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Baroreflex activation therapy for the treatment of heart failure with reduced ejection fraction in patients with and without coronary artery disease

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ABSTRACT

Background: In a randomized trial, baroreflex activation therapy (BAT) improved exercise capacity, quality of life and NT-proBNP in patients with heart failure with reduced ejection fraction (HFrEF). In view of different mechanisms underlying HFrEF, we performed a post-hoc subgroup analysis of efficacy and safety of BAT in patients with and without coronary artery disease (CAD).

Methods and results: Patients with left ventricular ejection fraction <35% and NYHA Class III were randomized 1:1 to guideline-directed medical and device therapy alone or plus BAT. Patients with a history of CAD, prior myocardial infarction or coronary artery bypass graft were assigned to the CAD group with all others assigned to the no-CAD group. Of 71 BAT treated patients, 52 had CAD and 19 had no CAD. In the control group, 49 of 69 patients had CAD and 20 had no CAD. The system- or procedure-related major adverse neurological or cardiovascular event rate was 3.8% in the CAD group vs. 0% in the no-CAD group ($p = 1.0$). In the whole cohort, NYHA Class, Minnesota Living with Heart Failure score, 6-minute hall walk distance and NTproBNP were improved in BAT treated patients compared with controls. Statistical analyses revealed no interaction between the presence of CAD and effect of BAT (all $p > 0.05$).

Conclusion: No major differences were found in BAT efficacy or safety between patients with and without CAD, indicating that BAT improves exercise capacity, quality of life and NTproBNP in patients with ischemic and non-ischemic cardiomyopathy.

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1. Introduction

Heart failure (HF) with reduced ejection fraction (HFrEF) is associated with increased sympathetic and decreased parasympathetic tone [1], related to a lower sensitivity of the inhibitory baroreflex [2]. This sympathovagal imbalance causes vasoconstriction, activation of the renin-angiotensin-aldosterone system and cardiac remodeling, leading to further decline in left ventricular (LV) function [1,3]. Baroreflex activation therapy (BAT) electrically stimulates carotid sinus baroreceptors and can cause a ~30% reduction in sympathetic nerve activity, which may disrupt this vicious circle [4,5].

The first randomized trial comparing guideline-directed medical and device-based therapy (GDMDT) alone with GDMDT plus BAT in patients

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with HFrEF demonstrated a reasonable safety profile of BAT with a system- or procedure-related major adverse neurological and cardiovascular event (MANCE)-free rate of 97.2% [6]. Significant improvements were found in New York Heart Association (NYHA) Class ranking (31% improvement), Minnesota Living with Heart Failure (MLWHF) quality of life (QOL) score (19.5 point decrease), 6-minute hall walk (6MHW) distance (58 m increase) and NT-proBNP (342 pg/ml decrease) compared with controls. A subgroup analysis of BAT in patients with or without cardiac resynchronization therapy (CRT) revealed an equal MANCE-free rate [7]. Significant differences in QOL, 6MHW distance and LV ejection fraction (LVEF) were found, favoring patients without CRT.

HFrEF etiology is diverse and comprises ischemic and non-ischemic causes. In ischemic cardiomyopathy, scar formation after myocardial infarction (MI) or hibernation of myocardium due to insufficient blood supply accounts for the reduced contractility [8]. Besides direct impairment of post-ischemic tissue, remote myocardium may undergo adverse remodeling, contributing to the reduction of global systolic function [8]. Non-ischemic dilated cardiomyopathy has a variety of causes, but per definition does not include ischemia due to macrovascular stenosis [9]. Ischemic vs. non-ischemic cardiomyopathy classification has prognostic implications [10], and device-based therapies have shown etiology-specific differences in therapeutic response [11]. Whether BAT effects in HFrEF are consistent across patient subgroups with different underlying mechanisms, especially ischemic versus non-ischemic dilated cardiomyopathy, has not yet been examined. Therefore, we sought to perform a post-hoc subgroup analysis of efficacy and safety of BAT in patients with and without coronary artery disease (CAD).

