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Baroreflex Activation Therapy for the Treatment of Heart Failure With a Reduced Ejection Fraction

William T. Abraham, MD,* Michael R. Zile, MD,†‡ Fred A. Weaver, MD,§ Christian Butter, MD,‖ Anique Ducharme, MD, MSc,¶ Marcel Halbach, MD,# Didier Klug, MD,** Eric G. Lovett, PhD,†† Jochen Müller-Ehmsen, MD,‡‡ Jill E. Schafer, MS,§§ Michele Senni, MD,‖‖ Vijay Swarup, MD,¶¶ Rolf Wachter, MD,## William C. Little, MD***

ABSTRACT

OBJECTIVES The objective of this clinical trial was to assess the safety and efficacy of carotid BAT in advanced HF.

BACKGROUND Increased sympathetic and decreased parasympathetic activity contribute to heart failure (HF) symptoms and disease progression. Baroreflex activation therapy (BAT) results in centrally mediated reduction of sympathetic outflow and increased parasympathetic activity.

METHODS Patients with New York Heart Association (NYHA) functional class III HF and ejection fractions ≤ 35% on chronic stable guideline-directed medical therapy (GDMT) were enrolled at 45 centers in the United States, Canada, and Europe. They were randomly assigned to receive ongoing GDMT alone (control group) or ongoing GDMT plus BAT (treatment group) for 6 months. The primary safety end point was system- and procedure-related major adverse neurological and cardiovascular events. The primary efficacy end points were changes in NYHA class, quality-of-life score, and 6-minute hall walk distance.

RESULTS One hundred forty-six patients were randomized, 70 to control and 76 to treatment. The major adverse neurological and cardiovascular event-free rate was 97.2% (lower 95% confidence bound 91.4%). Patients assigned to BAT, compared with control group patients, experienced improvements in the distance walked in 6 min (59.6 ± 14 m vs. 1.5 ± 13.2 m, $p = 0.004$), quality-of-life score (-17.4 ± 2.8 points vs. 2.1 ± 3.1 points, $p < 0.001$), and NYHA class ranking ($p = 0.002$ for change in distribution). BAT significantly reduced N-terminal pro-brain natriuretic peptide ($p = 0.02$) and was associated with a trend toward fewer days hospitalized for HF ($p = 0.08$).

CONCLUSIONS BAT is safe and improves functional status, quality of life, exercise capacity, N-terminal pro-brain natriuretic peptide, and possibly the burden of heart failure hospitalizations in patients with GDMT-treated NYHA class III HF. (Barostim Neo System in the Treatment of Heart Failure; NCT01471860; Barostim HOPE4HF (Hope for Heart Failure) Study; NCT01720160) (J Am Coll Cardiol HF 2015;■:■–■) © 2015 by the American College of Cardiology Foundation.

From the *Division of Cardiovascular Medicine, The Ohio State University, Columbus, Ohio; †Medical University of South Carolina, Charleston, South Carolina; ‡Ralph H. Johnson Department of Veterans Affairs Medical Center, Charleston, South Carolina; §Division of Vascular Surgery and Endovascular Therapy, Keck School of Medicine, University of Southern California, Los Angeles, California; ‖Department of Cardiology, Immanuel Heart Center Bernau - Medical School Brandenburg, Bernau, Germany; ¶Montreal Heart Institute, University of Montreal, Montreal, Quebec, Canada; #Department of Internal Medicine III, University Hospital of Cologne, Cologne, Germany; **Department of Cardiology A, University Hospital, Lille, France; ††Department of Research, CVRx, Inc., Minneapolis, Minnesota; ‡‡Department of Medicine, Asklepios Klinik Altona, Hamburg, Germany; §§Department of Statistics, NAMSA, Inc., Minneapolis, Minnesota; ‖‖Cardiovascular Department, Ospedale Papa Giovanni XXIII, Bergamo, Italy; ¶¶Department of Electrophysiology, Arizona Heart Hospital, Phoenix, Arizona; ##Clinic for Cardiology and Pneumology, University Medicine Göttingen and German Cardiovascular Research Center, Göttingen, Germany; and the ***Division of Cardiology, University of Mississippi Medical Center, Jackson, Mississippi. This study was funded by CVRx, Inc. (Minneapolis, Minnesota). Drs. Abraham, Little, Weaver, and Zile have received consulting fees and speaking honoraria from CVRx and are members of the CVRx Heart Failure Executive Steering Committee. Dr. Butter has received research fees from CVRx. Dr. Ducharme has received research fees and consulting fees from CVRx. Dr. Halbach has received research fees and speaking

