <80 mm) receiving optimal pharmacologic therapy were randomized at 10 sites. VNS systems were randomly implanted on the left (n = 31) or right (n = 29) side. All patients were successfully implanted and 59 were titrated over 10 weeks to a well tolerated stimulation intensity. One patient died 3 days after an embolic stroke that occurred during implantation. Common device-related adverse events after VNS titration were transient mild dysphonia, cough, and oropharyngeal pain, which were similar for left- and right-side VNS. After 6 months of ART, the adjusted left-right differences in LVEF, left ventricular end-systolic volume (LVESV), and left ventricular end-systolic diameter (LVESD) were 0.2% (95% CI -4.4 to 4.7), 3.7 mL (95% CI -7.0 to 14.4), and 1.3 mm (95% CI -0.9 to 3.6), respectively. In the combined population, absolute LVEF improved by 4.5% (95% CI 2.4−6.6), LVESV improved by -4.1 mL (95% CI -9.0 to 0.8), and LVESD improved by -1.7 mm (95% CI -2.8 to -0.7). Heart rate variability improved by 17 ms (95% CI 6.5−28) with minimal left-right difference. Six-minute walk distance improved an average of 56 m (95% CI 37−75); however, improvement was greater for right-side ART (77 m [95% CI 49-105]). NYHA functional class improved in 77% of patients (baseline to 6 months).

Conclusions: Chronic open-loop ART via left- or right-side VNS is feasible and well tolerated in HFrEF patients. Safety and efficacy measures are encouraging and warrant further study. (*J Cardiac Fail 2014;20:808−816*)

Key Words: Heart failure, autonomic regulation therapy, vagus nerve stimulation, nonpharmacologic therapy.

Patients with chronic heart failure (HF) have features of autonomic dysfunction characterized by excessive sympathetic activation and concomitant parasympathetic withdrawal.[1,2] Autonomic imbalance, manifested in part as a reduction in heart rate (HR) variability and reduced baroreflex sensitivity, is associated with worsening HF and increased risk of mortality independent of ejection fraction and ventricular arrhythmias.[3,4] Despite the widespread use

From the [1]Department of Cardiology, Krishna Institute of Medical Sciences, Secunderabad, India; [2]Department of Cardiology, Sanjivani Super Specialty Hospitals, Ahmedabad, India; [3]Department of Cardiology, Medanta, Medicity, Haryana, India; [4]Department of Cardiology, Vintage Hospital, Goa, India; [5]Emerging Therapies, Cyberonics, Houston, Texas; [6]Biodev, San Francisco, California; [7]Department of Medicine, University of California, Los Angeles, California and [8]Department of Medicine University of Minnesota, Minneapolis, Minnesota.

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Reprint requests: Inder S. Anand, MD, DPhil (Oxon), FRCP, VA Medical Center, Cardiology 111-C, One Veterans Drive, Minneapolis, MN 55417. Tel: +1 (612) 467-3663; Fax: +1 (612) 970-5899. E-mail: anand001@umn.edu

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of pharmacologic therapy and devices, the overall prognosis of HF patients remains poor and new therapies are needed.[5]

In response to a cardiac insult, the autonomic nervous system attempts to preserve cardiac output by upregulating sympathetic activity and withdrawing parasympathetic activity. These changes in autonomic regulatory control of the cardiovascular system lead to a host of pathophysiologic changes, including excessive adrenergic receptor system activation, with long-term deleterious consequences. It has been hypothesized that electrical stimulation of the vagus nerve may normalize parasympathetic activation of cardiac control reflexes and inhibit sympathetic hyperactivation known to be associated with chronic HF and reduced ejection fraction (HFrEF).[6–10]

Vagus nerve stimulation (VNS) has been used clinically for >25 years, and its safety profile has been well established in patients with refractory epilepsy and depression.[11–13] In a variety of acute and chronic nonhuman animal models, VNS has been shown to reduce vulnerability to ventricular arrhythmias, attenuate infarct size, and reduce mortality.[8,9,14–16] Recent animal studies have evaluated autonomic regulation therapy (ART) with VNS in HF and demonstrated sustained improvement in cardiac function and HF symptoms.[17–20] ART feasibility and tolerability was first evaluated in a 32-patient open-label clinical study, which showed that stimulation pulses (5.5 mA target), delivered to the right vagus nerve and synchronized to the cardiac cycle, were associated with a significant improvement in cardiac function, as measured by left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (LVESV), quality of life, and exercise performance.[21]

Although ART has been more widely studied through stimulation of the right vagus nerve,[17–23] there is experimental evidence to suggest that left-side stimulation also has therapeutic benefits in the setting of cardiac dysfunction.[16,24] ART as an HF therapy on the left side may have advantages, allowing the therapy to be combined with cardiac devices such as implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) devices, the vast majority of which are implanted on the left side of the thorax. The feasibility and tolerability of left-side VNS is well established in epilepsy patients[11–13]; however, left-side VNS has not been evaluated in HF patients, and the effects of left- and right-side VNS have not been directly compared.

The Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure (ANTHEM-HF) study is a multicenter open-label feasibility study designed to assess the safety, tolerability, and efficacy of a new approach to ART in patients with chronic, stable, symptomatic HFrEF, and to compare the effects of right- and left-side VNS. In contrast with the previously reported feasibility study,[21] ANTHEM-HF evaluated the effects of continuous cyclic stimulation applied to the vagus nerve at an amplitude of 1.5–3.0 mA and a constant frequency of 10 Hz. The study assessed whether the therapy improves LV structure and function and reduces symptom burden in patients with chronic stable HF.

