Federazione Italiana di Cardiologia
Italian Federation of Cardiology

Baroreflex activation therapy: a new approach to the management of advanced heart failure with reduced ejection fraction

Edoardo Gronda[a], Darrel Francis[b], Faiez Zannad[c], Christian Hamm[d], Josep Brugada[e] and Emilio Vanoli[a,f]

Chronic heart failure is a common clinical condition characterized by persistent excessive sympathetic nervous system activation. The derangement of the sympathetic activity has relevant implications for disease progression and patient survival. Aiming to positively impact patient outcome, autonomic nervous system modulatory therapies have been developed and tested in animal and clinical studies. As a general gross assumption, direct vagal stimulation and baroreflex activation are considered equivalent. This assumption does not take into account the fact that direct cervical vagal nerve stimulation involves activation of both afferent and efferent fibers innervating not only the heart, but the entire visceral system, leading to undesired responses to and from this compartment. The different action of baroreflex activation is based on generating a centrally mediated reduction of sympathetic outflow and increasing parasympathetic activity to the heart via a physiological reflex pathway. Thus, baroreflex activation rebalances the unbalanced autonomic nervous system via a specific path. Independent and complementary investigations have shown that sympathetic nerve activity can be rebalanced via control of the arterial baroreflex in heart failure patients.

Results from recent pioneering research studies support the hypothesis that baroreflex activation can add significant therapeutic benefit on top of guideline-directed medical therapy in patients with advanced heart failure. In the present review, baroreflex activation therapy results are discussed, focusing on critical aspects like patient selection rationale to support clinician orientation in opting for baroreflex activation therapy when, on top of current guideline-directed medical treatment, other therapies are to be considered.

[a]Cardiovascular Department, IRCCS Multimedica, Sesto San Giovanni, Milan, Italy, [b]National Heart and Lung Institute, Imperial College London, London, UK, [c]Unité 1116, Department of Cardiology, Centre d'Investigations Cliniques, INSERM, CHU de Nancy, Université de Lorraine, Nancy, France, [d]Kerckhoff Heart Center, Bad Nauheim Medical Clinic I, University of Giessen, Giessen, Germany, [e]Cardiovascular Institute, Hospital Clínic de Barcelona, University of Barcelona, Barcelona, Spain and [f]Department of Molecular Medicine, University of Pavia, Pavia, Italy

Correspondence to Emilio Vanoli, MD, Cardiology Research Unit, Cardiovascular Department, Istituto di Ricovero e Cura a Carattere Scientifico Multimedica Via Milanese, 300, 20099 Sesto S. Giovanni, Milan, Italy
Tel: +39 0224209826; fax: +39 0224209085; e-mail: emivano@gmail.com

Received 18 December 2016 Revised 24 May 2017
Accepted 10 June 2017

The premises

Reports from trials in which autonomic nerve manipulation (denervation,[1,2] or stimulation,[3–6]) was employed to treat resistant arterial hypertension or heart failure have not provided, so far, convincing data, and this might frustrate the expectation of finding novel effective treatment approaches for these conditions. The present review will focus on heart failure that, so far, remains a major cause of death in Western countries, despite the impressive progress achieved over the last decades in its management. Current standard medical treatment, including renin–angiotensin–aldosterone system inhibitors, adrenergic antagonism, cardiac resynchronization therapy (CRT), and implantable defibrillators improve survival, but this benefit appears to decline, at most, after 15 years.[7] This time limit is related to the general population aging process, but it also underscores the unsatisfactory effectiveness of contemporary heart failure state-of-the-art therapy. Heart failure is characterized by the lack of complete recovery after an acute event with a progressive, and currently irreversible, decline in cardiac function toward the end stages of heart failure that is specifically indexed by increasing diuretic dose.[8,9] The fact of the matter is that the management of an acute event paradoxically predisposes one to a subsequent event unless profound changes occur in the central control of the circulation. Thus, acute heart failure perpetuates heart failure worsening because of the unfavorable circulatory consequences of drugs used to restore hemodynamic balance in these circumstances. However, the ideal approach is to develop effective therapies that prevent acute heart failure decompensation. In this article, we will briefly review the fundamentals of the baroreflex physiology specifically relevant to heart failure therapeutics, and examine the differences between baroreflex activation therapy (BAT) and vagal nerve stimulation (VNS). The authors of this paper have all been involved in BAT therapy development. It is outside the scope of this