2. Methods

2.1. Patients

The study protocol was described in detail before [6]. Briefly, patients on stable GDMDT with NYHA Class III HF and LVEF ≤35% due to either ischemic or non-ischemic cardiomyopathy were included. Exclusion criteria included CRT device implantation within 6 months before randomization, baroreflex failure or autonomic neuropathy, prior carotid artery surgery/stenting or >50% stenoses. 146 patients were randomized across 45 centers (70 to the control and 76 to the BAT group). The disposition of patients is shown in Supplementary Fig. 1.

The protocol conformed to the Declaration of Helsinki and was approved by ethics committees/institutional review boards and regulatory authorities. Due to varying regulatory requirements, each country's protocol was slightly different. Patients provided written informed consent before enrollment.

2.2. BAT device, implantation, and therapy titration

The Barostim *neo*™ system (CVRx, Minneapolis, MN) and implantation procedure have been described before [6,12]. The unipolar disk electrode was affixed to the carotid sinus at the location producing the greatest response to BAT. The lead was tunneled subcutaneously to the pulse generator implanted infraclavicularly.

Electrical stimulation intensity was up-titrated over a series of follow-up visits. Each patient's maximum tolerable dose was unique, so no standard BAT dosage was implemented.

2.3. Study design

Baseline assessments included NYHA Class, MLWHF QOL score, 6MHW distance, echocardiography, and NT-pro-BNP. Blood pressure (BP) was collected using standard office cuff measurements. Patients were randomized 1:1 to the GDMDT control group or the GDMDT plus BAT group. BAT was activated within two weeks after implantation. Variables assessed at baseline were re-evaluated at 6 months. Adverse event reporting was collected continuously. In the US, hospitalization data were collected 6 months prior to enrollment and prospectively for 6 months following BAT activation. Outside of the US, hospitalization data were collected retrospectively at a subset of centers.

2.4. Subgroup analysis of patients with and without CAD

A subgroup analysis of patients with and without CAD was performed post hoc. Baseline evaluations comprised of documentation of known CAD, prior MI or prior coronary artery bypass graft in the patient case report forms. Patients with a history of CAD, prior MI or coronary artery bypass graft at baseline were assigned to the CAD group, with all others assigned to the no-CAD group. Per study protocol, patients did not undergo a structured assessment of coronary anatomy or ischemia, thus patient allocation to the CAD or no-CAD group was based on medical history alone.

2.5. Statistical analysis

The primary safety objective was to determine the overall system- or procedure-related MANCE-free rate, as previously described [6]. Efficacy endpoints included 6 month changes in NYHA Class, MLWHF QOL score, 6MHW distance, cardiac structure and function by echocardiography, serum biomarkers and HF hospitalization. Echocardiographic measurements were performed in a blinded fashion by a core laboratory. Causes of hospitalization were determined by an adjudication committee.

Three sets of statistical comparisons were performed:

1-. Changes from baseline to 6 months in BAT patients as a single group and control patients as a single group (separately in CAD and no-CAD patients). For example, in CAD patients, baseline measures in BAT patients were compared with measures after 6 months in the same patients using a paired *t*-test.
2-. Differences in the changes from baseline to 6 months in BAT compared with control patients in CAD or no-CAD patients. For example, in CAD patients, the differences in the change from baseline to 6 months between BAT and control patients were compared using two-sample *t*-tests.
3-. Differences in BAT response in CAD compared with no-CAD patients. The treatment differences in CAD patients were compared with the treatment differences in no-CAD patients using a contrast statement in a mixed effects model.

Effects on continuous variables that passed tests of normality were assessed with paired and two-sample *t*-tests. In the case of non-normal data, Wilcoxon signed-rank and rank-sum tests were used. Categorical variables were analyzed using a Fisher's exact test. Confidence intervals for proportions were calculated using the exact binomial method. For hospitalization data, comparisons between groups were based on the Wilcoxon Test. Hospitalization data were annualized to account for variable periods of post-randomization follow-up. The statistical analysis plan did not include adjustment for multiplicity of comparisons, and a nominal p value <0.05 was considered suggestive of efficacy. Analyses were performed in SAS v9.3 by an independent statistician.