Methods

Study Design

The ANTHEM-HF study design was published previously.[25] Briefly, 60 subjects in New York Heart Association (NYHA) functional class II–III HF, age ≥18 years, were enrolled at 10 sites in India over 13 months (July 2012 to July 2013). Inclusion criteria included LVEF ≤40%, LV end-diastolic diameter 50 mm to <80 mm, QRS width ≤150 ms, and receiving optimal medical management, including stable β-blocker therapy for HF as indicated and tolerated for ≥3 months and all other oral pharmacologic therapy for HF, including angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), loop diuretics, and spironolactone, for ≥1 month. Patients were also required to be physically capable of performing the 6-minute walk test (6MWT) with a baseline distance of 150–425 m, as limited by HF symptoms.

Objectives

The main objective of ANTHEM-HF was to evaluate the safety and efficacy of ART for the treatment of patients with chronic symptomatic HFrEF. The study also evaluated ART system performance by assessing feasibility, the percentage of randomized patients who were successfully implanted with the device, and tolerability, the ability to maintain therapy throughout the 6-month follow-up period after the tolerable level of stimulation was determined during the 10-week titration period.

The primary safety endpoint was the incidence of procedure and device-related adverse events. The primary efficacy endpoints were changes in LVEF and LVESV at 6 month. The secondary exploratory endpoints included left ventricular end-systolic diameter (LVESD), NYHA functional class; 6MWT, Minnesota Living with Heart Failure Questionnaire (MLHFQ), mean HR and HR variability during 24-h Holter electrocardiography (ECG), and plasma biomarkers, including N-terminal pro–B-type natriuretic peptide (NT-proBNP) and high-sensitivity C-reactive protein (hs-CRP). All outcome measurements were made at baseline and 3 and 6 months after VNS titration.

System Implantation and ART Implementation

Subjects fulfilling the inclusion and exclusion criteria were randomized 1:1 to receive VNS Therapy System implantation (Demipulse Model 103 pulse generator and PerenniaFLEX Model 304 lead; Cyberonics, Houston, Texas) with lead placement on either the right or left cervical vagus nerve. The pulse generator was activated 15 ± 3 days after implantation. All patients were initially stimulated at a pulse width of 130 μs and a pulse frequency of 10 Hz, continuous cyclic 14 s active (on) and 66 s inactive (off; 1,080 cycles/d). Stimulation parameters were systematically adjusted during periodic clinic visits over a 10-week titration period to a pulse width of 250 μs, a pulse frequency of 10 Hz, and target output current amplitude of 1.5–3.0 mA. VNS activation and inactivation periods were unrelated to the cardiac cycle (ie, open loop), so no intracardiac sensing lead was used. During titration sessions, VNS intensity was gradually increased in 0.25-mA steps with the use of a radiofrequency programmer (Model 250 programming system; Cyberonics) to levels that produced acute VNS-related side

effects (tolerance zone boundary), such as activation of the expiratory reflex (mild cough) or modest HR reduction. When the VNS tolerance zone boundary was established by evidence of expiratory reflex activation or HR reduction, the output current was reduced by ≥1 output current step (0.25 mA) to insure that the therapy was well tolerated. During all titration sessions, lead II ECG was continuously monitored (Model MP150 Data Acquisition System; Biopac Systems, Goleta, California) to provide baseline HR (30-s average) along with real-time HR (3-beat average) to determine HR effects associated with VNS and confirm that acute HR change did not exceed 4−6 beats/min.

Echocardiographic and Safety Adjudication

All transthoracic echocardiographic recordings and blood samples were deidentified of patient and sample information and sent to designated core laboratory facilities (echocardiography: Care Hospital, Hyderabad, India; blood: Metropolis Healthcare, Mumbai, India) for blinded analysis. The investigators did not have access to the core laboratory (echocardiography or blood) results. The study was overseen by an independent Data Safety and Monitoring Committee (Appendix). All adverse events were documented by study investigators and adjudicated by an independent Clinical Events Adjudication Committee (Appendix), which determined whether events were related or unrelated to the therapy system being evaluated after thoroughly reviewing patient records and investigator narratives. Adverse events were further adjudicated as being related or unrelated to implantation or stimulation.

Statistical Analysis

Continuous variables are described by mean and SD or median (interquartile range [IQR]) for skewed distributions. Left-versus right-side differences in 6-month changes in efficacy variables were estimated with the use of linear regression (Stata v13.1 software). Baseline values of the change variable were included in the regression models of 6-month changes to help control for regression to mean. In addition, the left-versus right-side comparisons were adjusted for ischemic etiology, baseline HR, and HF medications, including ACE inhibitor or ARB, loop diuretic, spironolactone, and digoxin. All subjects (100%) were on a beta-blocker. The average changes after 3 months (Supplemental Table 2) were nearly equal to the changes after 6-months, so 1 echocardiography and 2 HR variability 3-month values were carried forward to fill in missing 6-month values; carry-forward analysis had no material effect on computed values. Three subjects died before the 3-month follow-up. Marginal (adjusted) means are reported with 95% confidence intervals (CIs) for the left, right, and combined treatment groups. One subject who was randomized to treatment on the right side was treated on the left side based on the investigator's judgment, and was included in the left-side treatment group.