manuscript to review in detail the outcomes of the VNS trials, but rather to review some critical aspects of BAT in view of its specific differences with VNS.

Approaches to autonomic cardiac control

The understanding that pharmacologic antagonism of adrenergic receptors is far from being a complete block of cardiac sympathetic activity led to the successful use of left cardiac sympathetic denervation in highly arrhythmogenic conditions.[10,11] A similar philosophy encouraged the use of radiofrequency ablation techniques to attain renal denervation in patients with resistant hypertension. The results of renal denervation in resistant arterial hypertension remains encouraging, despite the outcome of the most recent trial, SYMPLICITY HTN-3.[1] In heart failure, however, cumbersome results[2] and significant uncertainty regarding the capability of the current technology to easily achieve adequate denervation in a trial involving a large number of centers (i.e. inadequate learning time) limit the conclusiveness of these reports. Vagal activation (reflex or direct) also has potential to treat heart failure as inhibition of sympathetic cardiac overdrive can also be accomplished by increasing afferent and efferent parasympathetic activity by the use of vagal stimulation. The background for this concept is sound. It can be synthetically described by the evidence that depressed reflex vagal control of the heart predicts elevated sympathetic responses to acute myocardial ischemia,[12] increases the risk for sudden death in post-myocardial infarction patients with a depressed left ventricular ejection fraction (LVEF) and contributes to heart failure progression.[13,14] The predictive value of baroreflex sensitivity (BRS) is unaffected by β-blocker administration, which despite producing an increase in overall survival, still retains a limited therapeutic efficacy in those patients whose BRS remains below the threshold for cardiac risk despite the adrenergic blockade.[14] The autonomic imbalance associated with higher risk after myocardial infarction and in heart failure is of central origin.[15] Thus, end-organ adrenergic antagonism can only partly prevent its consequences as it does not directly influence the origin of the problem. As matter of fact, β-adrenergic blockade does not limit cardiac sympathetic activity, but simply shields the heart against the adverse effects of sympathetic activation. Central and peripheral sympathetic modulation by vagal cardiac nerve stimulation is a conceivable approach because of its many pathways involving sympathetic inhibition as well as anti-inflammatory effects.[16,17] Vagal activation can be attained by either stimulating specific vagal reflexes (BAT) or by directly activating vagal traffic at the cervical level (VNS).

Reflex vs. direct stimulation

Technology

Vagal nerve stimulation

Various technology has been developed for VNS, all of which involve the application of cuff electrode(s) (with different shapes) around the cervical vagus. The first device taken into the cardiac field was CardioFit (Bio Control Medical, Yehud, Israel) which is a 'closed loop' device with an intracardiac right ventricular sensing lead and a bipolar cuff placed around the right cervical vagus nerve. The stimulation intensity of VNS, which was limited by patient symptoms of hoarseness and/or referred jaw pain, was uptitrated to 4.1 ± 1.2 mA. Devices employed in other trials did not synchronize VNS with the heartbeat eliminating the need of an intracardiac sensing electrode.