3. Results

3.1. Baseline characteristics

CAD vs. no-CAD groups had similar baseline characteristics, except for age and proportion of Caucasians (Supplementary Table 1). The proportion of CRT patients was comparable. In the BAT arm, 17/52 patients (33%) were treated with CRT in the CAD group and 7/19 (37%) in the no-CAD group ($p = 0.78$). In the control arm, 12/49 patients (24%) in the CAD group and 9/20 (45%) patients in the no-CAD group were treated with CRT ($p = 0.15$).

3.2. Safety and tolerability

BAT was well tolerated and safe in both groups. The system- or procedure-related MANCE rate at 6 months was 3.8% (2/52 patients, both hematomas) in the CAD group vs. 0% in the no-CAD group ($p = 1.0$). The system- or procedure-related complication rate was 11.5% (7 events in 6/52 patients) in the CAD group and 21.1% (4/19 patients) in the no-CAD group ($p = 0.44$). Complications in the CAD group included hematoma, urinary tract infection, atrial fibrillation, hypotension, pneumothorax, and transection of cervical skin nerves. Complications in the no-CAD group included urinary retention, HF worsening, bradycardia, and paroxysmal atrial tachycardia.

Patients tolerated BAT well at titration levels just below electrical stimulation intensities producing side effects, such as pain, paresthesia, dysphagia, or cough. In CAD patients, pulse amplitude upon activation was 4.5 ± 2.5 mA and steadily increased to 7.0 ± 2.5 mA at 3 months, remaining stable thereafter. In no-CAD patients, pulse amplitude upon activation was 4.3 ± 2.6 mA and steadily increased to 6.3 ± 1.9 mA at 3 months, remaining stable thereafter. In CAD patients, pulse width and frequency were stable throughout follow-up, averaging 116.2 ± 81.6 μs and 62.8 ± 20.7 pulses per second, respectively. In no-CAD patients, pulse width and frequency were also stable throughout follow-up, averaging 88.0 ± 51.5 μs and 59.3 ± 21.2 pulses per second, respectively. Symptoms associated with chronic BAT settings were rare in both groups.

Table 1
Outcomes in CAD patients (6 months vs. baseline).

Measure	N	BAT	N	Control	Difference	p-Value
QOL score (points)	47	−16.8 ± 3.4*	36	1.7 ± 4.1	−18.6 ± 5.2	<0.001
6MHW distance (m)	41	72.7 ± 17.2*	29	−6.6 ± 17.8	79.3 ± 25.3	0.003
NYHA Class	47	−0.6 ± 0.1*	36	−0.2 ± 0.1*	−0.4 ± 0.1	0.003
NT-proBNP (pg/mL)[a]	34	−67.5 [−395, 320]	28	99.0 [−137, 593]	−212.5 ± 227.4	0.13
LVEF (%)	35	1.2 ± 1.4	25	−0.2 ± 1.6	1.5 ± 2.1	0.5
SBP (mm Hg)	47	2.7 ± 3.6	36	−1.4 ± 1.9	4.2 ± 4.4	0.35
DBP (mm Hg)	47	−1.0 ± 1.9	36	0.9 ± 2.0	−1.9 ± 2.8	0.5
Pulse pressure (mm Hg)	47	3.7 ± 2.7	36	−2.3 ± 2.2	6.1 ± 3.6	0.1
HR (bpm)	47	−1.7 ± 1.7	34	−0.2 ± 1.4	−1.5 ± 2.3	0.52
HF hospitalizations (n/year)	41	−0.59 ± 0.26*	36	0.10 ± 0.28	−0.68 ± 0.38	0.058
HF hospitalization (days/year)	41	−7.32 ± 3.63*	36	0.95 ± 2.23	−8.26 ± 4.41	0.048

QOL, quality of life; 6MHW, 6-minute hall walk; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; SBP, systolic BP; DBP, diastolic BP; HR, heart rate; HF, heart failure; Brackets represent interquartile range.
[a] Non-parametric analysis.
* Within group change p-value ≤ 0.05.