ABBREVIATIONS AND ACRONYMS

BAT = baroreflex activation therapy

BP = blood pressure

CRT = cardiac resynchronization therapy

GDMT = guideline-directed medical therapy

HF = heart failure

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

MANCE = major adverse neurological and cardiovascular events

MLWHFQ = Minnesota Living with Heart Failure Questionnaire

NT-proBNP = N-terminal pro-brain natriuretic peptide

NYHA = New York Heart Association

OUS = outside the United States

QoL = quality of life

US = United States

6MHW = 6-min hall walk

Despite currently available drug and device therapies, 25% to 35% of patients with heart failure (HF) and a reduced left ventricular ejection fraction (LVEF) remain categorized in New York Heart Association (NYHA) functional class III (1). Although these patients are not considered sick enough for advanced invasive HF therapies, such as a left ventricular assist device or heart transplantation, they exhibit moderate to severe HF symptoms, poor quality of life (QoL), and substantial limitation in exercise capacity. They are also at substantial risk for HF morbidity (e.g., HF hospitalization) and mortality, thereby incurring significant health care costs (2). Thus, there is a need for new therapies that can improve clinical status and outcomes in these patients.

Considerable clinical and experimental evidence supports a major role for activation of the adrenergic nervous system and parasympathetic nervous system withdrawal in the genesis of HF symptoms and in HF disease progression (3,4). This autonomic imbalance exerts adverse effects on the heart, blood vessels, and kidneys, resulting in pathological left ventricular remodeling, peripheral vasoconstriction, and salt and water retention, respectively. These observations, along with the success of adrenergic receptor blockade in the treatment of HF, provide a rationale for therapies that inhibit adrenergic activity, enhance parasympathetic activity, or, preferably, accomplish both (5,6). Such therapies should ideally produce natural physiological autonomic adaptation, as a trial of total pharmacological adrenergic blockade with moxonidine worsened, rather than improved, clinical outcomes (7).

One such therapy that has shown promise in preliminary human studies of HF is baroreflex activation therapy (BAT), an electrical stimulation technology delivered by an implanted device resembling a cardiac pacemaker (8,9). Stimulation of the carotid baroreceptor with BAT results in centrally mediated reduction of sympathetic outflow and increased parasympathetic activity, resulting in increased arterial and venous compliance and reduced peripheral resistance. In patients with resistant hypertension, BAT has been shown to be safe and effective for lowering excessive blood pressure (BP) (9). In patients with HF, a small, single-center, open-label study demonstrated safety, a significant and sustained 30% reduction in sympathetic nerve activity measured directly by peroneal nerve microneurography, and improvement in HF clinical status assessed by changes in NYHA class, QoL score, and 6-min hall walk (6MHW) distance (10). Cardiac structure and function, assessed by 3-dimensional echocardiography, also improved. The rate of HF hospitalization was also substantially decreased compared with the 12 months before implantation of the BAT system. We report the results of a multinational, prospective, randomized, parallel-controlled, clinical trial of BAT in HF, performed to confirm and extend these findings.

METHODS

PATIENTS. Patients were eligible for the study if they had moderately severe (NYHA class III) chronic HF due to either ischemic or nonischemic cardiomyopathy, with LVEFs of 35% or less. Patients were required to be treated with chronic stable guideline-directed medical therapy (GDMT) for HF including a diuretic agent, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and a beta-blocker, if tolerated. Other inclusion criteria were resting heart rate between 60 and 100 beats/min, systolic BP of at least 100 mm Hg, estimated glomerular filtration rate of at least 30 ml/min/1.73 m^2, and a demonstrated impairment in functional capacity as evidenced by a 6MHW distance of 150 to 450 m. Patients were also required to be suitable surgical candidates for BAT device implantation, as determined by a study cardiologist and surgeon, and had to meet certain anatomical criteria, including bilateral carotid bifurcations below the level of the mandible and freedom from plaques or atherosclerosis reducing the linear diameter of the internal or distal common carotid arteries by 50% or greater.

Patients were excluded from the study if they had experienced NYHA class IV HF symptoms with acute pulmonary edema within 45 days of randomization or myocardial infarction, unstable angina, syncope,

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cerebrovascular accident, or aborted sudden cardiac death (including appropriate implantable cardioverter-defibrillator [ICD] therapies) during the 3 months before randomization. Patients who had received pacemakers or ICDs within 90 days of enrollment were excluded. Patients who had received cardiac resynchronization therapy (CRT) devices within 6 months of enrollment or were anticipated to receive them within 90 days were excluded to minimize the likelihood that latent CRT effects could influence study end points. Known or suspected baroreflex failure or autonomic neuropathy necessitated disqualification, as did prior surgery, radiation, or endovascular stent placement in the carotid sinus region that limited the ability to place the carotid sinus lead. Other exclusion criteria included current treatment with inotropes, life expectancy < 1 year, body mass index >40 kg/m^2, symptomatic uncontrolled bradyarrhythmias, previous or current consideration of solid organ transplantation, asthma requiring long-term medication, severe chronic obstructive pulmonary disease or restrictive lung disease, noncardiovascular conditions interfering with 6MHW distance assessment, active malignancy, nonadherence to medical therapy, and inability to fulfill protocol requirements.