Baroreflex activation therapy

The system for delivering BAT (Barostim neo system, CVRx, Inc., Minneapolis, Minnesota, USA) consists of a carotid sinus lead and a pulse generator. The lead comprises a 40-cm lead body that terminates in a circular backer 7 mm in diameter with a 2-mm iridium oxide coated platinum–iridium disk electrode centered on the backer. Similar to a pacemaker, the pulse generator is implanted subcutaneously in an infraclavicular chest wall pocket. Electrode implantation begins by surgically exposing the carotid sinus through a transverse cervical incision over the carotid bifurcation. The sinus region is then mapped by temporarily placing the electrode in various locations and applying electrical stimulation to determine the location with greatest sensitivity to BAT.

Figure 1 illustrates the integrated pathway activated by BAT via electrical stimulation of the carotid baroreceptors. The response elicited from the arterial vascular bed reaches the nervous centers located in the medulla oblongata, where the integrated efferent response is generated and delivered to the heart and blood vessels mitigating the excess in sympathetic activity.

Physiology

With remarkable consistency, competing scientific research groups using different methods have all concluded that, even in advanced heart failure, baroreflex circuits are not intrinsically malfunctioning.[18] In a healthy condition, the carotid sinus baroreceptor input appears to be dominant, and baroreflex responses are modulated and balanced by afferent excitatory signaling with inhibitory effects of vagal outflow from skeletal muscle, kidney, cardiopulmonary mechanoreceptors, and chemoreceptors.[18] The occurrence of cardiac damage, specifically if combined with renal damage, can suddenly disrupt such balance by enhancing excitatory reflexes that are able to strongly offset the baroreceptorial ones and create the condition of detrimental sympathetic hyperactivity. A functional baroreceptorial impairment would also occur as a consequence of decreased mechanical stretching that accompanies decline in left ventricular (LV) function, as evidenced by the negative prognostic value of a lower pulse pressure in heart failure.[19]
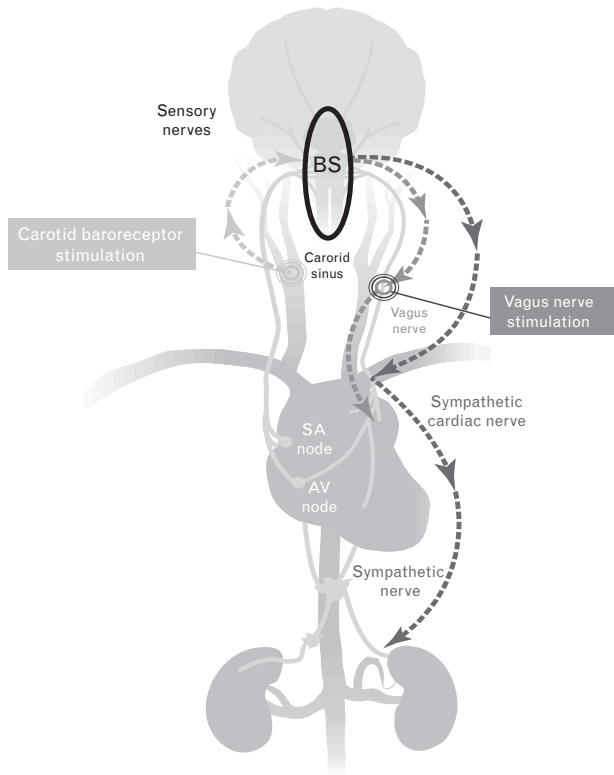
Baroreflex physiology. The baroreflex feedback signal originates predominantly in the carotid sinus (light grey dashed arrow) and aortic arch receptors (not depicted in the figure). Baroreceptors are stimulated by arterial distention mostly as a consequence of arterial pressure and blood flow. They can detect arterial distention corresponding to a single mmHg pressure change. Afferent fibers from baroreceptors innervate the nucleus of the solitary tract, in the medulla. Via complex neural interactions, inhibition occurs in the rostral ventrolateral medulla, the principal site of sympathetic outflow (dark grey dashed arrow) in the brainstem encircled by the brown line. This inhibition reduces sympathetic activity to the heart, blood vessels, adrenal glands, kidneys, lungs, and other organs. Moreover, baroreceptor-related traffic ascends the carotid sinus nerve to the nucleus ambiguous and vagal motor nucleus, both placed in the BS, to modulate parasympathetic efferent traffic (medium grey dashed arrow) to the heart and other organs through the vagus nerves. BS, brainstem.

