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Chronic baroreflex activation effects on sympathetic nerve traffic, baroreflex function, and cardiac haemodynamics in heart failure: a proof-of-concept study

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Aims Heart failure (HF) pathophysiology is believed to be mediated by autonomic dysfunction, including chronic sympathoexcitation and diminished baroreflex sensitivity, which correlate with mortality risk. Baroreflex activation therapy (BAT) is a device-based treatment providing chronic baroreflex activation through electrical stimulation of the carotid sinus. BAT chronically reduces sympathetic activity in resistant hypertension. The purpose of this investigation is to determine BAT effects in clinical HF.

Methods and results In a single-centre, open-label evaluation, patients with NYHA class III HF, EF <40%, optimized medical therapy, and ineligible for cardiac resynchronization received BAT for 6 months. Efficacy was assessed with serial measurement of muscle sympathetic nerve activity (MSNA) and clinical measures of quality of life and functional capacity. Eleven patients participated in the trial. MSNA was reduced over 6 months from 45.1 ± 7.7 to 31.3 ± 8.3 bursts/min and from 67.6 ± 12.7 to 45.1 ± 11.6 bursts/100 heartbeats, decreases of 31% and 33%, respectively ($P < 0.01$). Concomitant improvements occurred in baroreflex sensitivity, EF, NYHA class, quality of life and 6 min hall walk (6MHW) distance ($P \leq 0.05$ each). On an observational basis, hospitalization and emergency department visits for worsening HF were markedly reduced. One complication, perioperative anaemia requiring transfusion, occurred during the study.

Conclusion BAT was safe and provided chronic improvement in MSNA and clinical variables. Based on present understanding of HF pathophysiology, these results suggest that BAT may improve outcome in HF by modulating autonomic balance. Prospective, randomized trials to test the hypothesis are warranted.

Keywords Heart failure • Sympathetic nervous system • Non-pharmacological therapy • Baroreflex

Introduction

Congestive heart failure (HF) is characterized by changes in autonomic regulation, including (i) impairment of cardiac vagal drive;[1] (ii) hyperactivation of sympathetic drive to the heart and the peripheral circulation;[2–5] and (iii) dysfunction of baroreceptor modulation of heart rate and arterial vasomotor tone.[4,6] Sympathetic activation in HF is independent of aetiology[7] and is aggravated with concomitant obesity and/or hypertension.[8,9] Evidence indicates that these alterations emerge early in HF and escalate as severity progresses. Although initially playing a compensatory role, the changes become detrimental with time,

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favouring disease progression and independently predicting and contributing to cardiovascular complications and death of treated HF patients.[10–12]

Evidence of the adverse prognostic role of sympathetic activation in HF provides a strong rationale for treatment-related reduction of adrenergic influences. This can be accomplished with beta-blockers, ACE inhibitors, and angiotensin receptor antagonists.[13,14] Chronic electrical activation of the carotid baroreflex, known as baroreflex activation therapy (BAT), has the potential to benefit HF patients. This therapy reduces elevated blood pressure (BP) in resistant hypertension,[15,16] via profound inhibition of adrenergic hyperactivity.[17] Indeed, although no information on sympathetic effects is available, preliminary data suggest that beneficial effects of this intervention may extend to HF. (i) In a microembolization canine model of HF,[18] it reduced plasma norepinephrine, increased EF, and decreased susceptibility to induction of life-threatening ventricular tachyarrhythmias. (ii) In a rapid pacing model of HF, the device reduced LV filling pressure, decreased plasma norepinephrine and angiotensin II, and doubled survival duration.[19] (iii) A case report in HF with preserved EF described favourable cardiac remodelling, increased functional capacity, and reduced burden of medical therapy.[20]

The primary aim of this investigation was to determine whether chronic baroreflex stimulation, using an implanted stimulatory device, can persistently reduce adrenergic overdrive in HF patients despite multifold sympathoexcitatory influences, e.g. from chemoreceptors, muscle receptors, and central structures[21] that are known to operate in HF. Secondary aims were to assess effects on baroreflex sensitivity, cardiac function, central haemodynamics, and clinical and safety profiles of the patients. Adrenergic activity was assessed by recording muscle sympathetic nerve traffic (MSNA) before and several months after device implantation and activation. MSNA was selected to measure sympathetic activity because, although addressing sympathetic influences regionally, it is highly reproducible.[22] Furthermore, measuring sympathetic nerve traffic avoids the inconvenience of plasma norepinephrine measurements in HF, i.e. major and variable dependence on tissue clearance rather than increased production.[23]