The protocol conformed to the Declaration of Helsinki and was approved by the appropriate ethics committees, institutional review boards, regional ethics boards and regulatory authorities in Canada, France, Germany, Italy, and the United States (US). Because of varying regulatory requirements, the protocol for each country was slightly different, but major eligibility criteria and end points were harmonized. Patients provided their written informed consent before enrollment.

DEVICE DESCRIPTION, IMPLANTATION TECHNIQUE, AND THERAPY TITRATION. The system for delivering BAT (Barostim *neo* system, CVRx, Inc., Minneapolis, Minnesota) consists of a carotid sinus lead and a pulse generator. The lead comprises a 40-cm lead body that terminates in a circular backer 7 mm in diameter with a 2-mm iridium oxide-coated platinum-iridium disk electrode centered on the backer. System implantation is generally performed by a vascular surgeon. The pulse generator is implanted in the fashion of a pacemaker, by making a subcutaneous infraclavicular chest wall pocket to hold the pulse generator. Electrode implantation begins by surgically exposing the carotid sinus through a transverse cervical incision over the carotid bifurcation, with care taken to ensure that the adventitial layers are preserved. The sinus region is then mapped by temporarily placing the electrode in various locations and applying electrical stimulation to determine the location with greatest sensitivity to BAT. Sensitivity is measured by observing hemodynamic changes associated with acute baroreflex activation, namely, reductions in heart rate and/or BP associated with increased parasympathetic traffic and/or decreased sympathetic traffic, respectively. With the correct position identified, the electrode is directly affixed by applying 6 sutures, evenly spaced around the perimeter of the electrode backer, through the backer and adventitia. The opposite end of the lead is brought to the pulse generator pocket by means of a subcutaneous tunnel and attached to the pulse generator. All incisions are then closed and the procedure is complete.

BAT dose is up-titrated over a series of follow-up visits, much like medications are up-titrated. As with medical therapy, the focus is on achieving a therapeutic dose in the absence of side effects. Thus, therapy is initiated at a moderate level in the absence of side effects such as excessive reductions in heart rate or BP. At later follow-up visits, therapy levels are increased as the patient is able to tolerate higher doses, with the objective of achieving full titration at around 3 months. Because the electrode-baroreceptor interface is unique to each patient, there is no standard dose of the therapy. The stated programmed parameter statistics (see the Results section) represent the dosing in the average patient absent side effects, thereby representing an analog to pharmacologic dosing.

STUDY DESIGN. Patients meeting the criteria for entry underwent the following baseline assessments: NYHA class (11), QoL assessed by the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) (12), 6MHW distance (assessed using a standardized protocol [13]), cardiac structure and function assessed by echocardiography, serum biomarkers including N-terminal pro-brain natriuretic peptide [NT-proBNP], and an accounting of HF medications.

After this initial evaluation, patients were randomized (1:1) to receive ongoing GDMT alone (control group) or ongoing GDMT plus BAT (treatment group). Randomization occurred in permuted blocks to ensure a balance between groups within centers. To receive a randomization assignment, the intended date of BAT initiation was identified as the "activation date." The activation date determined the schedule for all follow-up visits for both the control and treatment groups. Patients randomized to receive BAT were implanted with the BAT system, as previously described. If a preexisting cardiac rhythm management device was present, interaction testing was conducted to confirm unimpeded performance of the systems (14). BAT was

initiated either before discharge or within 2 weeks after discharge. Mandatory follow-up visits for patients receiving BAT occurred at 2 weeks and at 1, 2, 3, 5, and 6 months after initiation. The protocol called for BAT to be gradually up-titrated over the first several visits. For control patients, the follow-up schedule in the United States was identical to that for treatment patients. Control patients outside the United States (OUS) were seen at 3 and 6 months. Variables assessed at baseline were reevaluated in all patients at 6 months and constituted the evaluation of efficacy. Adverse event reporting was collected continuously. In the US, hospitalization data were collected at baseline for the 6 months before enrollment and prospectively for 6 months after system activation, at all centers. OUS, hospitalization data were collected retrospectively, at a subset of centers.

