Original Article

Long-term chronic baroreflex activation: persistent efficacy in patients with heart failure and reduced ejection fraction

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Aims: Baroreflex activation therapy (BAT) has recently been shown to reduce muscle sympathetic nerve activity and hospitalization rate while improving clinical variables through 6 months of therapy in patients with heart failure and reduced ejection fraction (HFrEF). The objective of the present study is to extend the information on this patient cohort over a long-term follow-up.

Methods and results: Eleven patients were enrolled in the study and presented with optimized, stable medical therapy, New York Heart Association Class III HFrEF with left ventricular ejection fraction 40% or less, impaired functional capacity and no active cardiac resynchronization therapy. For the present report, muscle sympathetic nerve activity, baroreflex sensitivity data and hospitalization rate together with standard clinical data were collected at 12 and 21.5 ± 4.2 months following BAT activation. Two patients died during long-term follow-up. The remaining nine patients maintained the improvements observed at 6 months, including reduced sympathetic activity and rates of hospitalization.

Conclusion: BAT provides long-term chronic reductions in sympathetic activity and utilization of hospital resources in patients with HFrEF. General clinical presentation, quality of life and functional capacity are likewise improved and maintained. The temporal association of BAT with sympathetic drive diminution and improvement in objective clinical measures suggests a cause-and-effect relationship that will be verified in future randomized controlled trials of outcome.

Keywords: autonomic nervous system, baroreflex, heart failure

Abbreviations: BAT, baroreflex activation therapy; BNP, B-type natriuretic peptide; BP, blood pressure; BRS, baroreflex sensitivity; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MSNA, muscle sympathetic nerve activity; NYHA, New York Heart Association

BACKGROUND

Although medical and device therapies continue to improve the clinical course of patients with heart failure, morbidity, mortality and healthcare costs remain unacceptably high [1]. Therefore, additional therapy options must continue to be developed. Antagonism of sustained sympathetic hyperactivity remains, hitherto, the only therapeutic approach to effectively alter the progression of heart failure to its end stage. The latest evidence indicates that adrenoreceptor blockade fails in this goal over the long term and that impaired vagal control over sympathetic activity, as measured by baroreflex sensitivity (BRS), portends a more unfavorable outcome even when β-blocker therapy is in place [2]. Through reductions in sympathetic activity and peripheral resistances [3] as well as increases in venous capacitance [4], baroreflex activation therapy (BAT) has been shown to improve blood pressure (BP) control in patients with resistant hypertension [5–7], including those with heart failure [8]. Results from chronic use of BAT in 11 patients with heart failure and reduced ejection fraction (HFrEF) have been recently reported [9]. The main finding was that muscle sympathetic nerve activity (MSNA) was reduced by 30% over 6 months. In association with this chronic sympathetic inhibition, hospitalization rates were reduced and clinical presentation improved. The major pathophysiologic and clinical implications of these findings motivate an assessment of long-term effects.

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AIMS

The purpose of this report is to describe the effects of BAT in the 11-patient HFrEF cohort over an extended duration of follow-up, comprising quantification of sympathetic nerve activity, hospitalization rate and clinical variables.

METHODS

Therapeutic intervention

Patients received chronic BAT administered by the Barostim *neo* System (CVRx, Inc., Minneapolis, Minnesota, USA). The system and implant procedure have been previously described [7]. Briefly, the system comprises an implanted pulse generator similar to a conventional implanted defibrillator coupled to a lead with an electrode assembly affixed to the carotid sinus and a lead body tunneled ipsilaterally to the pectoral pocket. Carotid sinus access is obtained with a small (typically 2.5–5 cm) incision in the neck above the carotid bifurcation as identified by duplex ultrasound. The system is preferentially implanted on the right side to avoid conflict with any preexisting or future cardiac rhythm management devices. Intensity of BAT is progressively uptitrated over the first 3months of therapy, primarily by increasing electrical pulse amplitude.

Study design

The investigation was a single-center, open-label evaluation of BAT in patients with HFrEF. The prospectively defined study duration was 6 months. The study protocol conformed to the Declaration of Helsinki and was approved by the local Ethics Committee as well as the Italian Ministry of Health. Patients provided their informed consent to participate in the trial.

Patient population

Patients qualified for the initial study protocol if they presented with fully titrated and stable optimal medical therapy, New York Heart Association (NYHA) Class II heart failure, left ventricular ejection fraction (LVEF) reduced to 40% or lower, limited functional capacity (6-minute walk distance of 150–450 m), controlled heart rate (HR) of 60–100 bpm, chronic kidney disease Stage 3 or better [estimated glomerular filtration rate (eGFR) $\geq$ 30%] and freedom from dialysis with the expectation of remaining so for at least 1 year. Patients also needed to be appropriate surgical candidates, including carotid bifurcations below the level of the mandible and freedom from ulcerative carotid arterial plaques or atherosclerosis producing a reduction in diameter of the internal or distal common carotid artery of at least 50%.