The study complied with the Declaration of Helsinki. The study protocol was approved by local Ethics Committees at all sites, and all patients gave written informed consents translated into local languages.

Results

Baseline Characteristics of Patients

Patient enrollment and follow-up are summarized in Figure 1. All 60 randomized patients were successfully implanted with a pulse generator and lead system. One patient who was randomized to receive a right-side implant received a left-side implant based on physician judgment. This approved protocol deviation was not due to lack of feasibility of right-side implantation. The baseline characteristics of the randomized patients are summarized in Table 1. All patients (n = 60) were NYHA functional class II (57%) or III (43%), with an average LVEF of 32 ± 7%. The average LVESD and LVEDD were 51.6 ± 7.9 mm and 61.7 ± 6.7 mm, respectively, uncorrected for a mean body surface area of 1.66 ± 0.15 m^2. Patients received optimal pharmacologic therapy for HF, with 100% receiving beta-blocker therapy and 85% receiving ACE inhibitor or ARB therapy. Medication changes were permitted according to physician judgment; however, there were no significant changes in HF medications during the study.

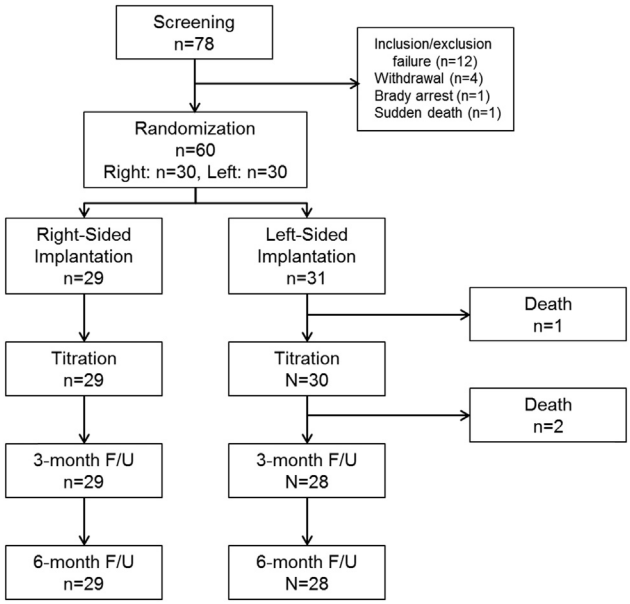

Fig. 1. Flowchart of patient progress through study phases. One patient who was randomized to receive a right-side implant received a left-side implant based on physician judgment. F/U, follow-up.

Heart failure etiology was ischemic in 75% of patients, and 33% of patients had mitral regurgitation (grade ≥1). Five patients had mitral regurgitation grade ≥3. Baseline median NT-proBNP (868 pg/mL, IQR 322−1,875 pg/mL) was elevated. None of the patients had an ICD or CRT device at enrollment. The baseline characteristics of patients randomly implanted on the left or right side were similar except for ischemic etiology and use of HF medications.

Titration and Tolerance of Stimulation

During the titration period (10 ± 2 visits), the tolerance zone boundary increased in all patients, allowing for progressive increase in VNS intensity. At the end of the 10-week titration period, the average up-titrated output current in 59 patients was 2.0 ± 0.6 mA (right side: 1.7 ± 0.5 mA; left side: 2.2 ± 0.5 mA). Of the 59 patients,

Table 1. Baseline Characteristics of Enrolled Patients

	Left (n = 31)	Right (n = 29)	Overall (n = 60)
Demographics			
Age (y)	51.2 ± 12.4	51.9 ± 12.4	51.5 ± 12.2
Male (%)	87	86	87
Medical history			
Duration of HF (y)	3.7 ± 3.9	3.9 ± 4.7	3.8 ± 4.3
Heart failure etiology (%)			
Ischemic	68	83	75
Nonischemic	32	17	25
Clinical examination			
NYHA II/III	18/13	16/13	34/26
MLHFQ score	38 ± 15	41 ± 11	40 ± 14
Body mass index (kg/m^2)	24.0 ± 3.5	24.2 ± 4.7	24.1 ± 4.1
LVEF (%)	32.8 ± 8.0	31.9 ± 6.4	32.4 ± 7.2
LVESV (mL)	109.1 ± 40.8	106.6 ± 40.1	107.9 ± 40.1
LVESD (mm)	51.5 ± 7.4	51.6 ± 8.6	51.6 ± 7.9
LVEDD (mm)	61.7 ± 6.7	62.2 ± 7.1	61.7 ± 6.7
HR (beats/min)	78 ± 11	77 ± 10	78 ± 10
Systolic BP (mm Hg)	114 ± 14	112 ± 15	113 ± 15
Diastolic BP (mm Hg)	73 ± 8	74 ± 10	73 ± 9
6MWT (m)	291 ± 60	282 ± 73	287 ± 66
QRS width (ms)	98 ± 32	95 ± 30	96 ± 31
Clinical chemistry			
Creatinine (mg/dL)	1.1 ± 0.4	1.0 ± 0.3	1.1 ± 0.3
eGFR (mL min^{-1} 1.73 m^{-2})	87 ± 36	94 ± 38	90 ± 37
NT-proBNP (pg/mL), median (IQR)	864 (322–1,788)	874 (324–2,101)	868 (322–1,875)
CRP (mg/dL), median (IQR)	1.9 (1.0–7.2)	1.6 (0.8–3.8)	1.7 (0.9–6.0)
Heart failure drug treatment (%)			
β-blocker	100	100	100
ACE-I or ARB	83	87	85
Aldosterone antagonist	71	79	75
Digoxin	39	24	32
Loop diuretics	97	79	88
ICD use (n)			
Implanted before randomization	0	0	0
Implanted during the study period	0	2	2

HF, heart failure; NYHA, New York Heart Association functional class; MLHFQ, Minnesota Living with Heart Failure Questionnaire; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic volume; HR, heart rate; BP, blood pressure; 6MWT, 6-minute walk test; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CRP, C-reactive protein; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICD, implantable cardioverter-defibrillator.