3.3. Efficacy in CAD patients (within group comparisons)

At 6 months in CAD patients, significant improvements were observed in NYHA Class, MLWHF QOL score and 6MHW distance in BAT patients compared with controls (Table 1, Fig. 1). NYHA Class was reduced from 3.0 ± 0.0 at baseline to 2.4 ± 0.5 at 6 months ($p < 0.001$) in BAT patients, and was numerically lowered in the control group from 3.0 ± 0.0 at baseline to 2.8 ± 0.5 at 6 months ($p = 0.05$). Changes in NYHA Class from baseline to 6 months in BAT vs. control patients were statistically different (−0.4 ± 0.1, $p = 0.003$). There were similar findings in MLWHF QOL score. In BAT patients, QOL score fell from 48.8 ± 21.3 at baseline to 33.4 ± 21.4 at 6 months ($p < 0.001$), reflecting an improvement in QOL. MLWHF QOL score remained stable in the control group with a score of 43.0 ± 21.1 at baseline and 42.2 ±22.2 at 6 months ($p = 0.67$). The changes in QOL from baseline to 6 months in BAT vs. control patients were statistically different (−18.6 ± 5.2, $p < 0.001$). 6MHW distance improved from 293.2 ±76.2 m at baseline to 373.1 ± 119.7 m at 6 months in BAT patients with CAD ($p < 0.001$), while it was stable in control patients (308.7 ±87.4 m at baseline and 304.3 ± 119.9 m at 6 months, $p = 0.71$). Changes in 6MHW from baseline to 6 months in BAT vs. control patients were statistically different (79.3 ± 25.3 m, $p = 0.003$).

BAT-treated patients with systolic BP above median (116 mm Hg) at baseline showed a significant decrease in systolic BP, while there was a significant increase in patients with systolic BP below median (Supplementary Table 2), resulting in a stable systolic BP in all BAT-treated patients with CAD (117 ± 20 mm Hg at baseline and 120 ± 20 mm Hg at 6 months, $p = 0.45$). Systolic BP in the control group with CAD remained stable, too (Table 1). There was no significant difference in systolic BP changes from baseline to 6 months in BAT-treated vs. control patients ($p = 0.35$).

