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Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction: safety and efficacy in patients with and without cardiac resynchronization therapy

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Aims Increased sympathetic and decreased parasympathetic activity contribute to heart failure (HF) symptoms and disease progression. Carotid baroreceptor stimulation (baroreflex activation therapy, BAT) results in centrally mediated reduction of sympathetic and increase in parasympathetic activity. Because patients treated with cardiac resynchronization therapy (CRT) may have less sympathetic/parasympathetic imbalance, we hypothesized that there would be differences in the response to BAT in patients with CRT vs. those without CRT.

Methods and results New York Heart Association (NYHA) Class III patients with an ejection fraction (EF) ≤35% were randomized (1 : 1) to ongoing guideline-directed medical and device therapy (GDMT, control) or ongoing GDMT plus BAT. Safety endpoint was system-/procedure-related major adverse neurological and cardiovascular events (MANCE). Efficacy endpoints were Minnesota Living with Heart Failure Quality of Life (QoL), 6-min hall walk distance (6MHWD), *N*-terminal pro-brain natriuretic peptide (NT-proBNP), left ventricular ejection fraction (LVEF), and HF hospitalization rate. In this sample, 146 patients were randomized (70 control; 76 BAT) and were 140 activated (45 with CRT and 95 without CRT). MANCE-free rate at 6 months was 100% in CRT and 96% in no-CRT group. At 6 months, in the no-CRT group, QoL score, 6MHWD, LVEF, NT-proBNP and HF hospitalizations were significantly improved in BAT patients compared with controls. Changes in efficacy endpoints in the CRT group favoured BAT; however, the improvements were less than in the no-CRT group and were not statistically different from control.

Conclusions BAT is safe and significantly improved QoL, exercise capacity, NTpro-BNP, EF, and rate of HF hospitalizations in GDMT-treated NYHA Class III HF patients. These effects were most pronounced in patients not treated with CRT.

Keywords Baroreflex • Heart failure • Resynchronization • Autonomic nervous system • Randomized controlled trial

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Introduction

Both clinical and experimental evidence indicate that activation of the adrenergic nervous system and inhibition of the parasympathetic nervous system play a major role in the genesis of symptoms and disease progression in patients with heart failure (HF) and a reduced ejection fraction (HFrEF).[1,2] This autonomic imbalance exerts adverse cardiac, vascular, and renal effects resulting in pathological myocardial remodelling, peripheral vasoconstriction, and salt and water retention. Both these pathophysiological observations and the success in treatment of HFrEF with adrenergic receptor blockade provide a rationale for therapies that inhibit adrenergic activity, enhance parasympathetic activity, or preferably, accomplish both.[3,4,5]

One example of a novel neuromodulation therapy is baroreflex activation therapy (BAT), an electrical stimulation technology delivered by an implanted device resembling a cardiac pacemaker.[6–9] 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. Recently, in a multinational, prospective, randomized, parallel-controlled, clinical trial in HFrEF patients, BAT was safe with a system- and procedure-related major adverse neurological and cardiovascular events (MANCE)-free rate of 97.2%; in addition, compared with control patients, BAT was effective as shown by a 58 m increase in the distance walked in 6 min ($P = 0.004$), a 20-point decrease in quality of life score ($P < 0.001$), a 31% improvement in New York Heart Association (NYHA) class ranking ($P = 0.002$ for change in distribution), a 342 pg/ml decrease in *N*-terminal pro-brain natriuretic peptide (NT-proBNP) ($P = 0.02$), and a trend toward fewer days hospitalized for HF in patients treated with BAT compared with control patients.[9] However, whether these results were consistent across all subgroups of patients examined in this study has not yet been examined, particularly as it relates to guideline-directed medical and device therapies (GDMT) that alter autonomic imbalance.

The GDMT for HFrEF include the use of cardiac resynchronization therapy (CRT) in 25–35% of patients with HFrEF. Recent studies, including one from DeMazumder *et al.*,[10] have demonstrated that CRT has salutary effects on both the sympathetic and parasympathetic nervous systems that act to restore the sympathovagal balance in patients with HFrEF. Because patients treated with CRT may thus have less sympathetic/parasympathetic imbalance even when they have NYHA class III symptoms of HF, we hypothesized that there would be differences in the response to BAT in patients with CRT vs. those without CRT. Therefore, the purpose of this study was to define the differences in treatment effect produced by BAT in two protocol prespecified groups of patients: those with vs. those without CRT present at randomization.