VNS intensity was limited by side effects (such as mild cough, voice alteration, sensation of stimulation) in 50 patients, by maximum current amplitude of 3.0 mA in 5, and by acute HR change in 4. In these 4 patients, an HR reduction of 3–5 beats/min was seen during the VNS "on" time at the end of the titration period, and further increase in intensity would have decreased their HR even more. At the end of each titration session, no patients were programmed to a VNS intensity that elicited side effects or an acute HR reduction of >4–6 beats/min.

Continuous cyclic stimulation was maintained at a tolerable level throughout the titration period and the 6-month follow-up period. None of the patients or investigators requested discontinuation of ART during the study, and none of the patients used the magnet to temporarily inhibit stimulation, suggesting that therapy was tolerable throughout the study period. At the end of the 6-month follow-up period, the average output current in 57 patients was 2.0 ± 0.6 mA (right side: 1.7 ± 0.5 mA; left side: 2.3 ± 0.6 mA). After completion of the ANTHEM-HF study, patients are being followed in a separate extension study for an additional 12 months.

Safety Assessment

Table 2 summarizes the adverse events. During the study, continuous cyclic stimulation was delivered for a cumulative 43 patient-years. A total of 21 serious adverse events (SAEs) occurred in 16 patients (Supplemental Table 1). Of these SAEs, 1 was related to the ART system: a death due to an embolic stroke that occurred 3 days after surgery in a patient who had extensive atherosclerosis of the carotid arteries and that was adjudicated to be implantation procedure related.

The remaining 20 SAEs were adjudicated to be unrelated to the ART system. There were 2 other deaths during the study that occurred after the titration period but before the 3-month follow-up visit: 1 sudden cardiac death and 1 due to worsening HF related to HF medication noncompliance. Both patients had left-side VNS, and the events

Table 2. Adverse Events (AEs)

	Left	Right	Overall
Serious AEs (SAEs)	10	11	21
Related	1	0	1
Unrelated	9	11	20
Related SAEs			
Death (embolic stroke)	1	0	1
Unrelated SAEs			
Death (sudden death)	1	0	1
Death (heart failure)	1	0	1
HF hospitalization	3	3	6
Unstable angina	0	2	2
Ventricular tachycardia	0	2	2
Bone fracture	1	0	1
Cataract	0	1	1
Dengue fever	0	1	1
Hernia	1	0	1
Pneumonia	0	1	1
Stroke	1	0	1
Urine retention	1	0	1
Weight loss	0	1	1
Other related AEs	82	91	173
Most common related AEs			
Dysphonia	11	8	19
Cough	6	7	13
Oropharyngeal pain	4	4	8
Device malfunctions	0	0	0

were adjudicated to be unrelated to the investigational therapy. Thus, the overall mortality in this study was 3/60 (5%), consistent with the severity of HF in this patient cohort,[26–28] and the mortality rate attributed to the therapy over the 9-month study period, from implantation to final follow-up, was 1/60 (1.7%).

There were 173 device-related nonserious adverse events (AEs); 82 AEs were reported in the group receiving left-side VNS and 91 were reported in the group receiving right-side VNS. Among the 82 AEs that occurred in the group receiving left-side VNS, 34 were implantation related and 48 were stimulation related. Among the 91 AEs that occurred in the group receiving right-side VNS, 37 were implantation related and 54 were stimulation related. The most common nonserious AEs (Table 2) were mild dysphonia (19), cough (13), and oropharyngeal pain (8). The most common procedure-related side effects were transient dysphonia and oropharyngeal pain at the implant site. The most common stimulation-related side effects were transient mild dysphonia and cough, limited to the active phase of ART. Stimulation-related AEs were transient, could be ameliorated with adjustment of stimulation parameters, and subsided over time. Most AEs (93%) occurred between implant and end-titration. All device-related AEs resolved without consequence. There were no device-related infections or malfunctions, no unexpected device-related adverse events, and no patients who discontinued therapy during the study.

An exploratory analysis of the 24-hour Holter monitoring records demonstrated an average decrease in mean HR of 3.9 ± 9.8 beats/min from baseline to 6 months (right side: 4.3 beats/min; left side: 3.4 beats/min). Investigator review of the Holter records did not reveal any clinically

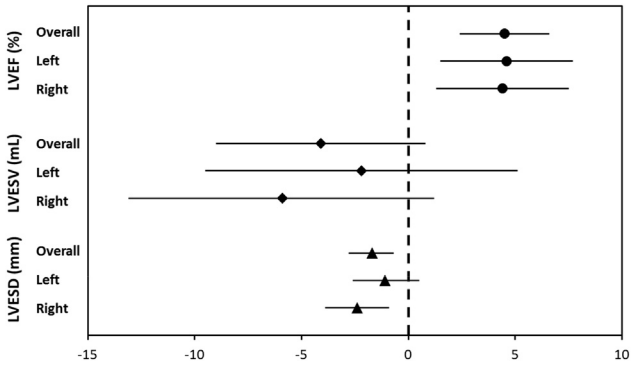

Fig. 2. Mean and 95% confidence intervals of echocardiographic changes after 6 months of autonomic regulation therapy (overall, left-side treatment, and right-side treatment). LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESD, left ventricular end-systolic diameter.

significant changes in atrial or ventricular ectopic activity, no increase in bradycardia or tachycardia events, and no new-onset atrial fibrillation. However, 2 patients received an ICD during the study after presenting with ventricular tachycardia. Both of these patients had received right-side VNS, and these events were adjudicated to be unrelated to the therapy. In these 2 patients implanted with ICDs during the study, there was no device interaction between the ICD and the ART systems.