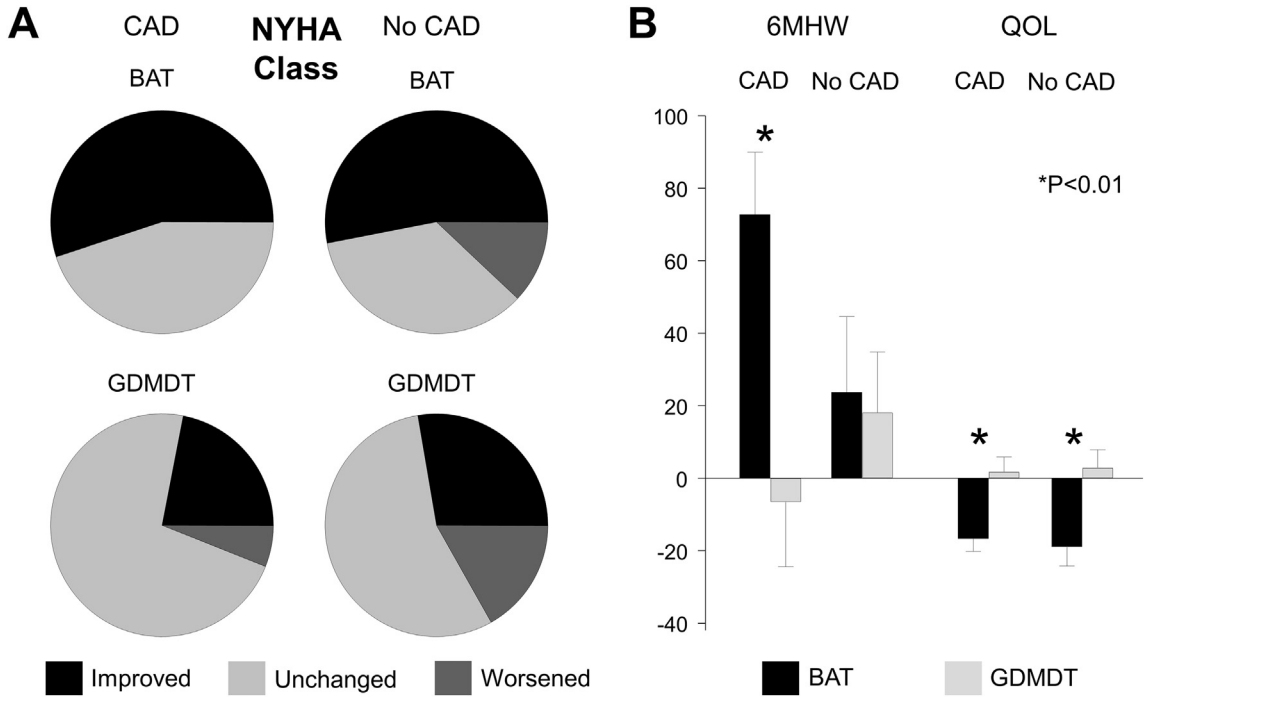

Fig. 1. Efficacy of BAT in patients with and without CAD. A: NYHA Class. From baseline to 6 months, more patients treated by BAT compared with patients on GDMDT showed an improvement in NYHA Class. The difference was significant for patients with CAD ($p = 0.003$), but did not reach significance in patients without CAD ($p = 0.35$), possibly due to the lower number of patients. An interaction analysis revealed no difference in treatment effect of BAT on NYHA Class between patients with and without CAD ($p = 0.34$). **B: 6MHW distance and MLWHF quality of life (QOL) score.** 6MHW distance and QOL score were improved in BAT treated patients from baseline to 6 months compared with controls. The difference in QOL score was significant for patients with and without CAD, and the difference in 6MHW distance reached statistical significance only in patients with CAD. However, the interaction analysis showed no difference in treatment effect of BAT between patients with and without CAD for 6MHW distance ($p = 0.10$) and QOL score ($p = 0.75$).

Table 2
Outcomes in no-CAD patients (6 months vs. baseline).

Measure	N	BAT	N	Control	Difference	p-Value
QOL score (points)	17	−18.9 ± 5.3*	18	2.9 ± 4.9	−21.8 ± 7.2	0.005
6MHW distance (m)	15	23.7 ± 21.9	14	18.2 ± 16.6	5.6 ± 27.7	0.84
NYHA Class	17	−0.4 ± 0.2*	18	−0.1 ± 0.2	−0.3 ± 0.2	0.21
NT-proBNP (pg/mL)[a]	9	−167 [−504, 132]	12	362.0 [46, 1679]	578.5 ± 504.3	0.05
LVEF (%)	14	5.2 ± 1.9*	15	0.1 ± 2.2	5.1 ± 2.9	0.09
SBP (mm Hg)	17	0.2 ± 2.6	18	−16.4 ± 6.5	16.6 ± 7.2	0.03
DBP (mm Hg)	17	−4.5 ± 2.3	18	−4.2 ± 2.5	−0.2 ± 3.4	0.94
Pulse pressure (mm Hg)	17	4.7 ± 2.0*	18	−12.2 ± 6.1	16.9 ± 6.6	0.01
HR (bpm)	17	−1.5 ± 3.0	18	3.9 ± 3.0	−5.4 ± 4.3	0.21
HF hospitalizations (n/year)	16	−0.25 ± 0.17	14	−0.43 ± 0.31	0.18 ± 0.34	0.86
HF hospitalization (days/year)	16	−3.63 ± 2.80	14	−2.14 ± 1.73	−1.48 ± 3.41	0.677

QOL, quality of life; 6MHW, 6-minute hall walk; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; SBP, systolic BP; DBP, diastolic BP; HR, heart rate; HF, heart failure; Brackets represent interquartile range.
[a] Non-parametric analysis.
* Within group change p-value ≤ 0.05.