TABLE 1 Baseline Characteristics for Activated Subjects

Variable	Treatment Group	Control Group
Age (yrs)	64 ± 11 (71)	66 ± 12 (69)
Gender (female)	12.7% (9/71)	15.9% (11/69)
Race (Caucasian)	81.7% (58/71)	89.9% (62/69)
Geography (U.S./Europe/Canada)	53% (40)/45% (34)/3% (2)	46% (32)/51% (36)/3% (2)
Coronary artery disease	66.2% (47/71)	68.1% (47/69)
Atrial fibrillation	45.1% (32/71)	43.5% (30/69)
Diabetes mellitus type 2	36.6% (26/71)	33.3% (23/69)
Hypertension	57.6% (19/33)	56.8% (21/37)
Chronic kidney disease	33.8% (24/71)	24.6% (17/69)
NYHA (class III)	98.6% (70/71)	100.0% (69/69)
6-min walk (m)	297 ± 79 (69)	308 ± 85 (67)
MLWHFQ QoL*	51 ± 21 (70)	43 ± 22 (69)
BMI (kg/m^2)	29 ± 5 (71)	29 ± 5 (69)
SBP (mm Hg)	115 ± 18 (71)	119 ± 17 (69)
DBP (mm Hg)	72 ± 11 (71)	73 ± 11 (69)
HR (beats/min)	73 ± 11 (71)	75 ± 12 (66)
eGFR (ml/min)	58 ± 21 (58)	59 ± 19 (61)
Creatinine (mg/dl)	1.4 ± 0.5 (58)	1.3 ± 0.4 (61)
Cystatin C (mg/l)	1.3 ± 0.6 (37)	1.3 ± 0.4 (32)
NT-proBNP (pg/ml)	1,422 (455–4,559) (49)	1,172 (548–2,558) (47)
BNP* (pg/ml)	123 (47–417) (17)	209 (34–517) (12)
LVEF (%)	24 ± 7 (70)	25 ± 7 (67)
CRT	33.8% (24/71)	30.4% (21/69)
ICD	88.7% (63/71)	85.5% (59/69)
HF hospitalization rate before randomization	0.63 ± 1.47 (57)	0.36 ± 1.12 (50)
Number of medications	4.8 ± 1.6 (70)	4.4 ± 1.9 (68)
ACE inhibitors/ARBs	78.9% (56/71)	79.4% (54/68)
Beta-blockers	87.3% (62/71)	85.3% (58/68)
Calcium-channel blockers	5.6% (4/71)	8.8% (6/68)
Digitalis	21.1% (15/71)	10.3% (7/68)
Diuretic agents	93.0% (66/71)	77.9% (53/68)
Ivabradine	4.2% (3/71)	1.5% (1/68)
MRA	59.2% (42/71)	50.0% (34/68)

Values are mean ± SD (n), % (n), median (interquartile range) (n), or % (n/N). *p ≤ 0.05 for between-group difference.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = brain natriuretic peptide; BP = blood pressure; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HR = heart rate; MRA = mineralocorticoid receptor antagonist; SBP = systolic blood pressure.

STATISTICAL ANALYSIS. The primary safety objective was to determine the event-free rate of all system- and procedure-related major adverse neurological and cardiovascular events (MANCE), and the primary efficacy end points were changes in NYHA class, QoL score, and 6MHW distance. MANCE included cardiovascular-related death, stroke, cardiac arrest, acute myocardial infarction, acute decompensated HF, hypertensive crisis, severe complications of HF treatment, systemic and pulmonary thromboembolism, infection requiring explantation of any portion of the BAT system, cranial nerve damage that was permanent (not resolved within 12 months of onset) or required invasive intervention to correct, and events requiring nonelective major restorative procedures. All potential MANCE underwent an independent adjudication process. Multiple MANCE adjudicated as causally or temporally linked were treated as 1 event. Between-group differences in changes of the following parameters constituted the efficacy evaluation: NYHA class, MLWHFQ QoL score, 6MHW distance, cardiac structure and function by echocardiography, and serum biomarkers. Among these efficacy end points, changes in NYHA class, MLWHFQ QoL score, and 6MHW distance were considered to be of primary interest. Other end points (echocardiographic parameters, biomarkers) were considered to be supportive of these clinical measures. Echocardiographic measurements were performed in a blinded fashion by a central core laboratory. Within-group changes and between-group differences in the rate of HF hospitalization were considered to be exploratory analyses. Cause of hospitalization was determined using a blinded adjudication committee and process.