Efficacy Assessments

Echocardiographic measures are presented in Figure 2 and Table 3. After the 6-month study period, the observed mean (95% CI) differences between the left and right treatment groups in changes in LVEF, LVESV, and LVESD were 0.2% (-4.4 to 4.7), 3.7 mL (-7.0 to 14.4), and 1.3 mm (-0.9 to 3.6), respectively. After pooling the left- and right-side data, the average estimated increase in LVEF was 4.5% [2.4 to 6.6]. LVESV decreased by -4.1 mL [-9.0 to 0.8], and LVESD decreased by -1.7 mm [-2.8 to -0.7].

Heart rate variability (SD of normal to normal intervals) also improved in the pooled sample by 17 ms (95% CI 6.5−28) with relatively little left-right difference (Table 3). Changes in NT-proBNP levels were highly variable, with wide, inconclusive confidence intervals. CRP significantly decreased in the pooled sample by 2.9 mg/dL on average with relatively small left-right difference. Renal function, as measured by estimated glomerular filtration rate, did not change. BNP, angiotensin II, and norepinephrine levels also did not change over the 6-month study period (data not shown).

The NYHA functional class of 77% of patients improved from baseline to the 6-month follow-up visit. No patients showed worsening NYHA functional class at 6 months. Measurements of patient functional status and quality of life are presented in Table 3. The improvement in the 6-minute walk distance over the 6-month study period was significantly less with left-side VNS (-43 m [95%

Table 3. Efficacy Measures

	Left Treatment	Right Treatment	Left−Right Difference*	Combined
LVEF (%)	4.6 (1.5 to 7.7)	4.4 (1.3 to 7.5)	0.2 (−4.4 to 4.7)	4.5 (2.4 to 6.6)
LVESV (mL)	-2.2 (−9.5 to 5.1)	-5.9 (−13.1 to 1.2)	3.7 (−7.0 to 14.4)	-4.1 (−9.0 to 0.8)
LVESD (mm)	-1.1 (−2.6 to 0.5)	-2.4 (−3.9 to −0.9)	1.3 (−0.9 to 3.6)	-1.7 (−2.8 to −0.7)
6MWT (m)	34 (5.4 to 62)	77 (49 to 105)	-43 (−85 to −1.3)	56 (37 to 75)
MLHFQ	-17 (−20 to −13)	-20 (−24 to −17)	3.6 (−1.8 to 8.8)	-18 (−21 to −16)
Holter HR (beats/min)	-3.4 (−7.0 to 0.2)	-4.3 (−7.9 to −0.8)	0.9 (−4.4 to 6.2)	-3.9 (−6.3 to −1.5)
SDNN (ms)	20 (4.6 to 36)	14 (−1.8 to 30)	6.3 (−17 to 30)	17 (6.5 to 28)
NT-proBNP (pg/mL)	1,109 (−325 to 2,542)	-828 (−2,262 to 606)	1,936 (−179 to 4,052)	140 (−828 to 1,108)
CRP (mg/dL)	-3.3 (−6.6 to −0.1)	-2.5 (−5.7 to 0.7)	-0.8 (−5.6 to 3.9)	-2.9 (−5.1 to −0.7)
eGFR (mL min^{-1} 1.73 m^{-2})	-1.7 (−14 to 11)	-8.6 (−22 to 4.4)	6.8 (−12 to 26)	-5.2 (−13 to 3.6)

SDNN, standard deviation of normal to normal intervals; other abbreviations as in Table 1.

Values are presented as marginal mean (95% confidence interval) n = 28 left and 29 right except 28 right for blood levels and SDNN; 3 missing for all measurements owing to death.

*Regression coefficient (95% confidence interval) adjusted for baseline values of change variable, history of ischemic etiology, heart rate and heart failure medications, including angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, loop diuretic, spironolactone, and digoxin (all were on a beta-blocker).

CI -85 to -1.3]) compared with right-side VNS; overall, the mean increase in walk distance was 56 meters (95% CI 37−75). MLHFQ score in the pooled sample improved by 18 points (95% CI -21 to -16) with little difference between left- and right-side VNS.

Discussion

Safety, Feasibility, and Tolerability

The implementation of ART evaluated in the ANTHEM-HF study (open loop, low intensity, natural frequency) was feasible and well tolerated in this study population. No subjects were lost to follow-up or intentionally withdrew from the study.

The therapy-related nonserious AEs observed in the ANTHEM-HF study are consistent with those reported in the epilepsy population.[11,12] In all cases, stimulation parameters were programmed to avoid side effects; however, during the VNS titration phase, some patients did experience mild stimulation-related effects which could be ameliorated with parameter adjustment and subsided over time. Vagus nerve stimulation on the left side is a well established therapy in refractory epilepsy, with a total of $>100{,}000$ device implantations, and has an excellent safety profile[11,12]; the results of the present study suggest that a similar therapy in HF, on either the left or the right side, would have a similar safety profile.