BAT significantly decreased HF hospitalization rate and the average number of days hospitalized for HF (Table 1). The number and days of HF hospitalizations were stable in the control group. The change in the number and days of HF hospitalizations between 6 months before and 6 months after enrollment in BAT vs. control patients was marginally different (−0.68 ± 0.38, p = 0.058 and − 8.26 ± 4.41, p = 0.048).

In CAD patients, no significant changes in any other efficacy parameters were found in BAT or control patients comparing baseline to 6 months.

3.4. Efficacy in no-CAD patients (within group comparisons)

At 6 months in patients without CAD, significant changes were observed in MLWHF QOL score, systolic BP and pulse pressure in BAT patients compared with control patients (Table 2, Fig. 1). MLWHF QOL score was lowered from 58.2 ± 19.9 at baseline to 41.4 ± 26.5 at 6 months (p = 0.002) in patients on BAT and remained stable in control patients (41.6 ± 23.3 at baseline and 43.1 ± 26.0 at 6 months, p = 0.56). The changes in QOL score from baseline to 6 months in BAT vs. control patients were statistically different (−21.8 ± 7.2, p = 0.005).

Systolic BP was stable in BAT treated patients (110.5 ± 13.4 mm Hg at baseline and 111.6 ± 12.3 mm Hg at 6 months, p = 0.93), with a non-significant decrease in patients with systolic BP above median (116 mm Hg) at baseline and a non-significant increase in those with systolic BP below median (Supplementary Table 2). Systolic BP dropped significantly in control patients without CAD (120.5 ± 19.8 mm Hg at baseline and 105.4 ± 18.2 mm Hg at 6 months, p = 0.02). The changes in systolic BP from baseline to 6 months in BAT vs. control patients were statistically different (16.6 ± 7.2, p = 0.03).

NYHA Class was lowered significantly from 2.9 ± 0.2 at baseline to 2.5 ± 0.6 at 6 months (p = 0.03) in BAT patients, while it was stable in the control group (3.0 ± 0.0 at baseline and 2.9 ± 0.7 at 6 months, p = 0.50). However, changes in NYHA Class from baseline to 6 months in BAT vs. control patients did not reach statistical significance (−0.3 ± 0.2, p = 0.21). At 6 months, 6MHW distance was numerically higher in BAT patients compared with baseline (308.1 ± 85.4 m at baseline and 347.3 ± 136.4 m at 6 months, p = 0.30), with the same trend observed in the control group (307.3 ± 80.2 m at baseline and 329.8 ± 128.1 m at 6 months, p = 0.29). The changes in 6MHW distance from baseline to 6 months in BAT vs. control patients were not statistically different (5.6 ± 27.7, p = 0.84). HF hospitalization rate and the average number of days hospitalized for HF were not affected significantly by BAT (Table 2).

3.5. Differences in response to BAT in CAD vs. no-CAD patients (between group comparisons)

An interaction analysis was performed to assess whether significant differences in the treatment effect of BAT were present in patients with and without CAD. The results of the interaction analysis showed there were no significant differences in the response to BAT in patients with CAD vs. those without CAD in all analyzed parameters (Table 3).

Responder rates to BAT were also similar. 71% of BAT patients with CAD and 60% of BAT patients without CAD had an increase of >20 m in 6MHW distance (p = 0.52); 55% of BAT patients with CAD and 77% of BAT patients without CAD had a decrease of >5 points in the MLWHF QOL score (p = 0.16).

4. Discussion

Previous studies have shown that HFrEF patients with ischemic cardiomyopathy display different outcomes and different responses to treatments than those with non-ischemic cardiomyopathy [13]. Device-based therapies such as CRT have shown etiology-specific differences in therapeutic response with greater reverse LV remodeling occurring in non-ischemic compared with ischemic patients [11]. It is therefore important to understand etiology-dependent responses to HF therapies; this applies especially to BAT, since baroreflex sensitivity has been described to be lower in patients with CAD than in matched patients without coronary lesions [14].