Exclusion criteria included life expectancy less than 1 year, heart failure secondary to reversible cause or right ventricular failure, active resynchronization therapy, NYHA Class IV heart failure within 30 days, episodes of angina, myocardial infarction, sudden cardiac arrest, appropriate defibrillator therapy, syncope or cerebrovascular accident within 3 months, implant of pacemaker or implantable cardioverter defibrillator within 3 months, baroreflex failure, autonomic neuropathy, severe chronic obstructive pulmonary disorder, prior solid organ or hematologic transplant, prior surgery in the carotid sinus region limiting placement of system components, noncardiovascular conditions limiting assessment of functional capacity with the 6-minute walk test and conditions that would adversely affect participation in the investigation.

Measurements and endpoints

Study visits during which main results were collected scheduled for 1, 3 and 6 months following therapy activation. A long-term follow-up visit was added to the data collection schedule following completion of the prospective data acquisition. The primary study endpoint measure, MSNA, was collected via peroneal microneurography [10]. Six-minute hall walk distance, quality of life from the Minnesota Living With Heart Failure Questionnaire score, three-dimensional LVEF, B-type natriuretic peptide and eGFR were collected at baseline, month 3, month 6 and during long-term follow-up. General vital signs, including NYHA Class, were collected at every time point. BRS was calculated using a variation of the method of Kienbaum and Peters [10] as previously described [9]. All measurements were made while therapy was active. In addition to the predefined endpoints, heart failure hospitalization data were collected prospectively throughout the study and compared against the 12 months prior to device implant.

Data analysis

Effects of BAT on efficacy endpoints were assessed serially with repeated-measures analysis of variance. Comparisons with respect to baseline were made using the paired *t* test. Statistical significance was identified by *P* values less than 0.05. Absolute measures were reported as mean $\pm$ standard deviation whereas changes relative to baseline were reported as mean $\pm$ standard error.

RESULTS

Two patients died during long-term follow-up. One succumbed to septic shock that developed over pneumonia following a general decline in health 11.2 months postactivation, whereas the second one, who was an insulin-dependent diabetic patient, died 16.2 months postactivation of electromechanical dissociation in the context of a new (first after BAT activation) episode of acute heart failure. Both patients suffered a postischemic dilated cardiomyopathy.

The nine surviving patients suffered HFrEF of ischemic origin in six out of nine cases. In these patients, BAT maintained its beneficial effects over a long-term follow-up of 21.5 $\pm$ 4.2 (mean $\pm$ standard deviation, range: 15.7–28.8) months. The substantial reduction of MSNA, computed both as bursts/100 heartbeats and bursts/min, observed at 6 months [9] was maintained over time in association with a restored BRS (Table 1, Fig. 1a). These autonomic effects were coupled to persistent improvements in quality of life and 6-minute hall walk (Table 1). All of the eight patients who achieved NYHA Class I at 12 months maintained it at long-term follow-up, whereas one patient improved from Class III at 12 months to Class II at long-term follow-up.

TABLE 1. Muscle sympathetic nerve activity, clinical data and medications before and during chronic baroreflex activation ($N = 9$)

Vital signs and medications				
Baseline: mean ± standard deviation				
Δ: mean ± standard error	**Baseline**	**Δ6 months**	**ΔLong-term (21.5 ± 4.2 months)**	**Analysis of variance *P* value**
MSNA (bursts/min)	47.4 ± 6.2	−13.6 ± 1.6	−15.0 ± 2.6	<0.001
MSNA (bursts/100 heartbeats)	70.4 ± 10.5	−21.6 ± 2.3	−24.7 ± 4.3	<0.001
Baroreflex sensitivity (arbitrary units)	0.11 ± 0.13	+1.31 ± 0.17	+1.26 ± 0.16	<0.001
Six-minute walk distance (m)	306.4 ± 52.4	+69.7 ± 24.4	+58.4 ± 33.4[a]	0.01
Minnesota living with heart failure score	30.9 ± 27.8	−11.5 ± 4.6	−13.2 ± 5.4	0.006
SBP (mmHg)	119.2 ± 15.5	−0.3 ± 4.4	−9.8 ± 5.6	0.15
DBP (mmHg)	71.7 ± 9.7	−3.9 ± 2.2	−6.1 ± 3.6	0.11
Heart rate (bpm)	72.8 ± 9.0	−0.6 ± 2.2	−5.1 ± 2.6	0.30
3D left ventricular end-diastolic volume (ml)	163.7 ± 46.1	−14.1 ± 16.3	−18.8 ± 14.6	0.08
3D left ventricular ejection fraction (%)	32.6 ± 6.2	+3.3 ± 1.7	+0.8 ± 1.7	0.006
B-type natriuretic peptide (pg/ml)	230.8 ± 203.6	+9.2 ± 31.9	−0.2 ± 52.2	0.78
Estimated GFR (ml/min/1.73 m^2)	71.0 ± 27.2	+6.0 ± 5.8	−4.8 ± 6.1	0.28
BMI (kg/m^2)	27.3 ± 4.2	−0.4 ± 0.4	+0.1 ± 0.3	0.63
Number of medications	4.3 ± 1.2	−0.2 ± 0.1	−0.1 ± 0.3	0.71