Methods

Therapeutic device

The stimulation system (Barostim™ *neo*™, CVRx Inc., Minneapolis, MN, USA) consists of a lead coupled to a pulse generator similar in shape and size to an implanted defibrillator. The system has a safety profile similar to a pacemaker.[16] As previously described,[16] the device is implanted subcutaneously in the right or left pectoral region with the lead tunnelled from a small (2.5–5 cm) cutaneous incision to affix over the ipsilateral carotid bifurcation. In this study, system implant time averaged 93 ± 25 min, of which 48 ± 20 min comprised identification of optimal electrode location. Ten of 11 patients were implanted on the right side to avoid possible location conflict with future cardiac rhythm management devices.

Study design

The trial was an open-label, single-arm evaluation conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committees of the participating Institutions as well as the Italian Ministry of Health. All patients provided written informed consent.

Patient population

Major eligibility criteria specified patients with NYHA class III HF, LVEF ≤40%, 6 min hall walk (6MHW) distance of 140–450 m, heart rate of 60–100 b.p.m., and estimated glomerular filtration rate [eGFR, Modification of Diet in Renal Disease (MDRD) criterion] ≥30 mL/min/1.73 m^2. Patients were required to not have an indication for CRT to ensure that clinical status was unaffected by any latent effects. They were also required to (i) be free from dialysis and expected to remain so for at least 12 months; and (ii) present with a recent history of stable HF, i.e. no episodes of NYHA class IV HF with acute pulmonary oedema for at least 30 days before implant and no incident myocardial infarction, unstable angina, syncope, cerebral vascular accidents, sudden cardiac arrest, or appropriate defibrillation therapy for at least 3 months before implant. Atrial fibrillation was not an exclusion criterion unless the resting ventricular rate was >100 b.p.m. This was to avoid the potential effect of AF on MSNA. It is worth noting that persistent AF was a pre-existing condition in the three cases enrolled in the study, and no novel occurrence was observed during follow-up after BAT implant.

Patients with pre-existing pacemakers or implanted defibrillators were allowed to participate if implant occurred >90 days previously. Medical therapy was required to be optimized and stable for at least 4 weeks before obtaining the baseline 6MHW. Unless contraindicated or not tolerated, the medical regimen had to include a beta-blocker and an ACE inhibitor or an ARB. Stable medication was defined as no more than a 50% increase or decrease in dosage of any HF medication included in the treatment regimen.

Patients were excluded if plaque or atherosclerosis reduced the linear diameter of distal or common carotid arteries by >50% or if the carotid bifurcations were not readily accessible by surgery. Additional exclusion criteria included HF due to a secondary/reversible/treatable cause, known or suspected baroreflex failure, autonomic neuropathy, severe COPD, body mass index >40 kg/m^2, uncontrolled and symptomatic bradyarrhythmias, and resting heart rate not between 60 and 100 b.p.m.

Measurements

Multiunit post-ganglionic MSNA was recorded from the left or right peroneal nerve posterior to the fibular head as previously described.[4] Heart rate (cardiotachometer), ECG and beat-to-beat finger BP were measured simultaneously with sympathetic nerve traffic. Measurements were taken over 30 min with the patient in the supine position. MSNA was measured as the incidence of bursts over time (bursts/min) and the incidence of bursts corrected for heart rate values (bursts/100 heart beats). Baroreflex control of MSNA was determined by a method similar to that of Kienbaum *et al.*[24] Specifically, diastolic BP values obtained for each cardiac cycle during the 30 min data collection were grouped into 3 mmHg intervals (bins). For each bin, the average incidence of bursts (i.e. number of bursts/100 cardiac cycles) was calculated and related to the corresponding bin mean BP value by linear regression analysis (SigmaStat 8.0). The slope of the regression was taken to express the likelihood of a burst to be

related to the diastolic BP and, if so, to represent the slope of the relationship.

Clinical measurements comprised 6MHW distance, NYHA class, quality of life as measured by the Minnesota Living with Heart Failure questionnaire, BNP, and three-dimensional LVEF via echocardiography. Safety data were collected, including system- and procedure-related complications and eGFR. Although not prospectively defined as an endpoint, a comparison was made of hospital admissions for worsening HF before and after device activation.