Our subgroup analysis did not reveal significant differences in treatment effects or safety of BAT in HFrEF patients with and without CAD. Thus, the positive effects of BAT observed in the entire population of the randomized trial, i.e. significant improvements in NYHA Class, 6MHW distance, QOL and NT-proBNP, as well as a reasonable safety profile appear to be applicable to patients with and without CAD. This indicates that different mechanisms underlying systolic dysfunction, namely ischemic vs. non-ischemic dilated cardiomyopathy, do not interact with BAT efficacy or safety.

Table 3
Difference in outcome treatment effect in patients with and without CAD.

Measure	Estimate	Standard error	p-Value
QOL score (points)	2.0424	6.5071	0.754
6MHW distance (m)	48.9740	29.2315	0.097
NYHA Class	−0.1627	0.1698	0.340
NT-proBNP (pg/mL)	−83.2899	1820.69	0.964
LVEF (%)	−3.9843	2.5386	0.120
SBP (mm Hg)	2.4881	5.7743	0.667
DBP (mm Hg)	3.4706	3.3580	0.304
Pulse pressure (mm Hg)	−0.9825	4.9034	0.842
HR (bpm)	−0.2528	3.1147	0.935
HF hospitalizations (n/year)	−0.3690	0.4428	0.407
HF hospitalization (days/year)	−3.9464	5.0038	0.432

QOL, quality of life; 6MHW, 6-minute hall walk; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; SBP, systolic BP; DBP, diastolic BP; HR, heart rate; HF, heart failure.

In CAD patients, NYHA Class, MLWHF QOL score and 6MHW distance were significantly improved in BAT patients compared with control patients, which is in line with the overall study results [6]. In patients without CAD, MLWHF QOL score was significantly improved in BAT patients compared with controls. NYHA Class and 6MHW distance were numerically improved, but did not reach statistical significance, probably due to the low patient number in the no-CAD group. We cannot exclude minor differences in the response to BAT between patients with and without CAD. However, interaction analyses are the gold standard to evaluate differences in treatment effects in subgroups of patients, and no significant differences in BAT treatment effects occurred between CAD and no-CAD patients based on interaction analyses. Moreover, there were no significant differences in responder rates, which were in the range reported before for BAT patients with resistant hypertension [15]. Thus, lower baroreflex sensitivity in CAD patients [14] appears not to translate into clinically relevant differences in BAT efficacy. This finding is supported by a recent study in patients with resistant hypertension, confirming an equal reduction of BP by BAT in patients with and without CAD [16]. So it seems that BAT exerts a beneficial effect, no matter whether baroreflex sensitivity is diminished or not, and that activity of carotid sinus baroreceptors can be increased by electrical stimulation in patients with a preserved or reduced baroreflex sensitivity.

The proportion of patients treated with CRT, i.e. the only variable with a known influence on BAT response [7], was similar in CAD and no-CAD patients, thus an inhomogenous distribution of CRT does not account for potential minor differences between both groups.

It was not possible to identify influences of different programming parameters on outcomes in the HFrEF population, since similar stimulation patterns were employed in each patient. Analyses in patients with resistant hypertension suggest that BAT works in a wide range of stimulation settings and should be uptitrated to just below the threshold of extraneous sensations to achieve maximal benefit (unpublished observations).

In light of the BP reducing effect of BAT in patients with resistant hypertension, one might have expected lowering of BP in the HFrEF population. We observed a BP reduction under BAT in patients with baseline BP above median, while it was increased in those with baseline BP below median. One potential explanation may be an improved stroke volume under BAT, which may have stabilized BP despite the effect of BAT on sympathetic tone and vascular resistance. The difference in BP changes from baseline to 6 months in BAT vs. control patients was mainly driven by a BP reduction in the control group. It is unclear, why BP declined in the control group and why this decline was more pronounced in control patients without CAD. Such a drop of BP in the control group has been frequently observed in hypertension trials and has been attributed to improved adherence to medication (Hawthorne effect) and/or regression to the mean. Hypothetically, the Hawthorne effect may have been higher in the control group than in the BAT group, since BAT patients may have considered medication to be less important after interventional HF treatment. However, this cannot explain the larger BP drop in control patients without CAD as compared with those with CAD, which may well be a play of chance.