GFR, glomerular filtration rate. Baseline shown as mean ± standard deviation; Δ (versus baseline) as mean ± standard error. All significant differences are between mean values at baseline versus 6 and 21 months BAT therapy.'—' denotes data not collected.
[a]$N = 8$.

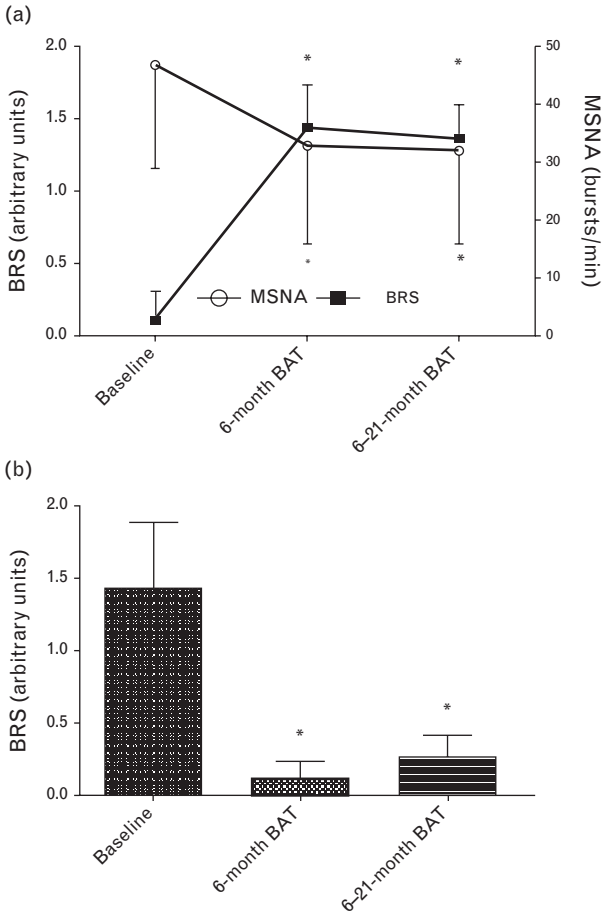

FIGURE 1 (a) Time course of muscle sympathetic nerve activity and baroreflex sensitivity in nine patients treated with baroreflex activation therapy who completed follow-up (see also Table 1). Note MSNA decline mirrored increasing BRS. (b) These changes were coupled with a marked decline in hospitalization rate. *$P < 0.01$ versus baseline. BAT, baroreflex activation therapy; BRS, baroreflex sensitivity; MSNA, muscle sympathetic nerve activity.

The following heart failure hospitalizations occurred after completion of the 6-month primary endpoint visit: one patient with ischemic heart disease, type 2 diabetes and obesity accumulated 16 days during four different acute decompensation episodes mostly due to noncompliance with medical therapy and diet. Another patient was hospitalized for 7 days each on two occasions, once for acute heart failure and a second time to receive resynchronization therapy after developing Mobitz II atrioventricular block with prolonged QRS interval. Finally, a third patient experienced a 6-day heart failure hospitalization due to limb ischemia, which resolved with percutaneous angioplasty.

Echocardiography revealed that LVEF remained stable whereas end-diastolic volume trended toward further improvement. DBP also remained stable, whereas SBP, HR trended toward a reduction. Patient weight, B-type natriuretic peptide, eGFR and background medical therapy were stable (Table 1).

Hospitalization rate decreased substantially with BAT. In the year prior to implant, patients accumulated 155 days, whereas with BAT, total days through 6 months and long-term follow-up were 7 and 45, respectively. The hospitalization rate measured as days/month decreased from 1.44 ± 1.3 preimplant to 0.13 ± 0.33 in the 6 months postactivation and 0.27 ± 0.44 between 6 and 21 months ($P < 0.01$, Fig. 1b). In general, hospitalizations with BAT were uncommon with the highest rate observed between approximately 6 and 18 months postactivation.