One device-related SAE was observed. This subject failed to regain consciousness after the implantation procedure involving the left vagus nerve. The patient had a history of carotid atherosclerosis and bilateral claudication, and subsequent computerized tomographic imaging revealed a nonhemorrhagic brain infarct in the left hemisphere. ART was not activated during or after the implantation procedure. The subject died on the 3rd day after implantation of the ART system. It is possible that manipulation of the common carotid artery in the neck during dissection of the vagus nerve caused plaque disruption or dislodged a thrombus. Careful selection of patients and avoidance of the procedure in patients with severe obstructive carotid disease is likely to minimize such occurrences.

Efficacy

In the overall combined cohort, there was significant improvement in LVEF; whereas improvement in LVESV was not statistically significant. There were also improvement in LVESD, HR variability, and hs-CRP. NT-proBNP did not show a statistically significant change, although the measurement may have been too variable to detect any changes. All subjective efficacy measures, including NYHA functional class, 6-minute walk distance, and MLHFQ scores, showed statistically significant improvements.

No statistically significant differences between left- and right-side VNS stimulation were observed in most objective and subjective efficacy criteria; however, the CIs were wide and inconclusive. There were consistent trends in most measures that appeared to favor right- compared with left-side VNS. However, a larger study is needed to determine whether right-side VNS may actually produce more favorable patient outcomes.

Autonomic Regulation Therapy

Early work examining VNS as a cardiovascular therapy focused on its effects on the sinus node.[29] It was thought that VNS provided a cardiac benefit primarily by slowing HR and allowing for more effective ventricular filling and improved pumping efficiency. However, recent studies have shown that ART at low levels, below what is necessary to induce an acute decrease in HR, has beneficial effects.[24,30] Experimental data increasingly suggests that the beneficial effects of ART derive from multiple mechanisms in which VNS improves regulatory control of the autonomic nervous system: VNS inhibits neural release of norepinephrine at cardiac effectors,[31] restores autonomic balance (as reflected in improvements in HR variability and baroreflex sensitivity),[19,21] reduces systemic inflammation,[32−34] increases coronary flow,[35]

exerts antiapoptotic effects,[19,36] and directly modulates reflex processing within peripheral ganglia of the cardiac nervous system.[38] In addition, ART therapy has been shown to have antiarrhythmic effects.[7–9,14–16]

In a recent proof-of-concept open-label phase 2 safety and feasibility trial, De Ferrari et al[21] studied 32 NYHA functional class II–IV HFrEF patients. The right cervical vagus nerve was stimulated with the Cardiofit system (Biocontrol Medical, Yehud, Israel), which uses an intracardiac sensing lead to synchronize high-amplitude VNS pulses with the cardiac cycle in an attempt to induce a mild bradycardia, an approach which the results of the ANTHEM-HF study suggest may be unnecessary to yield a clinical benefit. The De Ferrari et al study found that VNS was associated with a significant improvement in LVEF, LVESV, NYHA functional class, quality of life, and 6-minute walk distance at 6 months, and that those improvements were maintained at 12 months. Despite using a lower intensity of stimulation (a mean of 2.0 mA compared with a mean of 4.1 mA), the magnitude of improvements in efficacy measurements seen in ANTHEM-HF is similar to those reported by De Ferrari et al. These similarities may be due to the use of a higher stimulation frequency (10 Hz) in the present study.

Furthermore, De Ferrari et al reported a total of 26 SAEs over 6 months, including 3 deaths, with 7 SAEs (22%) definitely or possibly related to the therapy. The incidence of therapy-related SAEs in ANTHEM-HF (1 event, 1.7%) was much lower. The most common nonserious AEs reported by De Ferrari et al were mild pain, cough, and dysphonia, as seen in ANTHEM-HF. The Cardiofit system is now being evaluated in a 650-patient phase III trial, the Increase of Vagal Tone in Chronic Heart Failure (INOVATE-HF) study.[22]

ART is also being studied in a 96-patient phase II study sponsored by Boston Scientific (St Paul, Minnesota), the Neurocardiac Therapy for Heart Failure (NECTAR-HF) study.[23] In NECTAR-HF, as in ANTHEM-HF, low-amplitude stimulation is not synchronized with the cardiac cycle; however, the Boston Scientific VNS system uses a substantially higher stimulation frequency (20 Hz). Interestingly, chronic VNS at 10 Hz frequency (near the natural frequency of discharge of vagal fibers during reflex activation[27,39,40]), but not 5 Hz or 20 Hz, has been shown to reduce mean HR and increase HR variability over a 24-hour period.[37] As in INOVATE-HF, the NECTAR-HF study is evaluating ART restricted to the right vagus nerve.

ANTHEM-HF is the first clinical study to compare the feasibility and tolerance of left- and right-side ART, and to compare safety and efficacy measures. ART applied to either left or right cervical vagus nerve for the treatment of HFrEF appears to be both feasible and tolerable. Preclinical studies have demonstrated that ART engages multiple levels of the autonomic reflex hierarchy for cardiac control via its activation of both afferent and efferent projections of the vagus nerve.[41] Regardless of which vagus nerve is stimulated, left or right, it seems likely that cardiac and central effects are elicited, reflecting the interplay between central and peripheral aspects of the cardiac nervous system. Anatomically, both right and left vagus nerves show substantial projections to all chambers of the heart, as mediated by multiple ganglionated plexi of the intrinsic cardiac nervous system.[42,43]

Although some outcome measures show a trend toward greater efficacy with right-side stimulation, the data do not support the conclusion that ART applied to the right or left vagus nerve yields significantly different efficacy results, and further evaluation is required.