Methods

Patients

Patients were eligible for study if they had NYHA Class III chronic HF with an LVEF ≤35%, were treated with chronic stable GDMT for HF including a diuretic, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker, and beta-blocker, if tolerated, as well as implantable cardioverter-defibrillator (ICD) and CRT where indicated. Additional inclusion criteria were resting heart rate 60–100 bpm, systolic blood pressure ≥100 mmHg, estimated glomerular filtration rate (eGFR) ≥30 mL/min.1.73 m^2, 6MHW distance 150–450 m, and be suitable surgical candidates for BAT device implantation as previously described.[9]

Patients were excluded from the study if they had experienced NYHA Class IV HF symptoms with acute pulmonary oedema within 45 days of randomization, or myocardial infarction, unstable angina, syncope, cerebrovascular accident, or aborted sudden cardiac death (including appropriate ICD therapies) during the 3 months before randomization, or had received a pacemaker or ICD device within 90 days or a CRT device within 6 months of enrolment, had known or suspected baroreflex failure or autonomic neuropathy or had previous 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 less than 1 year, body mass index greater than 40, symptomatic uncontrolled bradyarrhythmias, previous or current consideration of solid organ transplant, asthma requiring chronic medication, severe chronic obstructive pulmonary disease (COPD) or restrictive lung disease, non-cardiovascular conditions interfering with 6MHW distance assessment, active malignancy, non-compliance with medical therapy, and inability to fulfil 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 USA. Owing to varying regulatory requirements, the protocol for each country was slightly different, but major eligibility criteria and endpoints were harmonized. Patients provided their written informed consent before enrolment.

BAT device and study design

The system for delivering BAT (Barostim *neo*™ system; CVRx, Inc., Minneapolis, MN, USA) consisting of a carotid sinus lead and a pulse generator and BAT dosage initiation and up-titration have been described previously.[9]

Patients underwent the following baseline assessments: NYHA Class,[11] quality of life (QoL) assessed by the Minnesota Living with Heart Failure (MLWHF) Questionnaire,[12] 6MHW distance (assessed using a standardized protocol,[13] cardiac structure and function assessed by echocardiography using a core laboratory blinded to treatment, serum biomarkers, including NT-pro-BNP, and an accounting of HF medications.

Patients were randomized (1 : 1) to receive ongoing GDMT alone (control group) or ongoing GDMT plus BAT (BAT group). Randomization occurred in permutated blocks to ensure a balance between groups within centres. 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. If a pre-existing cardiac rhythm management device was present, interaction testing was conducted to confirm unimpeded performance of the systems.[14] The BAT was initiated either before discharge or within 2 weeks following 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 USA was identical to the treatment patients. Control patients outside of the USA (OUS) were seen at 3 months and 6 months. Variables assessed at baseline were re-evaluated in all patients at 6 months and comprised evaluation of efficacy. Adverse event reporting was collected continuously. In the USA, hospitalization data were collected at baseline for the 6 months prior to enrolment and prospectively for 6 months following system activation, at all centres; 70 US patients had hospitalization data, 23 in the CRT and 47 in the no-CRT groups. Outside of the USA, hospitalization data were collected retrospectively, at a subset of centres; 37 OUS patients had hospitalization data, 12 in the CRT and 25 in the no-CRT groups.

As prespecified in the original protocol and statistical analysis plan, an analysis of patients divided into those with a CRT (CRT group) and those without a CRT (no-CRT group) present at the time of randomization was performed. Decision to treat patients with CRT was made by the local health-care team and was based on GDMT guidelines. All safety and efficacy endpoints were examined at baseline and 6-month follow-up in these two groups; results within groups and between groups compared control vs. BAT effects.

Statistical analysis

The primary safety objective was to determine the event-free rate of all system- and procedure-related MANCE. The efficacy endpoints were changes in NYHA class, QoL score, and 6MHWD, cardiac structure, and function by echocardiography, serum biomarkers, the rate of HF hospitalization, and the number of days hospitalized for HF.[9] Echocardiographic measurements were performed in a blinded fashion by a central core laboratory. Cause of hospitalization was determined using an adjudication committee and process.

There are three sets of statistical comparisons made in the above-listed efficacy variables:

1. Changes from baseline to 6 months in BAT patients considered as a single group, and changes from baseline to 6 months in control patients as a single group. These analyses were done in the CRT patients separately from analyses in the no-CRT patients. For example, in the CRT patients, baseline measures in patients assigned to BAT were compared to measures after 6 months of randomization in the same patients using a paired *t*-test. These analyses are included in *Table 2* and in the Supplementary material online, *Tables S1–4*.
2. Differences in the changes from baseline to 6 months in BAT compared with control patients in the CRT patients, and differences in the changes from baseline to 6 months in BAT vs. control patients in the no-CRT patients. For example, in the CRT patients, the differences in the change from baseline between BAT and control patients were compared using two-sample *t*-tests. These analyses are included in *Table 2* (columns 4 and 8) and in the Supplementary material online, *Tables 1* and *2*, (column 5), and *Tables 3* and *4* (columns 4–7).
3. Differences in the response to therapy with BAT in CRT compared with the no-CRT patients. The treatment differences in the CRT patients were compared with the treatment differences in the no-CRT patients using a contrast statement in a mixed effects model. These analyses are included in *Table 3*.