The sample size for this study was based on a desire to obtain initial experience with this device in the intended HF population. It was not determined on the basis of statistical requirements for a formal hypothesis test; rather it was chosen to inform future research in terms of logistical considerations and possible estimates of effect size and variability. Effects on continuous variables that passed tests of normality were assessed with paired *t* tests. In the case of non-normal data, the Wilcoxon rank sum test was used. Categorical variables were analyzed using Fisher exact tests. Confidence intervals for proportions were calculated using the exact binomial method. For HF hospitalization data, comparisons between groups were based on the exact permutation test or the negative binomial method (when indicated). Hospitalization data were annualized to

account for variable periods of post-randomization follow-up in those patients who did not complete 6 months (e.g., because of death). For the primary safety end point, no objective performance criterion was pre-specified. For the primary efficacy variables, the statistical analysis plan did not include adjustment for the multiplicity of comparisons, and a nominal p value of 0.05 or less was considered suggestive of efficacy. However, the study steering committee agreed to apply a more rigorous statistical approach whereby the study could achieve its primary efficacy end point if the differences between groups in all 3 end points (NYHA class, MLWHFQ QoL score, and 6MHW distance) had p values of 0.05 or less, if 2 end points had p values of 0.025 or less, or if 1 end point had a p value of 0.0167 or less, similar to the methodology used in the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial (15). Finally, several sensitivity analyses were performed to determine the effect of patient dropouts (e.g., withdrawal of consent and loss to follow-up) including last observation carried forward, best case imputed for all patients, worst case imputed for all patients, best case imputed for control and worst case imputed for BAT, and mean imputed for all patients. The best case/worst case analysis was also done using the 10th- and 90th-percentile values rather than minimal and maximal ones.

The investigators had full access to all data and performed analyses without restrictions or limitations from the study sponsor.

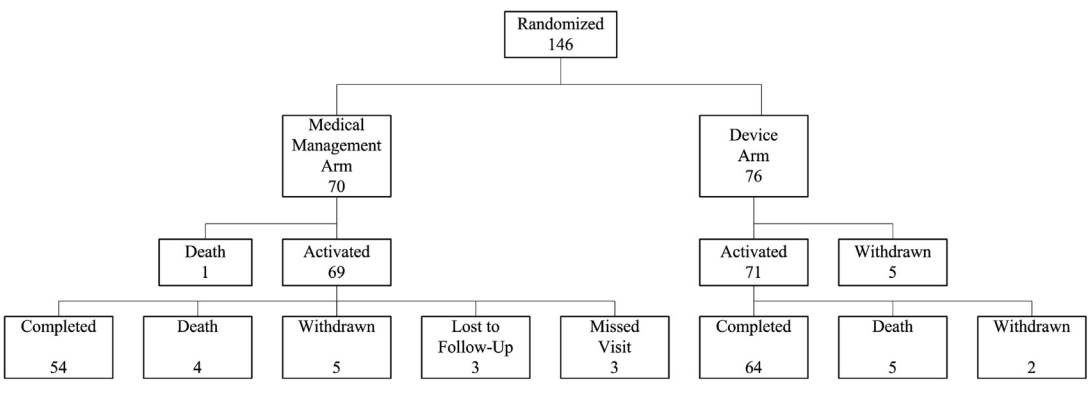
RESULTS

FOLLOW-UP AND DISPOSITION OF PATIENTS. Between May 2012 and April 2014, 146 patients at 45 centers were randomized in the trial; 70 (32 US and 38 OUS) were assigned to the control group and 76 (40 US and 36 OUS) were assigned to BAT. One patient in the control group died before the activation date, and 5 patients in the treatment group withdrew consent or were withdrawn by the site before system implantation and their activation dates. The 2 groups were similar with respect to baseline characteristics, except for a significantly worse QoL score in the treatment group, a significantly higher rate of diuretic agent use in the treatment group, and a trend toward a higher rate of HF hospitalization before enrollment in the treatment group (Table 1). The disposition of patients is shown in Figure 1. Of the 69 patients assigned to the control group who reached their activation dates, 15 did not complete 6 months of follow-up: 4 patients died, 5 withdrew consent, 3 were lost to follow-up, and 3 missed the visit. Of the 71 patients who received the BAT system and reached their activation date, 7 did not complete 6 months of follow-up: 5 died and 2 withdrew consent.

Poolability analysis indicated that the OUS and US populations were generally similar, except for a significantly greater proportion of Caucasian patients OUS compared with US (96% vs. 76%, $p < 0.01$), a significantly higher median NT-proBNP level OUS compared with US (1,684 pg/ml [interquartile range: 652 to 4,446 pg/ml] vs. 742 pg/ml [interquartile range: 278 to 2,445 pg/ml], $p = 0.03$), and a significantly better mean QoL score OUS compared with US (43 ± 19 vs. 51 ± 23, $p = 0.05$). Ivabradine, which is not available in the US, was used in 4 OUS patients.