Study Limitations

In this modest-size study, the CIs of the estimated differences between left- and right-side VNS were wide and could not rule out clinically important differences. The overall effects seen in this uncontrolled study cannot be solely attributed to the ART. It is possible that at least some of the clinical improvements are due to the placebo effect, especially in the more subjective assessments. Nevertheless, the overall directional change in all measured study parameters shown after 6 months of therapy is encouraging and sufficient to justify a randomized controlled study. The ANTHEM-HF study was conducted at clinical centers in India, and the results may not be generalizable to other populations.

Conclusion

The results of the ANTHEM-HF study demonstrate that ART with the use of chronic low-amplitude VNS, on either the left or the right side, is feasible and well tolerated in patients with HFrEF. No unexpected AEs were observed. The preliminary assessment of efficacy measures is promising, and reveals that outcomes may be more favorable with right-side VNS; however, this needs to be confirmed in a larger controlled trial. Further investigation of the safety and efficacy of this therapy in a controlled clinical study is warranted.

Disclosures

LAD, JLA, TSR, and ISA have served as scientific advisors to Cyberonics. IL, BA, and BHK are employees of Cyberonics.

Supplementary Data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.cardfail.2014.08.009.

References

1. Eckberg DL, Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart failure. N Engl J Med 1971;285:877–83.

2. Brunner-la Rocca HP, Esler MD, Jennings GL, Kaye DM. Effects of cardiac sympathetic nervous activity on mode of death in congestive heart failure. Eur Heart J 2001;22:1136−43.
3. Nolan J, Batin PD, Andrews R, Lindsay SJ, Brooksby P, Mullen M, et al. Prospective study of heart rate variability and mortality in chronic heart failure. Circulation 1998;98:1510−6.
4. La Rovere MT, Bigger JT, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. Lancet 1998;351:478−84.
5. Joffe SW, Webster K, McManus DD, Kiernan MS, Lessard D, Yarzebski J, et al. Improved survival after heart failure: a community-based perspective. J Am Heart Assoc 2013;2:1−9.
6. Schwartz PJ, Stone HL. Tonic influence of the sympathetic nervous system on myocardial reactive hyperemia and on coronary blood flow distribution in dogs. Circ Res 1977;41:51−8.
7. Schwartz PJ, Billman GE, Stone HL. Autonomic mechanisms in ventricular fibrillation induced by myocardial ischemia during exercise in dogs with healed myocardial infarction. Circulation 1984;69:790−800.
8. Zuanetti G, De Ferrari GM, Priori SG, Schwartz PJ. Protective effect of vagal stimulation on reperfusion arrhythmias in cats. Circ Res 1987;61:429−35.
9. Vanoli E, De Ferrari GM, Stramba-Badiale M, Hull SS, Foreman RD, Schwartz PJ. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. Circ Res 1991;68:1471−81.
10. Schwartz PJ. Vagal stimulation for heart diseases: from animals to men. Circ J 2010;75:20−7.
11. Morris G, Mueller W. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. Neurology 1999;53:1731−5.
12. Groves DA, Brown VJ. Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. Neurosci Biobehav Rev 2005;29:493−500.
13. O'Reardon JP, Cristancho P, Peshek AD. Vagus nerve stimulation (VNS) and treatment of depression: to the brainstem and beyond. Psychiatry 2006;3:54−63.
14. Kolman BS, Verrier RL, Lown B. The effect of vagus nerve stimulation upon vulnerability of the canine ventricle. Circulation 1975;52:578−85.
15. Li M, Zheng C, Sato T, Kawada T, Sugimachi M, Sunagawa K. Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats. Circulation 2004;109:120−4.
16. Shinlapawittayatorn K, Chinda K, Palee S, Surinkaew S, Thunsiri K, Weerateerangkul P, 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;10:1700−7.
17. Sabbah HN, Ilsar I, Zaretsky A, Rastogi S, Wang M, Gupta RC. Vagus nerve stimulation in experimental heart failure. Heart Fail Rev 2011;16:171−8.
18. Hamann JJ, Ruble SB, Stolen C, Wang M, Gupta RC, Rastogi S, et al. Vagus nerve stimulation improves left ventricular function in a canine model of chronic heart failure. Eur J Heart Fail 2013;15:1319−26.
19. Zhang Y, Popovic ZB, Bibevski S, Fakhry I, Sica DA, van Wagoner DR, 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;2:692−9.
20. Kusunose K, Zhang Y, Mazgalev TN, van Wagoner DR, Thomas JD, Popovic ZB. Impact of vagal nerve stimulation on left atrial structure and function in a canine high-rate pacing model. Circ Heart Fail 2014;7:320−6.
21. De Ferrari GM, Crijns HJ, Borggrefe M, Milasinovic G, Smid J, Zabel M, et al. Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. Eur Heart J 2011;32:847−55.