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 based on 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 and two-sample *t*-tests, as described above. In the case of non-normal data, the Wilcoxon signed-rank and rank-sum tests were used. Categorical variables were analysed using a Fisher's exact test. 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. 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. owing to death). For the primary safety endpoint, no objective performance criterion was prespecified. 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.

Investigators had full access to all data and performed analyses without restrictions or limitations from the study sponsor. Analyses were performed in SAS v9.3 (Cary, NC, USA) by an independent statistician.

Results

Follow-up and disposition of patients

The disposition of patients is shown in *Figure 1*. Between May 2012 and April 2014, 146 patients at 45 centres were randomized in the trial: 70 were assigned to the control group and 76 were assigned to BAT. One patient in the control group died before their 'activation date' and five patients in the treatment group withdrew consent or were withdrawn by the site before system implantation and their activation dates.

Of the 69 patients assigned to the control group who reached their activation date, 21 had a CRT, 48 did not have a CRT. In the CRT control group patients, four did not complete 6 months of follow-up: two patients died, one withdrew consent, and one missed the visit. In the no-CRT control group patients 11 did not complete 6 months of follow-up: two patients died, four withdrew consent, three were lost to follow-up, and two missed the visit. Of the 71 patients implanted with the BAT system reaching their activation date 24 had a CRT and 47 did not. In the CRT BAT group patients two did not complete 6 months of follow-up (owing to death). In the no-CRT BAT group patients, five did not complete 6 months of follow-up: three patients died and two withdrew consent.

The CRT vs. no-CRT groups were similar with respect to baseline characteristics, except for the following characteristics: the no-CRT patients were younger, more frequently had hypertension noted in their medical history, and had a shorter QRS (*Table 1*).

Safety and tolerability

It was found that BAT was well tolerated and safe in both the CRT and no-CRT groups. The system- or procedure-related MANCE-free rate at 6 months was 100% in the CRT group and 96% in the no-CRT group ($P = \text{ns}$). The system- and procedure-related complication event-free rate was 91.7% (lower 95% confidence bound 76.0%) in the CRT and 83.0% (lower 95% confidence bound 71.4%) in the no-CRT group ($P = \text{ns}$).