Device implant, sequence of measurements, and data analysis

Device implant was accomplished by a cross-functional team: anaesthesiology ensured preserved cardiac reflexes, vascular surgery performed the implant and collaborated with cardiology to confirm optimal electrode placement from therapy response. Following implantation, device therapy was chronically activated following a 2-week post-surgery recovery period. Details of the stimulation procedures have been reported previously.[16] Briefly, continuous baroreceptor stimulation was up-titrated over the first few months, generally by gradually increasing pulse amplitude at fixed pulse frequency and pulse width, with care taken to avoid any undesired side effects such as tingling sensations or excessive reductions in heart rate and/or BP. After device activation, patients returned to the clinic monthly for the next 6 months. MSNA (primary endpoint), ECG, heart rate, finger BP, and baroreflex sensitivity were collected 9 ± 7.6 days before the implantation (baseline) and at 1, 3, and 6 months after initiation of therapy. This was also done for the clinical measurements. Therapy was active during all data acquisition. Echocardiograms were analysed at the enrolling centre by blinded personnel. Comparisons between pre- and post-implantation data were assessed by paired *t*-test and analysis of variance (ANOVA). Baseline values are reported as means $\pm$ standard deviation (SD). Changes relative to baseline values are displayed as the mean $\pm$ standard error (SE). A *P*-value <0.05 was considered as indicating statistical significance.

Results

Study population characteristics

Eleven patients (10 Caucasian, 3 female, 3 diabetic, 3 with history of persistent AF, and 5 with chronic kidney disease) were implanted between December 2011 and January 2013. As shown in *Table 1*, average age was 67 ± 9 years, with body mass index of 26 ± 5 kg/m^2 and LVEF of 32 ± 7% (range 19–40%). Patients were taking 4.5 ± 1.2 HF medications, consisting primarily of beta-blockers, diuretics, and ACE inhibitors or ARBs. Four patients were taking amiodarone, while three patients were prescribed both digoxin and a potassium supplement. Medications were constant throughout the 4 weeks prior to implant. Four patients had no implantable cardioverter defibrillator (ICD) implanted: one had a 40% LVEF, and one had the device removed because of pocket infection. The third patient had primary dilated cardiomyopathy (DCM) with normal coronary angiogram and, within 3 months of BAT implant, showed a significant LVEF gain from 30% to 38%. The fourth patient had a standard pacemaker only, with no indication for CRT, and the high rate of cardiac decompensation discouraged the exposure to the risks related to ICD implant. All patients except one had a baseline QRS duration <130 ms.

Table 1 Baseline demographic and clinical characteristics

Variable	Mean $\pm$ SD or *n* (%)
Race: Caucasian	10 (90.9%)
Gender: female	3 (27.3%)
NYHA functional class III	11 (100.0%)
Age (years)	67 ± 9
Body mass index (kg/m^2)	26 ± 5
Systolic BP (mmHg)	118 ± 14
Diastolic BP (mmHg)	70 ± 9
Heart rate (b.p.m.)	72 ± 8
Left ventricular ejection fraction (%)	31 ± 7
Implanted cardioverter defibrillator	7 (63.6%)
Pacemaker	1 (9.0%)
Diabetes	3 (27.3%)
Chronic kidney disease	5 (45.5%)
History of atrial fibrillation	3 (27.3%)
Number of HF medications	4.5 ± 1.2
ACE inhibitor or ARB	10 (90.9%)
Beta-blocker	10 (90.9%)
Diuretics: loop	11 (100%)
Diuretics: thiazides	1 (9.1%)
Diuretics: other	3 (27.2%)
Other	7 (63.6%)

BP, blood pressure; HF, heart failure.

The patient with a prolonged QRS (137 ms) had the CRT-D removed prior to study enrolment because of infection. Also, 3 of the 11 patients enrolled had DCM of non-ischaemic origin (hypertension, primary). These patients had a clinical profile similar to those of patients with post-ischaemic cardiomyopathy.

Muscle sympathetic nerve activity and baroreflex sensitivity

Serial MSNA (*Figure 1*, *Table 2*) exhibited significant reductions at 1, 3, and 6 months following the device activation. The reduction was incremental between 1 and 3 months, and stable between 3 and 6 months. At 6 months, MSNA was reduced by one-third vs. baseline. It can be noted from *Figure 2* that two patients had a slight rebound in sympathetic activity. These patients had the worst baseline quality of life scores and suffered a high number of in-hospital days before BAT. Their response in terms of hospitalization was as good as in the other patients although quality of life did not improve. The reduced MSNA was accompanied by improved baroreflex control of MSNA, which became statistically significant at the third and sixth month visit (*Figure 2*).