22. Hauptman PJ, Schwartz PJ, Gold MR, Borggrefe M, van Veldhuisen DJ, Starling RC, et al. Rationale and study design of the Increase of Vagal Tone in Heart Failure study: INOVATE-HF. Am Heart J 2012;163:954−62.
23. De Ferrari GM, Tuinenberg AE, Ruble S, Brugada J, Klein H, Butter C, et al. Rationale and study design of the Neurocardiac Therapy for Heart Failure study: NECTAR-HF. Eur J Heart Fail 2014;16:692−9.
24. Shen MJ, Shinohara T, Park HW, Frick K, Ice DS, Choi EK, et al. Continuous low-level vagus nerve stimulation reduces stellate ganglion nerve activity and paroxysmal atrial tachyarrhythmias in ambulatory canines. Circulation 2011;123:2204−12.
25. DiCarlo L, Libbus I, Amurthur B, KenKnight BH, Anand IS. Autonomic regulation therapy for the improvement of left ventricular function and heart failure symptoms: the ANTHEM-HF study. J Card Fail 2013;19:655−60.
26. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, et al. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J 2006;27:65−75.
27. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. Am J Cardiol 2006;97:1759−64.
28. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877−83.
29. Bilgutay AM, Bilgutay IM, Merkel FK, Lillehei CW. Vagal tuning: a new concept in the treatment of supraventricular arrhythmias, angina pectoris, and heart failure. J Thorac Cardiovasc Surg 1968;56:71−82.
30. De Ferrari GM. Vagal stimulation in heart failure. J Cardiovasc Trans Res 2014;7:310−20.
31. Kawada T, Yamazaki T, Akiyama T, Li M, Ariumi H, Mori H, et al. Vagal stimulation suppresses ischemia-induced myocardial interstitial norepinephrine release. Life Sci 2006;78:882−7.
32. Aukrust P, Gullestad L, Ueland T, Damas JK, Yndestad A. Inflammatory and anti-inflammatory cytokines in chronic heart failure: potential therapeutic implications. Ann Med 2005;37:74−85.
33. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 2000;405:458−62.
34. Pavlov VA, Wang H, Czura CJ, Friedman SG, Tracey KJ. The cholinergic anti-inflammatory pathway: a missing link in neuroimmunomodulation. Mol Med 2003;9:125−34.
35. Henning RJ, Sawmiller DR. Vasoactive intestinal peptide: cardiovascular effects. Cardiovasc Res 2001;49:27−37.
36. Uemura K, Li M, Tsutsumi T, Yamazaki T, Kawada T, Kamiya A, et al. Efferent vagal nerve stimulation induces tissue inhibitor of metalloproteinase-1 in myocardial ischemia-reperfusion injury in rabbit. Am J Physiol Heart Circ Physiol 2007;293:H2254−61.
37. Ardell JL, Nier H, Ardell CL, Amurthur B, Beaumont E, Southerland EM, et al. Optimum heart rate response to autonomic regulation therapy is frequency dependent [abstract]. Circulation 2013;128:A15586.
38. McGuirt AS, Schmacht DC, Ardell JL. Autonomic interactions for control of atrial rate are maintained after SA nodal parasympathectomy. Am J Physiol 1997;272:H2525−33.
39. Cerati D, Schwartz PJ. Single cardiac vagal fiber activity, acute myocardial ischemia, and risk for sudden death. Circ Res 1991;69:1389−401.
40. Hardwick JC, Southerland EM, Girasole AE, Ryan SE, Negrotto S, Ardell JL. Remodeling of intrinsic cardiac neurons: effects of β-adrenergic receptor blockade in guinea pig models of chronic heart disease. Am J Physiol Regul Integr Comp Physiol 2012;303:R950−8.
41. Armour JA. Potential clinical relevance of the 'little brain' on the mammalian heart. Exp Physiol 2008;93:165−76.

42. Yuan BX, Ardell JL, Hopkins DA, Armour JA. Differential cardiac responses induced by nicotine sensitive canine atrial and ventricular neurones. Cardiovasc Res 1993;27:760–9.
43. Cardinal R, Page P, Vermeulen M, Ardell JL, Armour JA. Spatially divergent cardiac responses to nicotinic stimulation of ganglionated plexus neurons in the canine heart. Auton Neurosci 2009;145:55–62.

Appendix

Steering Committee

Inder S. Anand, Professor of Medicine, University of Minnesota; Jeffrey L. Ardell, PhD, Professor of Medicine, University of California, Los Angeles; Lorenzo DiCarlo, MD, FACC, Managing Director, Biodev, San Francisco, California; Sanjay Mittal, MD, Director, Research and Clinical Cardiology, Medanta, Medicity, Haryana, India; Badri Amurthur, MS, Senior Director, Cyberonics, Houston, Texas; Imad Libbus, PhD, Senior Principal Scientist, Cyberonics, Houston, Texas; Bruce H. KenKnight, PhD, Vice President, Emerging Therapies, Cyberonics, Houston, Texas

Data Safety and Monitoring Committee

Gary S. Francis, MD, FACC, FAHA, FACP, Professor of Medicine, University of Minnesota; and Thomas S. Rector, PharmD, PhD, Professor of Medicine, University of Minnesota.

Clinical Events Adjudication Committee

Lorenzo DiCarlo, MD, FACC, Managing Director, Biodev, San Francisco, California; and David Cannom, MD, FACC, Professor of Medicine, University of California, Los Angeles, California.

Independent Statistical Analyst

Thomas S. Rector, DPharm, PhD, Professor of Medicine, University of Minnesota