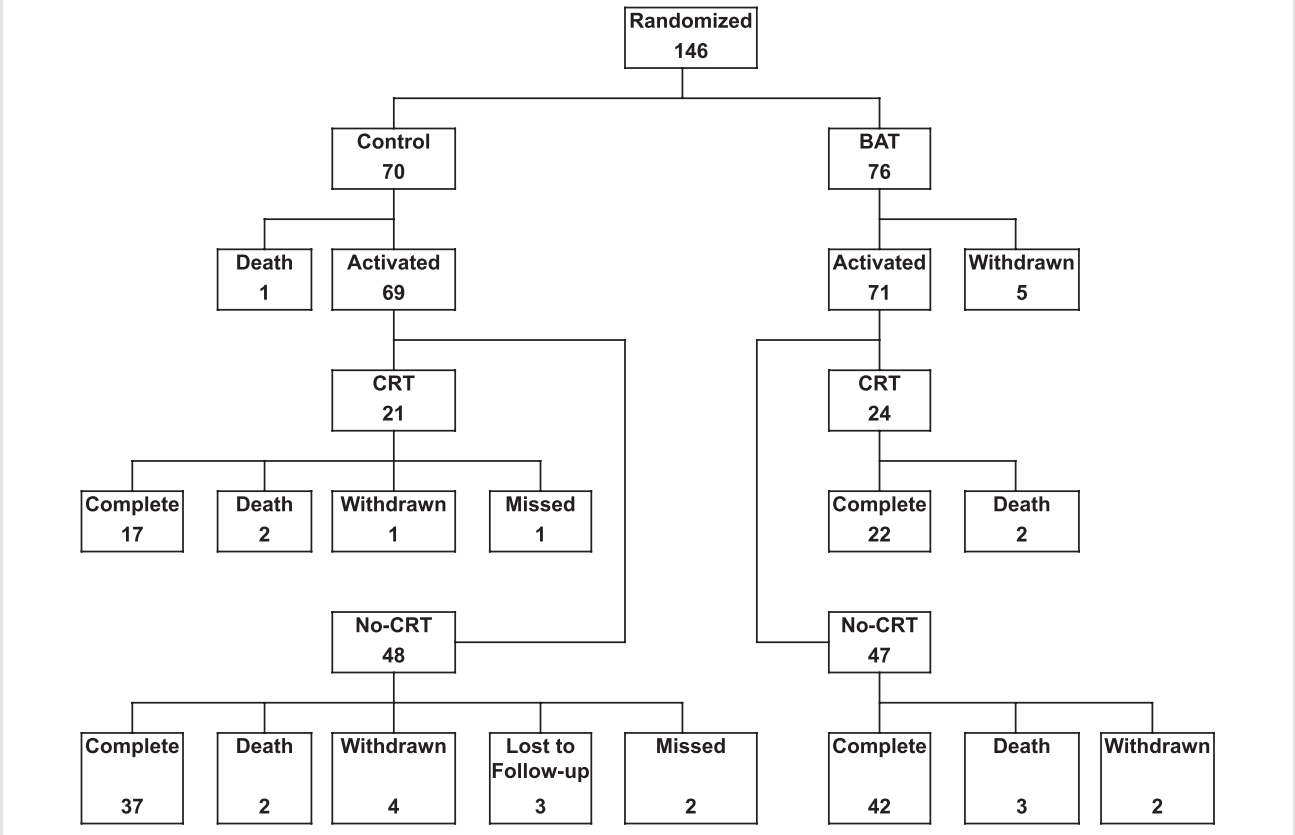

Figure 1 Disposition of patients randomized in the study. CRT, cardiac resynchronization therapy; BAT, baroreflex activation therapy.

Patients tolerated BAT well, as device programming was titrated so that patients did not experience side-effects (e.g. tingling or hypotension). In CRT patients, pulse amplitude upon activation was 4.0 ± 2.1 mA and steadily increased to reach 6.8 ± 2.4 mA at 3 months, remaining stable thereafter. In no-CRT patients, pulse amplitude upon activation was 4.7 ± 2.7 mA and steadily increased to reach 6.8 ± 2.4 mA at 3 months, remaining stable thereafter. In CRT patients, pulse width and frequency were stable throughout follow-up, averaging 128.1 ± 101.3 μs and 58.5 ± 20.3 pulses per second, respectively. In no-CRT patients, both pulse width and frequency were stable throughout follow-up, averaging 99.9 ± 58.9 μs and 63.4 ± 21.0 pulses per second, respectively. Symptoms associated with therapy titration were rare in the CRT and no-CRT groups. There were no differences between the CRT and no-CRT groups in any of these parameters.

The BAT in CRT and No-CRT patients did not produce any statistically significant differences in mean heart rate, the number of patients with at least a two-beat decrease in heart rate, or the number of patients with at least a five-beat decrease in heart rate.

Efficacy in CRT patients

At 6 months, in patients with CRT, statistically significant improvements were observed in NYHA class and MLWHF QoL score in BAT patients compared with control patients (*Table 2*; see the Supplementary material online, *Table S1* and *Table S3*). At 6 months, the NYHA score was lower by -0.7 ± 0.1 ($P < 0.001$) in the BAT patients compared with the baseline value; NYHA class was not statistically different in the control group between baseline and 6 months. The changes in NYHA Class from baseline to 6 months in the BAT vs. control patients were also statistically different (-0.6 ± 0.2, $p < 0.001$) (*Table 3*). Similar results were seen in NYHA class when analysed as a categorical variable: NYHA was improved $\geq$1 class in 68% of BAT vs. 18% in control ($P = 0.003$). There were similar findings in MLWHF QoL score. In the BAT patients, QoL score fell from baseline to 6 months (-9.3 ± 4.0, $P = 0.03$); there was no significant change in the control group. The changes in QoL from baseline to 6 months in the BAT vs. control patients were not statistically different (8.4 ± 7.0, $P = 0.23$).

At 6 months, in patients with CRT, no significant changes in any other efficacy parameter were found in the BAT patients or control patients comparing baseline with 6 months values or comparing changes in other efficacy parameters between baseline and 6 months in BAT vs. control patients.