Other variables

Contemporaneously with diminishing sympathetic tone, functional capacity measured by 6MHW distance increased significantly at 3

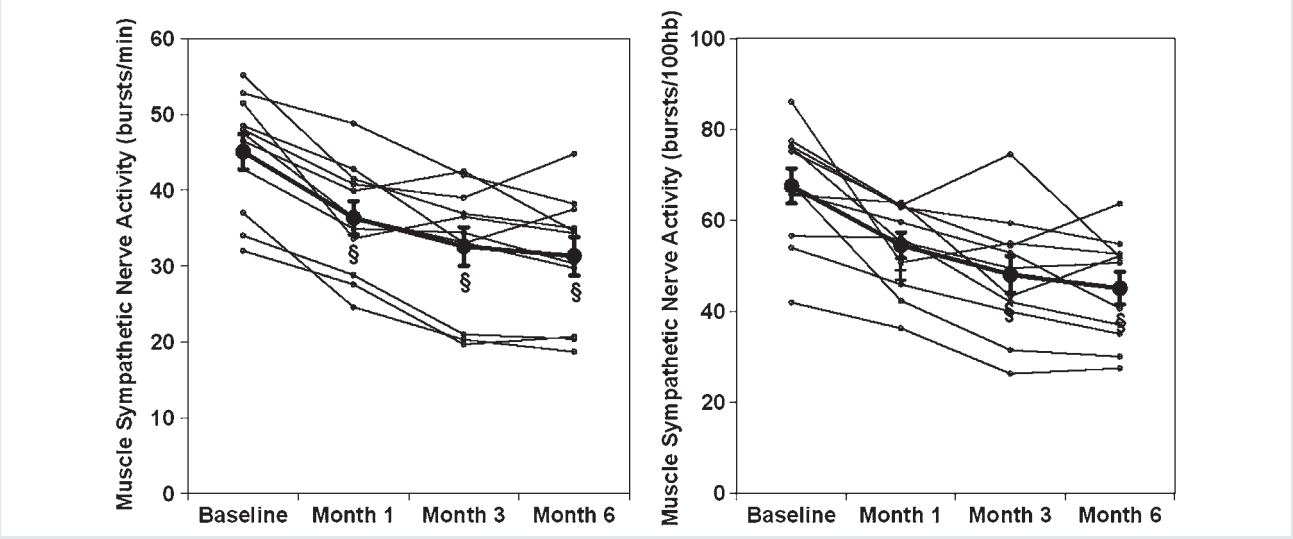

Figure 1 Change in muscle sympathetic nerve activity (MSNA) during treatment with baroreflex activation therapy. MSNA per unit time (bursts/min) and MSNA corrected for heart rate [bursts/100 heart beats (HB)] progressively decreased at 1 and 3 months, and stabilized at 6 months with reductions of 31% and 33%, respectively. Large circles with error bars denote the mean ± standard error. Individual patient trajectories are also shown. Significance vs. baseline: $^{‡}P < 0.005$, $^{§}P < 0.001$.

Table 2 Muscle sympathetic nerve activity, clinical data, and medications before and during chronic baroreflex activation ($n = 11$)