With an overall MANCE rate of 2.8% and a system- or procedure-related complication rate of 14.1%, the safety profile of BAT in HFrEF is comparable with the 12.4% complication rate of a pacemaker [17] and to the 10% complication rate observed with BAT in hypertensive patients [18]. Interaction testing has shown that BAT is compatible with pacemakers and ICDs, which are indicated in most HFrEF patients [19–21]. In this study, 88.7% of patients were implanted with both a BAT system and an ICD, and no device–device interaction occurred. No differences in safety profile were seen between CAD and no-CAD patients.

4.1. Limitations

The small number of patients limits interpretation of results, which applies to the overall trial and even more to this subgroup analysis. However, power calculations revealed that the statistical power to detect a 0.5 point difference in NYHA Class between CAD and no-CAD patients, which we considered clinically relevant, was 84% with the current number of patients. This is sufficient to support the conclusion that BAT effect on NYHA Class is similar in CAD and no-CAD patients. Regarding MLWHF QOL score, power was 80% to detect a difference of 18 points, which corresponds to the difference between BAT and control patients, while it was only 12% for detecting a 5 point difference, which may already be of clinical relevance. Thus, power was sufficient to exclude major differences in the effect of BAT on MLWHF QOL score between the studied subgroups, but minor differences could not be reliably excluded with the current population. Despite the small number of patients, BAT treatment effect was consistently observed across several efficacy parameters in CAD and no-CAD patients, further supporting BAT efficacy in HFrEF independent of the underlying cause.

This subgroup analysis was performed post hoc and not prespecified. Therefore, assessment of prior CAD was not based on standardized imaging or functional tests included in the study protocol, but on medical history assessed by local investigators. Baseline evaluations included documentation of known CAD, prior MI or prior coronary artery bypass graft in the case report forms. We cannot exclude that some patients classified as “no-CAD” may have had CAD unknown to the investigator. However, since a coronary angiography is part of the standard work-up for HFrEF and all patients were treated in experienced HF centers, we consider this misclassification to be unlikely.

The presence of CAD, prior MI or coronary revascularization has been traditionally used to define ischemic cardiomyopathy, and this definition has been shown to have prognostic implications [10]. However, some patients in the CAD subgroup may have had minor CAD not attenuating contractile function, while there was another main etiology of systolic dysfunction. Since coronary anatomy was not documented and no tests to detect ischemia were performed, determination of a potential causal link between the presence of CAD and HFrEF was not possible in this study. In a previous study, only 11% of patients with CAD were classified to have non-ischemic cardiomyopathy due to HF out of proportion to their degree of CAD [10]. Therefore, equal BAT efficacy and safety in patients with and without known CAD does not necessarily mean that BAT is equally effective and safe in patients with ischemic and non-ischemic cardiomyopathy, but we consider it to be a strong indicator.

In conclusion, BAT is safe and improves NYHA Class, QOL and exercise capacity in NYHA Class III HFrEF patients. This subgroup analysis found no major differences in safety or treatment effect in patients with and without CAD, indicating that BAT is safe and effective in patients with ischemic and non-ischemic cardiomyopathy. Larger studies are needed to address potential minor differences in the therapeutic response to BAT.

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Relationships with industry

Drs. Abraham, Little, Weaver, and Zile have received consulting fees and speaking honoraria from CVRx and are/were members of the CVRx Heart Failure Executive Steering Committee. Drs. Butter, Klug, Senni, and Swarup have received research fees from CVRx. Drs. Ducharme and Wachter have received research fees and consulting fees from CVRx. Drs. Halbach, Reuter and Müller-Ehmsen have received research fees and speaking honoraria from CVRx. Ms. Schafer is a statistical consultant for CVRx. Dr. Wilks is an employee of CVRx.

Conflict of interest

The relationship with industry is actually also the conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.04.075.

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