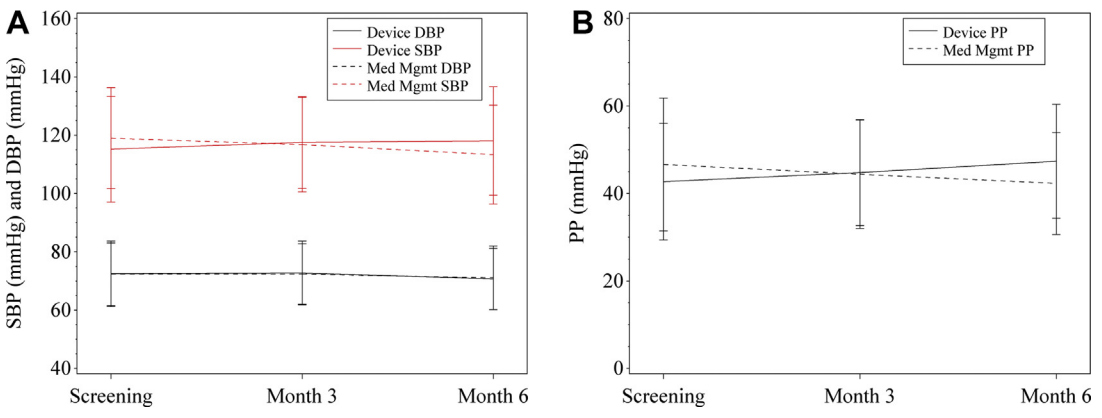
SAFETY AND TOLERABILITY. The overall MANCE-free rate was 97.2% (lower 95% confidence bound

FIGURE 1 Disposition of All Randomized Subjects Through 6 Months



See text for details.

FIGURE 2 Effect of BAT on BP



Baroreflex activation therapy (BAT) significantly increased systolic blood pressure (BP) **(A)** and pulse pressure **(B)**, with no effect on diastolic BP. In contrast, there were trends toward decreasing systolic BP and pulse pressure in the control group.

91.4%). Two system- or procedure-related MANCE occurred during the course of the study, consisting of 2 hematomas adjudicated as related to the procedure. The system- and procedure-related complication event-free rate was 85.9% (lower 95% confidence bound 77.3%). All but 1 event occurred within 7 days of implantation and resolved without residual side effects. Complications included urinary retention, urinary tract infection, hematoma (n = 2), bradycardia, atrial arrhythmia (n = 2), hypotension, worsening HF, pneumothorax, and cervical neuralgia. The majority of BAT patients (93%) had pre-existing cardiac rhythm management devices. Rigorous testing at the time of BAT system implantation revealed no device-device interactions impeding the performance of either system.

Patients tolerated BAT well, as device programming was titrated so that patients did not experience side effects (e.g., tingling or hypotension). On average, pulse amplitude upon activation was 4.5 ± 2.5 mA and steadily increased to 6.8 ± 2.4 mA at 3 months, remaining stable thereafter. Pulse width and frequency were stable throughout follow-up, averaging 108.8 ± 75.8 μs and 61.9 ± 20.8 pulses/s, respectively. Symptoms associated with therapy titration were rare, with a 0.67% incidence of transient bradycardia or hypotension requiring intervention beyond acute device reprogramming. No changes were detected in diastolic BP in either group. Systolic BP trended downward in control patients, while it trended upward in the treatment group. This difference in effect of BAT on systolic BP reached statistical significance (8.5 ± 3.8 mm Hg, p = 0.03), while pulse pressure also demonstrated a significant increase (9.6 ± 3.2 mm Hg, p = 0.004) (Figure 2).

TABLE 2 Effect of BAT on Primary Efficacy End Points (Change From Baseline to 6 Months)

	Treatment Group		Control Group		Difference	
Variable	n	Mean ± SE	n	Mean ± SE	Mean ± SE	p Value
NYHA class (% improved, same, worse)	64	55%, 42%, 3%	54	24%, 67%, 9%	0.002	
MLWHFQ QoL	64	−17.4* ± 2.8	54	2.1 ± 3.1	−19.5 ± 4.2	<0.001
6MHW distance (m)	56	59.6* ± 14.1	43	1.5 ± 13.2	58.1 ± 19.8	0.004

*p < 0.001 for within-group change.

6MHW = 6-minute hall walk; MLWHFQ = Minnesota Living with Heart Failure Questionnaire; NYHA = New York Heart Association; QoL = quality of life; SE = standard error.

EFFICACY. At 6 months, statistically significant improvements were observed in NYHA class, MLWHFQ QoL score, and 6MHW distance in BAT patients compared with control patients (p = 0.002, p < 0.001, and p = 0.004, respectively; Table 2). More patients in the treatment group (55%) demonstrated at least a 1-class improvement in NYHA class, compared with the control group (24%). The between-group difference in MLWHFQ QoL score was −19.5 ± 4.2 points, favoring BAT. Likewise, the between-group difference in 6MHW distance was 58.1 ± 19.8 m, also favoring BAT. Multiple sensitivity analyses generally supported the significance of these findings, with the exception of the best case/worst case sensitivity analyses.