Efficacy in no-CRT patients

At 6 months, in patients with no-CRT, statistically significant improvements were observed in NYHA Class, QoL score,

Table 1 Baseline characteristics for enrolled subjects

Variable	CRT ($n = 45$)	No-CRT ($n = 95$)	*P*-value
Race: Caucasian	91.1% (41/45)	83.2% (79/95)	0.30
Gender: female	8.9% (4/45)	16.8% (16/95)	0.30
NYHA: class III	100.0% (45/45)	98.9% (94/95)	1.00
Age, years	68 ± 9 (45)	63 ± 12 (95)	0.02
Body mass index, kg/m^2	29 ± 4 (45)	29 ± 5 (95)	0.40
Systolic blood pressure, mmHg	118 ± 19 (45)	117 ± 18 (95)	0.82
Diastolic blood pressure, mmHg	70 ± 10 (45)	73 ± 11 (95)	0.11
Heart rate, bpm	72 ± 10 (45)	74 ± 12 (92)	0.24
LVEF, %	24 ± 6 (44)	25 ± 7 (93)	0.72
eGFR, mL/min	55 ± 19 (34)	60 ± 20 (85)	0.18
Creatinine, mg/dL	1.4 ± 0.5 (34)	1.3 ± 0.5 (85)	0.41
NT-pro BNP[a], pg/mL	1457 [472, 4603] (32)	1144 [534, 3529] (64)	0.84
6MHWD (m)	303 ± 84 (45)	302 ± 81 (91)	0.96
MLWHF quality of life score	44 ± 24 (45)	48 ± 21 (94)	0.33
Number of medications	4.7 ± 2.0 (44)	4.6 ± 1.7 (94)	0.79
Coronary artery disease	60.0% (27/45)	70.5% (67/95)	0.25
Atrial fibrillation on medical history	51.1% (23/45)	41.1% (39/95)	0.28
Atrial fibrillation on holter	23.1% (9/39)	23.0% (20/87)	1.00
Diabetes mellitus type II	37.8% (17/45)	33.7% (32/95)	0.71
Hypertension	36.4% (8/22)	66.7% (32/48)	0.02
Chronic kidney disease	28.9% (13/45)	29.5% (28/95)	1.00
QRS	161.0 ± 33.4 (24)	122.0 ± 30.4 (53)	<0.01
Conduction disorder	42.9% (9/21)	44.2% (23/52)	1.00
Implantable cardiac defibrillator	91.1% (41/45)	85.3% (81/95)	0.42
Heart failure hospitalizations (number over 12 months before enrolment)	0.5 ± 1.3 (23)	0.3 ± 0.7 (47)	0.44
ACE-I/ARB	75.0% (33/44)	83.0% (78/94)	0.36
Beta-blocker	86.4% (38/44)	86.2% (81/94)	1.00
Calcium channel blocker	4.5% (2/44)	8.5% (8/94)	0.50
Digitalis	22.7% (10/44)	12.8% (12/94)	0.14
Diuretic	86.4% (38/44)	85.1% (80/94)	1.00
Ivabradine	2.3% (1/44)	3.2% (3/94)	1.00
Mineralocorticoid receptor antagonists	47.7% (21/44)	57.4% (54/94)	0.36

Round parentheses () show sample size and square brackets [] show interquartile range. 6MHWD, 6-minute hall walk distance
ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MLWHF, Minnesota Living with Heart Failure ; NYHA, New York heart Association class.
[a]Non-parametric analyses.

6MHWD, NT-proBNP, LVEF, number of HF hospitalizations and number of days hospitalized with HF in BAT patients compared to control patients (*Table 2*, the Supplementary material online, *Table S2* and *Table S4*).

At 6 months, the NYHA score was lower by -0.4 ± 0.1 ($P < 0.001$) in the BAT patients compared with the baseline value. The NYHA class was marginally different in the control group between baseline and 6 months, and the change in NYHA class from baseline to 6 months in the BAT vs. control patients was also marginally different (-0.2 ± 0.1, $P = 0.09$). Similar results were seen in NYHA class when analysed as a categorical variable: NYHA was improved ≥ 1 class in 48% of BAT vs. 27% in control ($P = 0.07$). At 6 months, the QoL score was lower by -21.6 ± 0.36 ($P < 0.001$) in the BAT patients compared with the baseline value. The QoL score was not statistically different in the control group between baseline and 6 months, but the changes in QoL score from baseline to 6 months in the BAT vs. control patients were statistically significantly different (-25.1 ± 5.2, $P < 0.001$). At 6 months, the 6MHWD was higher by 85.5 ± 20.5 ($P < 0.001$) in the BAT patients compared with the baseline value. However, 6MHWD was not statistically different in the control group between baseline and 6 months, but the changes in 6MHWD from baseline to 6 months in the BAT vs. control patients were statistically significantly different (81.9 ± 26.8, $P = 0.003$).