Vital signs and medications Baseline: mean ± SD Δ: mean ± SE	Baseline	Δ1 Month	Δ3 Months	Δ6 Months	ANOVA *P*-value
MSNA (bursts/min)	45.1 ± 7.7	−8.7 ± 1.3§	−12.5 ± 1.3§	−13.8 ± 1.4§	<0.001
MSNA (bursts/100 heartbeats)	67.6 ± 12.7	−13.1 ± 3.2‡	−19.5 ± 2.8§	−22.5 ± 2.5§	<0.001
Six minute walk distance (m)	304.4 ± 49.6	–	+49.7 ± 15.7†	+51.1 ± 25.6	0.05
Minnesota Living with Heart Failure score	33.4 ± 29.8	–	−11.7 ± 4.4*	−10.6 ± 3.8*	0.007
Systolic BP (mmHg)	118.5 ± 14.2	−8.5 ± 3.9	−0.3 ± 3.5	−1.2 ± 3.6	0.37
Diastolic BP (mmHg)	70.5 ± 9.3	−4.5 ± 3.0	+0.9 ± 2.8	−2.7 ± 2.2	0.51
Heart rate (b.p.m.)	72.3 ± 8.3	−2.6 ± 2.5	+0.2 ± 1.7	−0.5 ± 1.8	0.95
3D LV end-diastolic volume (mL)	168.6 ± 43.5	–	−11.3 ± 6.5	−8.7 ± 7.5	0.21
3D LV end-systolic volume (mL)	116.9 ± 40.9	–	−14.3 ± 5.5*	−11.3 ± 5.6	0.02
3D LV ejection fraction (%)	32.0 ± 7.3	–	+4.3 ± 1.0‡	+3.6 ± 1.4*	0.002
BNP (pg/mL)	314.4 ± 306.9	–	−8.9 ± 40.2	+33.1 ± 112.3	0.88
Estimated GFR (mL/min/1.73 m^2)	65.1 ± 27.7	–	+2.1 ± 2.8	+5.7 ± 4.9	0.41
Body mass index (kg/m^2)	26.1 ± 4.6	−0.1 ± 0.1	+0.1 ± 0.2	−0.3 ± 0.3	0.55
Number of medications	4.5 ± 1.2	−0.4 ± 0.2*	−0.4 ± 0.2*	−0.3 ± 0.1	0.007

ANOVA, analysis of varaince; BP, blood pressure; GFR, glomerular filtration rate; MSNA, muscle sympathetic nerve activity; SE, standard error;
Baseline is shown as the mean ± SE; Δ (vs. baseline) as mean ± SE.
'–' denotes data not collected.
t-test vs. baseline: $^{*}P < 0.05$; $^{‡}P < 0.005$; $^{§}P < 0.001$.

and 6 months, with an average increase of ~50 m. Concomitant improvements were observed in NYHA class, quality of life, and EF (*Table 2*, *Figure 3*). Specifically, LVEF increased by at least two points in 7 of the 11 patients (range +2 to + 12%), becoming normal (52%) in one case. In three patients LVEF did not change and in one case a four point loss (39 to 35%) was observed. Nonetheless, the patients showed clinical benefit from BAT equivalent to the others. Coherent with LVEF behaviour, LV volumes also ameliorated (*Table 2*, ANOVA $P < 0.01$). Quality of life improved in most patients within 3 months and did not appreciably change in those two who had very high baseline scores (93 and 73). No significant changes were observed through 6 months for heart rate, systolic BP, or diastolic BP (*Table 2*). No trends were detected in BNP. The prescribed number of HF medications was significantly reduced at

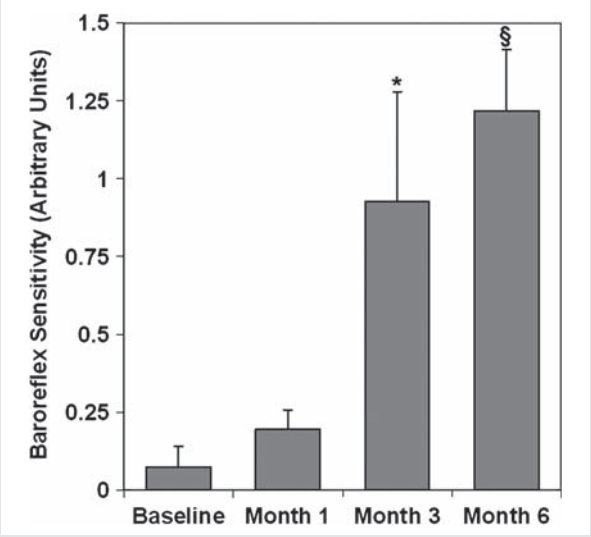

Figure 2 Change in baroreflex sensitivity with baroreflex activation therapy. Baroreflex sensitivity as measured by a variation of the method of Kienbaum *et al.*[24] mirrored reductions in MSNA, with baroreflex modulation progressively increasing at 1 and 3 months and remaining elevated at 6 months. Values are presented as the mean ± standard error. Significance vs. baseline: $^{*}P < 0.05$, $^{\S}P < 0.001$; ANOVA *P*-value < 0.001.

1 and 3 months and not increased relative to baseline in any patient. The three patients treated with digitalis (one for AF and two with the highest hospitalization rate) showed important benefit from BAT. Renal function and body mass index were stable throughout follow-up.