NT-proBNP was reduced in the treatment group and increased in the control group, with a significant

between-group difference (median −69.0 pg/ml [interquartile range: −504 to 198 pg/ml] vs. 129.5 pg/ml [interquartile range: −67 to 619 pg/ml], p = 0.02). No significant changes were observed in other biomarkers (creatinine, estimated glomerular filtration rate, and cystatin C). Echocardiographic analysis indicated a nonsignificant trend toward improved LVEF in the BAT group and a slight reduction in the control group, with a between-group difference of 2.5 ± 1.7% (p = 0.15). Other echocardiographic parameters were not significantly altered by BAT.

The effect of BAT on the rate of HF hospitalization and on the mean number of days hospitalized for HF is summarized in **Table 3**. During the 6 months before enrollment, there was an apparent difference between groups in the annualized rate of HF hospitalization and the mean number of days hospitalized for HF, especially in the US (p = 0.08 and p = 0.05, respectively). Globally, there was a significant reduction in the rate of HF hospitalization from pre- to post-enrollment in the treatment group (0.63 ± 1.5 to 0.14 ± 0.5 hospitalizations/patient/year, p = 0.01), with no change seen in the control group (0.36 ± 1.1 to 0.31 ± 0.97 hospitalizations/patient/year, p = 0.85). However, the between-group difference in the post-randomization rate of HF hospitalization did not reach statistical significance (p = 0.35). The effect of BAT on the mean number of days hospitalized for HF followed a similar pattern of significance and non-significance. However, the between-group difference in post-randomization days hospitalized for HF demonstrated a trend favoring the treatment group (p = 0.08).

DISCUSSION

The results of the present study indicate that BAT is safe and significantly improves NYHA class, QoL, and exercise capacity in patients with NYHA class III HF with reduced LVEFs. The magnitude of these benefits was similar to, if not greater than, that reported with currently available effective drug and device therapies for HF, and yet they were seen in patients already receiving these therapies (15,16). These results corroborate the single-center, open-label experience previously reported by Gronda et al. (10). The present study extends the results of Gronda et al. by demonstrating significant improvement in NT-proBNP, a significant correlate of clinical outcome in patients with HF (17).

Although the present study was not adequately powered to evaluate clinical outcomes, the effect of BAT on the rate of HF hospitalization and on the mean number of days hospitalized for HF was explored to aid in the design of future studies. An apparent imbalance between groups in both measures at baseline (i.e., during the 6 months before enrollment) makes the interpretation of post-randomization HF hospitalization data difficult. However, there was a significant reduction in both the rate of HF hospitalization and the mean number of days hospitalized for HF from pre- to post-enrollment in patients treated with BAT, which was not seen in patients randomized to the control group, and the post-randomization between-group difference in the average number of days hospitalized for HF nearly reached statistical significance.

TABLE 3 Effect of BAT on the Annualized Rate of HF Hospitalization and the Mean Number of Days Hospitalized for HF

	US and OUS			US			OUS		
Variable	Device (n = 57)	Med Mgmt (n = 50)	Difference (Mean ± SE)	Device (n = 38)	Med Mgmt (n = 32)	Difference (Mean ± SE)	Device (n = 19)	Med Mgmt (n = 18)	Difference (Mean ± SE)
Number of HF hospitalizations per year									
Before enrollment	0.63 ± 1.5	0.36 ± 1.1	0.27 ± 0.3	0.58 ± 1.2	0.13 ± 0.5	0.45* ± 0.2	0.74 ± 1.9	0.78 ± 1.7	−0.04 ± 0.6
Post-randomization	0.14 ± 0.5	0.31 ± 1.0	−0.17 ± 0.1	0.11 ± 0.5	0.24 ± 1.0	−0.13 ± 0.2	0.21 ± 0.6	0.44 ± 0.9	−0.23 ± 0.2
Change from pre to post	−0.49† ± 0.2	−0.05 ± 0.2	−0.44 ± 0.3	−0.47† ± 0.2	0.11 ± 0.2	−0.58† ± 0.3	−0.53 ± 0.5	−0.33 ± 0.5	−0.19 ± 0.7
Negative binomial 6 months post-randomization	0.12	0.25	52% RR‡	0.07	0.16	54% RR‡	0.20	0.42	52% RR‡
HF hospitalizations days per year									
Before enrollment	6.95 ± 20.7	2.40 ± 8.6	4.55 ± 3.1	2.21 ± 4.6	0.44 ± 1.7	1.77† ± 0.9	16.42 ± 33.9	5.89 ± 13.6	10.53 ± 8.6
Post-randomization	0.67 ± 2.5	2.48 ± 7.4	−1.82* ± 1.0	0.58 ± 2.5	0.88 ± 4.0	−0.30 ± 0.8	0.84 ± 2.6	5.33 ± 10.8	−4.49* ± 2.5
Change from pre to post	−6.28† ± 2.7	0.08 ± 1.7	−6.36† ± 3.3	−1.63* ± 0.8	0.44 ± 0.8	−2.07* ± 1.2	−15.58 ± 7.7	−0.56 ± 4.5	−15.02 ± 9.1
Negative binomial 6 months post-randomization	0.38	2.10	82% RR*‡	0.09	0.67	86% RR‡	0.80	4.91	84% RR‡