Table 2 Differences in efficacy outcomes in BAT vs. control in CRT Patients and No-CRT patients

Change from baseline	No-CRT				CRT			
	BAT ($n=47$)	Control ($n=48$)	Difference	*P*-value	BAT ($n=24$)	Control ($n=21$)	Difference	*P*-value
QoL score	-21.6 ± 3.6[a]	3.5 ± 3.7	-25.1 ± 5.2	<0.001	-9.3 ± 4.0[a]	-0.9 ± 6.0	-8.4 ± 7.0	0.23
NYHA class	-0.4 ± 0.1[a]	-0.2 ± 0.1	-0.2 ± 0.1	0.09	-0.7 ± 0.1[a]	-0.1 ± 0.1	-0.6 ± 0.2	<0.001
6MHWD, m	85.5 ± 20.5[a]	3.6 ± 16.3	81.9 ± 26.8	0.003	16.4 ± 10.6	-3.5 ± 22.9	20.0 ± 22.4	0.38
NT-proBNP, pg/ml	−97 [−504, 93][b]	116 [−74, 700][b]	-318 ± 274[b]	0.03[b]	80 [−452, 402][b]	433 [64, 537][b]	-337 ± 483[b]	0.16[b]
LVEF, %	4.3 ± 1.2[a]	-0.1 ± 1.7	4.4 ± 2.0	0.03	-1.2 ± 2.2	-0.1 ± 2.1	-1.2 ± 3.1	0.71
Heart failure hospitalizations, *n*	-0.53 ± 0.2[a]	0.05 ± 0.3	-0.57 ± 0.4	0.08[b]	-0.42 ± 0.3	-0.25 ± 0.3	-0.17 ± 0.5	0.78[b]
Heart failure hospitalization, days	-8.89 ± 4.0[a]	0.18 ± 2.2	-9.07 ± 4.7	0.09[b]	-1.05 ± 1.2	-0.13 ± 2.5	-0.93 ± 2.6	0.78[b]

Round parentheses () show sample size and square brackets [] show interquartile range. 6MHWD, 6-minute hall walk distance
BAT, baroreflex activation therapy; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; QoL, quality of life
[a]*P* for within group change <0.05.
[b]Non-parametric.

Table 3 Differences in response to therapy with BAT in no-CRT compared with CRT patients

Measure	Estimate	Standard error	*P*-value
QoL score	−12.3161	5.9321	0.040
NYHA class	0.2987	0.1561	0.058
6MHWD, m	69.0571	26.2714	0.010
NT-proBNP, pg/mL	−841.32	1576.15	0.595
LVEF (%)	5.5162	2.3698	0.022
Heart failure hospitalizations, *n*	−0.1430	0.4245	0.737
Heart failure hospitalizations, days	−8.0756	4.7212	0.090

6MHWD, 6-minute hall walk distance; BAT, baroreflex activation therapy; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; QoL, quality of life.

At 6 months, NT-proBNP, reported as median (interquartile range), was lower by −97 pg/mL (−504, 93) ($P=0.14$) in the BAT patients compared with the baseline value. The amount of NT-proBNP was higher 116 pg/mL (−74, 700) ($P=0.13$) in the control group between baseline and 6 months, and the changes in NT-proBNP from baseline to 6 months in the BAT vs. control patients were statistically significantly different (-318 ± 274 pg/ml, $P=0.03$). No significant changes were observed in other biomarkers (creatinine, eGFR, and Cystatin C).

At 6 months, echocardiographic analysis indicated a significant increase in LVEF by 4.3 ± 1.2 ($P<0.001$) in the BAT patients compared with the baseline value. The LVEF was not statistically significantly different in the control group between baseline and 6 months, but the changes in LVEF from baseline to 6 months in the BAT vs. control patients were significantly different (4.4 ± 2.0, $P=0.03$). No significant changes were observed in other echocardiographic parameters.

We found that BAT significantly decreased the rate of hospitalization because of HF and the average number of days hospitalized for HF. During the 6 months following enrolments, hospitalizations because of HF, reported as number of hospitalizations and days hospitalized, was lower by 0.53 ± 0.2 and 8.89 ± 4.0 (both $P<0.05$) in the BAT patients compared with 6 months prior to enrolment. The number and days of HF hospitalizations were not statistically different in the control group between 6 months before and 6 months after enrolment, but the changes in the number and days of hospitalization because of HF between 6 months before and 6 months after enrolment in the BAT vs. control patients were marginally different (-0.57 ± 0.4, $P=0.08$, and -9.07 ± 4.7, $P=0.09$, respectively).

Use of BAT resulted in changes in pulse pressure but no changes in systolic blood pressure, diastolic blood pressure, or heart rate. At 6 months, the pulse pressure was higher by 4.6 ± 2.6 mmHg ($P=0.09$) in the BAT patients compared with the baseline value. Pulse pressure was lower by 4.9 ± 2.3 ($P=0.04$) in the control group between baseline and 6 months, and the changes in pulse pressure from baseline to 6 months in the BAT vs. control patients were statistically significantly different (9.4 ± 3.5, $P=0.009$).