Safety and hospitalizations

One system- and procedure-related complication was observed from implant through the course of 179 patient-months of follow-up: at implant, the patient experienced anaemia requiring a transfusion. The patient recovered with no residual effects.

In the 6 months before implant, 8 of the 11 patients were admitted for worsening HF and remained in hospital for a total of 125 days. Through 6 months of follow-up, one patient was admitted for worsening HF and stayed for 6 days. Another patient presented to the emergency department with worsening HF, but symptoms were addressed without need for admission. Overall, all patients benefitted from BAT in terms of days in hospital.

Discussion

Main results

The present study provides the first evidence that chronic stimulation of carotid baroreceptors markedly and persistently reduces the sympathetic activation characterizing HF patients.[1–9] It also shows that the reduction is accompanied by improvement of a major modulator of sympathetic activity, the arterial baroreflex, whose function is impaired in HF.[4,6,25] Finally, it shows that baroreflex activation is accompanied by favourable effects on cardiac function and clinical profile, i.e. increased EF, increased exercise tolerance, reduced NYHA class, and improved quality of life. The suggestion can thus be made that chronic carotid baroreceptor stimulation may have favourable therapeutic impact in HF.

Additional data

Several other results of our study deserve mention. First, carotid baroreceptor stimulation reduced the elevated sympathetic nerve traffic by about one-third relative to baseline, comparing favourably with sympathoinhibitory effects of therapeutic interventions that do not primarily involve a baroreflex mechanism, such as inhibitors of the renin–angiotensin system[26,27] or centrally acting agents.[28] In the two patients in which MSNA rebounded slightly between 3 and 6 months, clinical improvement was comparable with that of the other patients. However, stress-related central mechanisms (very high quality of life scores) may have influenced MSNA. Furthermore, one patient was an insulin-dependent diabetic with peripheral vascular disease, while the other experienced worsening of non-Parkinsonian limb tremor.

Effects of BAT also compare favourably with CRT, an intervention aimed at improving cardiac function[29] which has been shown to also reduce adrenergic drive.[30,31] The fundamental difference between CRT and BAT is that CRT produces autonomic recovery as a consequence of recovery of LV function whereas BAT acts directly on symaptho/vagal balance with obvious, and here documented, positive consequences on cardiac function. Given their different mechanisms of action, CRT and BAT may be complementary tools to manage advanced HF.

Secondly, baroreceptor-induced sympathetic deactivation was accompanied by increased exercise tolerance, reduced NYHA class, and enhanced quality of life, suggesting that the sympathoinhibitory effect may have favourably affected patients' clinical status. This is further suggested by individual patient data which showed the clinical improvement to be more marked when sympathetic inhibition was greater, and small or absent in the three patients who exhibited a small increase of MSNA from the third to the sixth month of follow-up. In two of these patients, this was coupled with a small decrease in or a failure to increase the distance covered by the 6MHW. The third patient maintained a stable clinical course despite the slight MSNA increase.

Thirdly, BAT was accompanied by a greater ability of arterial baroreceptors to modulate sympathetic nerve traffic in response to spontaneous BP changes. Whether this was due to (i) more intense baroreceptor discharge in response to better cardiac contractility and a more rapid BP upstroke[32] or (ii) more effective central integration of the baroreceptor signal[33] is not clarified by our data. Regardless of the mechanisms, this may represent a favourable phenomenon because the prognosis of HF is independently related to reflex cardiovascular modulation.[34] The observation that heart rate did not change during BAT deserves two brief considerations: (i) MSNA does not correlate with HR;[35] and (ii) the trial included three patients in AF. Of the remaining eight patients in sinus rhythm, one showed a 3 b.p.m. increase while in the remaining