DISCUSSION

The present study documents for the first time a long-term inhibition of the sympathetic hyperactivity typically underlying heart failure, particularly in the lethal HFrEF phenotype. The clinical impact of the inhibitory effects of chronic BAT on cardiac sympathetic outflow is not limited to the heart failure arena but extends to the hypertension arena where efficacy of BAT was documented first. It is well

known that sympathetic hyperactivity, possibly due to a loss of baroreflex restraint on it, is among the primary mechanism of BP increase. Relevant to this, though, is the fact that a HR higher than 70 bpm, reflecting a high sympathetic activity, is a specific risk factor in hypertensive patients [5]. Our study population was in optimal therapy including optimally titrated β-blocker therapy. This reflected in an average HR of 73 bpm and in the fact that the changes with BAT were relatively small, although biologically significant (5 bpm).

The novel observation presented here was made possible by a unique series of repeated measurements of MSNA, documenting, for the first time, a persistent inhibition of sympathetic hyperactivity by a direct neural intervention. In association with its effects on an important aspect of HFrEF pathophysiology, the clinical benefits of BAT in HFrEF, when administered along with optimized medical therapy, appear to endure for at least 21 months. To the knowledge of the authors, no other heart failure therapy has been shown, by direct measurement, to chronically reduce sympathetic activity over the time frame reported here. The staying power of BAT in terms of consistent clinical benefit is also noteworthy. Such a benefit over long-term therapy mirrors what has been shown in pooled data from multicenter trials in hypertensive patients. Specifically, of the 322 patients implanted, 76% ($n = 245$) qualified as clinically significant responders. Among long-term responders receiving BAT, the mean BP drop was 35/16 mm Hg. This BP reduction was maintained over long-term follow-up of 22–53 months [6].

The present study, together with the novel pathophysiological information on MSNA long-standing action, brings some intriguing data on clinical outcome of BAT-treated patients: namely, a major sparing in hospital resources utilization.

It is worth noting that the two patients who died during extended follow-up still benefited from BAT: in-hospital days were 24 and 11 in the year prior to BAT activation and 0 and 6 afterward, respectively. This clinical benefit was associated with ameliorated MSNA measured at 6 months [9]. The small cohort of the present study, though, does not allow any conclusion to be drawn about effects of BAT on mortality in the general heart failure population.

Increased BRS, coupled with reduced MSNA, indicates persistent restoration of autonomic balance that was contemporaneous with reduced hospital resource utilization, suggesting a cause–effect relationship, for, prior to enrollment in the study, all patients suffered rapid progression of HFrEF [11–13]. Normalized sympathetic and parasympathetic activity implies inhibition of catecholamine toxicity at the source rather than blockade at the end-organ level, thereby inhibiting release of other neurotransmitters including substance P and neuropeptide Y that may contribute to disease progression [14,15]. Moreover, the inhibitory effects of vagal activation on proinflammatory interleukins are well documented [16]. In this context, a slightly reduced LVEF at long-term follow-up relative to month 6 must not be taken as an adverse finding. Indeed, at this stage of the disease, organ damage is irreversible but, evidently, autonomic balance restoration allows a dramatic and sustained attenuation of central and peripheral disease progression, with a positive recovery of overall performance.

BAT is advantageous in HFrEF; by directly counteracting sympatho-excitation, it avoids limitations encountered with medical therapies including adverse drug interaction, patient compliance, therapy intolerance or responsiveness limited by variation in genotype. Considering the relative simplicity of the implant procedure and the excellent safety profile, the value of BAT is clear in bridging the gap between understanding and treating the pathophysiology of heart failure.

Conclusions from the present study should be drawn with caution given the cohort size, the open-label trial design and the absence of a control group. However, the objective evidence for benefit of BAT supports the possibility that its widespread adoption may significantly impact the social and economic burden of heart failure and hypertension.

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Conflicts of interest

E.G. is a paid consultant of CVRx, Inc.; E.G.L. is an employee of CVRx, Inc.; and G.G. and G.M. received speaking honoraria from CVRx.

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Reviewers' Summary Evaluations

Reviewer 1

In this prospective well conducted single-center study Gronda *et al.* assessed the effect of chronic baroreflex activation therapy (BAT) on sympathetic nerve traffic, baroreflex function and cardiac parameters in patients with NYHA Class III heart failure (HF) on optimal medical therapy who were ineligible for cardiac resychronization. Although limited by the small number of patients included in the study, the findings are novel and provide evidence that BAT could be an additional therapeutic modality to be further tested in the setting of HF in order to improve outcome.

Reviewer 2

This study showed the long-term effects of baroreflex activation therapy (BAT) on muscle sympathetic nerve activity (MSNA), baroreflex function and clinical features in 11 chronic heart failure (HF) patients. In view of the high global hospitalization rate and cardiovascular mortality in this patient cohort, the present results are novel with considerable pathophysiological relevance showing both feasibility of BAT and its implantation lowering effect on MSNA and hospital admission rate in addition to improved clinical parameters. The small sample size is the major limitation of the present study.