There were no statistically significant differences in baseline EF among any of the four patient groups (BAT CRT, BAT No-CRT, control CRT, control No-CRT). There were no statistically significant differences in baseline end-diastolic volume (EDV) or change in EDV from baseline to 6 months among any of the four patient groups. There were, however, some important trends in end-systolic volume (ESV) from baseline to 6 months that corresponded to the statistically significant differences in EF. Specifically, in the BAT No-CRT patients ESV fell 6.7 mL with a *P*-value of 0.13 vs. control; the differences in the effect of BAT on ESV in No-CRT vs. CRT was 14 mL ($P=0.085$). These trends may be sufficient to explain the differences in EF seen in the same patient group analyses.

Differences in response to therapy with BAT in CRT vs. no-CRT

There were significant differences in the response to BAT in patients with CRT vs. those without CRT in some but not all

efficiency parameters (Table 3). The difference was statistically significant in QoL score ($P = 0.04$), 6MHWD ($P = 0.01$), and LVEF ($P = 0.02$), marginally significant in NYHA ($P = 0.06$ examined as a continuous variable and $P = 0.12$ as a categorical variable) and HF hospitalization days ($P = 0.09$) and not significant in NT-proBNP and number of HF hospitalizations.

Discussion

The results of the present study indicate that BAT is safe and significantly improves NYHA class, QoL, exercise capacity, EF, and NT-proBNP in NYHA class III patients with HFrEF; BAT was most effective in patients that do not have CRT at randomization but was less effective in patients already being treated with CRT. The magnitude of these benefits in the no-CRT patients was similar to, if not greater than, that reported with currently available effective drug therapies for HFrEF, and yet they were seen in patients already receiving these therapies.[15−19] The present study extends the results from Abraham *et al.*,[9] by demonstrating significant improvement in EF, a reduction in HF hospitalizations, and demonstrates selectivity for these results in patients receiving or not receiving CRT.

While the present study was not adequately powered to evaluate clinical outcome, the effect of BAT in the no-CRT patients on the rate of HF hospitalization and on the average number of days hospitalized for HF was explored to aid in the design of future studies. There was a significant reduction in both the rate of HF hospitalization and the average number of days hospitalized for HF from pre- to post-enrolment in no-CRT patients treated with BAT, which was not seen in patients randomized to the control group. These data provide critical insights into the design of future pivotal studies evaluating the effectiveness of BAT. These data allow selective targeting of a patient population with the highest likelihood of responding the BAT.

The safety profile of BAT in HF is comparable to that observed in the resistant hypertensive population and similar to a pacemaker.[7,20]. No differences in safety profile were seen between the CRT and no-CRT patients. Baroreflex activation therapy did not produce hypotension in these normotensive HF patients, in contrast to the known blood pressure lowering effect of BAT in hypertensive subjects. In no-CRT patients, BAT resulted in significant increases in pulse pressure in these HF patients, perhaps caused by improved stroke volume owing to reduced vascular resistance. These BAT-induced effects on pulse pressure and systolic pressure were not seen in the CRT patients treated with BAT. This effect of BAT on no-CRT patients to maintain or improve blood pressure in HF patients is not only important from the safety standpoint but may also contribute to efficacy, as lower blood pressures are associated with poorer outcome in HF patients, and confirms the consistency of the data indicating that BAT in no-CRT patients is efficacious.[18] Mechanistically, the postulated decrease in vascular resistance may result from previously demonstrated reductions in peripheral sympathetic nerve activity with BAT.[8]

Both baroreflex and vagal reflex sensitivity are reduced in patients with HFrEF and this decreased sensitivity has independent prognostic significance[23−25] Thus far, studies using pharmacological intervention have not altered these abnormalities in reflex sensitivity. It is in part for this reason that devices that directly stimulate the baroreflex (BAT) and the vagal reflex (vagal nerve stimulation, VNS) have been developed. Two recent studies using VNS have reported conflicting results.[21,22] The Neural Cardiac Therapy for Heart failure' (NECTAR-HF) study failed to demonstrate a significant effect on primary and secondary endpoint measures of cardiac remodelling and functional capacity in symptomatic HF patients.[22] In NECTAR-HF, 8% of the treated patients and 12% of the control patients had CRT prior to enrolment in the study. By contrast, in the Autonomic Neural Regulation Therapy to Enhance Myocardial Function in HF (ANTHEM_HF) study VNS treatment increased LVEF by 4.5%, decreased LV ESV by −4.1, increased heart rate variability by 17 ms, increased 6MHWD by 56 m and decreased NYHA class in 77% of patients (baseline to 6 months.[21] These changes are very similar to the changes in these same efficacy variables in the BAT treated No-CRT patients. It is also interesting to note that no patient in the ANTHEM-HF study had CRT before to enrolment; all patients in ANTHEM-HF were No-CRT patients.