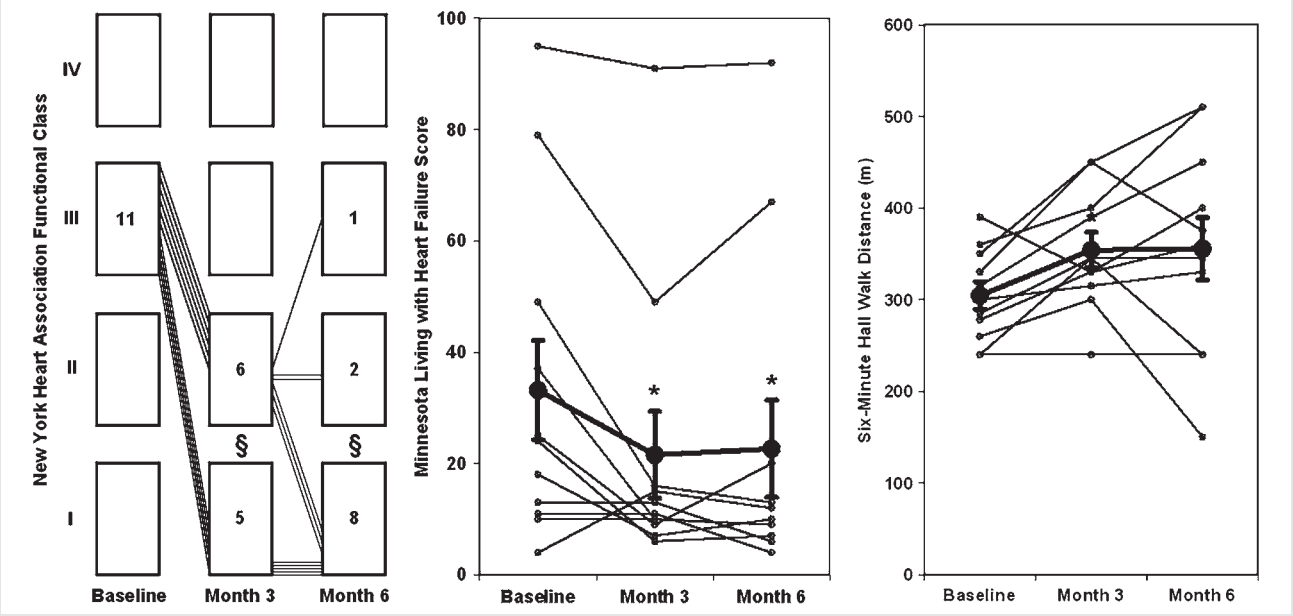

Figure 3 Change in NYHA functional class, quality of life, and 6 min hall walk (6MHW) distance with baroreflex activation therapy. Congruent with improvement in baroreflex sensitivity, clinical presentation, quality of life, and 6MHW distance improved from baseline to 3 months, with improvements that were sustained or improved at 6 months. Large circles with error bars denote the mean ± standard error. Individual patient trajectories are also shown. Significance vs. baseline: $^{*}P < 0.05$, $^{\S}P < 0.001$.

seven patients heart rate decreased on average by 5 b.p.m. (range −2 to −9 b.p.m.).

Finally, from a safety perspective, BAT was associated with a low complication rate, similar to the pacemaker-like safety profile observed in a recent study of patients with resistant hypertension.[16] Haemodynamics were stable, with no tachycardia or BP reduction. Lack of a fall in BP with baroreceptor stimulation is of special interest because it implies that baroreceptor-dependent systemic vasodilatation was accompanied by improved cardiac contractile function that increased stroke volume and opposed BP decline.[36]

Strengths and limitations

A strength of our study is that MSNA was measured serially for several months during BAT, thereby providing unequivocal data about the ability of the therapy to inhibit sympathetic overdrive of HF patients acutely and persistently. To our knowledge, no other therapy of HF has been characterized as thoroughly in terms of direct measurement of sympathetic activity.

Limitations are that influences based on the results of the current study require caution due to the small cohort size, the limited duration of the follow-up, and the lack of a control group. As this was a pilot study with the objective of proof-of-concept, we felt that a careful internal analysis study was adequate. Indeed, the fairly consistent clinical picture over the 12 months prior to BAT implant, despite all efforts to implement the best available medical and device therapy for all patients, serves as a dependable control vs. BAT. Furthermore, the results refer to HF with reduced EF, and whether they apply to the similarly frequent HF with preserved systolic function[37] is unknown. Finally, while the improvements of clinical endpoints are encouraging, the prognostic value of carotid baroreceptor stimulation in HF needs to be established by randomized trials and hard endpoints. In this context, it is encouraging that carotid baroreceptor stimulation was accompanied by markedly reduced hospital admissions compared with the period before the stimulation.

In conclusion, chronic baroreflex activation markedly and persistently reduced sympathetic tone of patients with NHYA class III HF and reduced LVEF, while increasing baroreflex sensitivity and improving EF, functional capacity, clinical status, and quality of life. This motivates the hypothesis that BAT therapy will improve outcome in patients with severe HF. A large-scale trial of appropriate design is needed to test this hypothesis.

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