The p values for between-group comparisons are based on the exact permutation test (except for the negative binomial comparison). The p values for the within-group comparisons are based on a paired Wilcoxon test. *p ≤ 0.10. †p ≤ 0.05. ‡RR = relative reduction adjusted for 12 months before enrollment HF hospitalizations based on the negative binomial model.

BAT = baroreflex activation therapy; HF = heart failure; OUS = outside United States; SE = standard error; US = United States.

The safety profile of BAT in HF is comparable with that observed in the resistant hypertensive population and similar to that of a pacemaker (9). The BAT system was safely implanted with few complications, resulting in no untoward effects, and the therapy was very well tolerated. The risk for major adverse neurological and cardiovascular events over 6 months (the primary safety end point) compares favorably with similar device-based therapies. No interactions with implantable cardiac rhythm management devices (pacemakers or ICDs) were seen. This observation is important, because a majority of patients with HF with reduced ejection fractions are indicated for such devices (1).

Also of consequence, BAT did not produce hypotension in these normotensive patients with HF, in contrast to the known BP-lowering effect of BAT in hypertensive subjects. Rather, BAT resulted in significant increases in systolic BP and pulse pressure in these patients with HF, perhaps caused by improved stroke volume due to reduced vascular resistance. This effect of BAT to maintain or improve BP in patients with HF is not only important from the safety standpoint but may also contribute to efficacy, because lower BPs are associated with poorer outcomes in HF patients (18). Mechanistically, the postulated decrease in vascular resistance may be due to previously demonstrated reductions in peripheral sympathetic nerve activity with BAT (10).

The relatively small number of patients studied may limit the interpretation of some of the results of the present study. Another potential limitation may be the lack of patient blinding and a sham control, leading to a "placebo effect" in the treatment arm, or a lack of blinding in investigator assessment of end points, leading to bias. However, the magnitude of improvement in the primary end points is substantially larger than that attributable to such a placebo effect or bias in prior device trials. For example, in prior studies of CRT, the implantation of an inactive device was associated with a 10-m improvement in 6MHW distance (15), a placebo effect that falls far short of the nearly 60-m improvement seen with BAT in the present study. In addition, at least 1 of the end points significantly improved by BAT, NT-proBNP, is not prone to a placebo effect. The difference in follow-up schedule between study groups OUS has the potential to bias the results. However, there were no statistically significant differences in the treatment effect between the US and OUS subjects. Similarly, the differential collection of hospitalization data by world region could also introduce bias. However, data presented in **Table 3** indicate similar hospitalization trends in both major geographies of the study.

Our study results are strengthened by a high standard of baseline pharmacologic and device-based therapy (87% ICD, 32% CRT). For comparison, in a recently published HF drug trial, only 15% of patients received ICDs and 7% received CRT devices, despite a quite similar ejection fraction boundary for inclusion (19). Hence, our results indicate that HF therapy can be improved in an already very well treated, but very symptomatic HF population.

In summary, BAT is safe and significantly improves functional status, QoL, exercise capacity, and NT-proBNP in well-treated patients with NYHA class III HF. The data also support the possibly that BAT reduces the rate of HF hospitalization and the number of days hospitalized for HF. This latter observation should be confirmed in an adequately powered prospective outcome trial.

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. William T. Abraham, Division of Cardiovascular Medicine, Davis Heart and Lung Research Institute, 473 West 12th Avenue, Room 110P, Columbus, Ohio 43210-1252. E-mail: william.abraham@osumc.edu.

PERSPECTIVES

Despite currently available drug and device therapies, many patients with HF remain highly symptomatic and limited in their daily activities. Carotid BAT results in centrally mediated reduction of sympathetic outflow and increased parasympathetic activity, thus potentially restoring autonomic balance in patients with HF. The present study indicates that BAT is safe and significantly improves NYHA class, QoL, exercise capacity, NT-proBNP, and possibly the burden of HF hospitalizations in patients with NYHA class III HF with reduced LVEFs. If these observations are confirmed in larger studies, BAT may offer a new addition for the treatment of patients with advanced HF with reduced LVEFs.

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KEY WORDS autonomic nervous system, baroreflex, device, heart failure, randomized controlled trial

APPENDIX For a list of the participants in the study, please see the online version of this article.