There may be several potential mechanisms responsible for differences in response to device-based neuromodulation and interaction with components of GDMT for HFrEF, including the use of CRT. Recent studies, including DeMazumder *et al.*[10] and Gademan *et al.*[26] have demonstrated that CRT has salutary effects on both the sympathetic and parasympathetic nervous systems that act to restore the sympathovagal balance in patients with HFrEF. For example, it has been demonstrated that CRT acutely reduces MSNA in clinical responders by acute deactivation of the cardiac sympathetic afferent reflex (CSAR).[26] In addition to sympathoexcitation, CSAR inhibits the arterial baroreflex at the level of the nucleus tractus solitarii. Hence, in responders, CRT removes/reduces this inhibition. Recent studies showed that CRT acutely increased baroreflex sensitivity and heart rate variability. In addition, the effect of CRT on cholinergic signalling in patients with HFrEF and animal models of HFrEF was examined in a recent study.[10] The muscarinic acetylcholine receptors (M2-mAChR) were upregulated in HFrEF compared with non-failing controls. Cardiac resynchronization therapy attenuated the increased M2-mAChR expression and Gαi-coupling, and enhanced M3-mAChR expression in association with enhanced calcium cycling, sarcomere shortening, and β-adrenergic responsiveness. These data suggested that remodelling of cholinergic signalling is an important mechanism underlying HFrEF and that CRT enhances sympathovagal balance in these patients. Because patients treated with CRT may thus have less sympathetic/parasympathetic imbalance even when they have NYHA class III symptoms of HF, we hypothesized that there would be differences in the response to BAT in patients with CRT compared with those without CRT.

In addition, there may be other potential mechanisms responsible for differences in response to device-based neuromodulation and interaction with CRT. The demographic characteristics of the CRT patients in the current study might indicate that they are 'CRT-non responders'. If BAT was applied to CRT non-responders, because this group of patients may have among the poorest prognosis of all NYHA III patients, the effect of BAT may be less

evident. However, given the design of the current study no such definitive determinations of the presence of a CRT non-responder could be made.

The relatively modest number of CRT vs. no-CRT patients studied may limit interpretation of some of the results of the present study. However, particularly in the no-CRT patients, there is a clear consistency across multiple important efficacy parameters. 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 endpoints, leading to bias. However, the magnitude of improvement in the primary endpoints is substantially larger than that attributable to such a placebo effect or bias in previous device trials. For example, in previous studies of cardiac device therapy, the implantation of an inactive device was associated with a 10-m improvement in the 6MHWD,[15] a placebo effect that falls far short of a more than 80-m improvement seen with BAT on no-CRT patients in the present study. In addition, at least one of the endpoints significantly improved by BAT in no-CRT patients, NT-pro-BNP, is not prone to a placebo effect. Similarly, data indicate important trends in the reduction of hospitalization because of HF in the no-CRT patients which are also not prone to a placebo effect. In the present pilot study, the efficacy endpoints specifically focused on clinically relevant changes in objective measurements of symptoms and cardiac structure and function. No substudies examining heart rate variability, baroreflexes, etc., were performed, thus no attempts were made to define differences in autonomic function between CRT and No-CRT patients. While previous small mechanistic studies have examined the effects of BAT on sympathetic nervous system activity and baroreflex function in patients with HFrEF, the lack of these studies represents a limitation to the present study that should be addressed in future studies.

In summary, BAT is safe and significantly improves NYHA class, quality of life, exercise capacity, EF, and NT-proBNP in NYHA class III patients with HFrEF; these results were most pronounced and statistically significant in patients that did not have CRT. The data also support the possibility that BAT reduces the rate of HF hospitalization and the number of days hospitalized for HFrEF. Each of these observations should be confirmed in an adequately powered, prospective, randomized clinical outcome trial.

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Supplementary Information

Additional Supporting Information may be found in the online version of this article:

TableS1. Differences in efficacy outcomes in BAT vs. control in CRT patients.

TableS2. Differences in efficacy outcomes in BAT vs. control in No-CRT patients

TableS3. Differences in hospitalization outcomes in BAT vs. control in CRT patients.

TableS4. Differences in Hospitalization Outcomes in BAT vs. Control in No-CRT Patients

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