These latter considerations form the background for using direct stimulation of the vagal nerve to directly modulate its activity independently from the complex afferent traffic to the central nervous system originating from the whole cardiovascular and visceral apparatus.

A specific problem with VNS originates from the complexity of its nerve bundle structure, which is constituted largely of afferent fibers and 20% efferent fibers.[20] The name 'vagus' (wandering) refers to the extensive and varied distribution of its nerve endings. It innervates numerous major organs (liver, lung, spleen, kidneys, and gut; i.e. all reticular endothelial organs), where the local specific responses may not be desirable in patients with heart failure. Such complexity has led to different and apparently contrasting approaches to stimulation

techniques. The critical difficulty stands, indeed, in setting the level of stimulation to recruit efferent fibers with direct action and simultaneously recruiting afferent vagal components that have reflex inhibitory effects on sympathetic nerve activity. The lack of consensus on the matter of the optimal 'dose' has led to a wide range of electrical stimulation parameters ranging from 1 mAmp at 20 Hz[6] to almost 4 mAmp at 1 Hz,[21] to different modalities of current delivery (synchronized or not with the heartbeat). A good correlation has been described both experimentally and clinically between current intensity and heart rate reduction during the acute implant phase, which supported the choice of high current VNS in the INcrease of Vagal ToneE in heart failure (INOVATE-heart failure)[21] trial, with the goal of producing prevalent efferent stimulation of b-fibers and blocking any afferent effects. This latter choice disregarded central sympathetic inhibition as a potential contributor to the beneficial effects of VNS, whereas sustained central sympathetic inhibition has been advocated as one of the fundamental mechanisms of BAT efficacy.[22] On the other hand, vagal afferent activation has been experimentally proposed as inhibitory of the vagal efferent activity[23] in apparent contrast with the evidence obtained by single fiber recordings of rapid and strong sympathetic inhibition by vagal afferent activation.[24] Thus, a wide spectrum of options exist for vagal stimulation, leaving open many opportunities for an appropriate tailoring of treatment delivery.

Clinical studies
The pioneering approach
Both BAT and VNS benefit from a solid experimental background, and pioneering small clinical studies have been conducted for both approaches. However, a thorough proof of concept study has been conducted with BAT only, in 11 patients with advanced heart failure at elevated recurrence of hospitalization, despite receiving guideline-directed therapy. This small study was meaningful to the progression of BAT use as it provided combined pathophysiological and clinical information. In these 11 heart failure patients, muscle sympathetic nerve activity (MSNA) was measured at baseline and periodically after BAT activation. MSNA dropped significantly at 3 months and remained equally reduced at 6 months.[25] This finding was coupled with a highly significant decline in the number of in-hospital days compared with the year before BAT and persisted after 21 months of follow-up.[26] On the VNS side, the background pathophysiology was documented at the experimental level only and then brought into the clinical arena by Schwartz *et al.*[3] in a feasibility study in eight patients with advanced heart failure. The main finding of this pilot investigation was feasibility and good tolerability of VNS as well as a potential beneficial effect on plasma interleukin 6 levels.

Table 1 Comparison of changes between the baroreflex activation therapy arm and the medical management arm on clinical endpoints and N-terminal probrain natriuretic peptide in the controlled trial

| Variables	BAT treated arm	Medical mgnt arm	P
6MHD (m)	+59.6 ± 14 m	+1.5 ± 13.2 m	0.004
NYHA f. Cl. (change in distribution)	I 55%, II 42%, III 3%	I 24%, II 67%, III 9%	0.002
MLWHF QoL Score (points)	−17.4 ± 2.8	2.1 ± 3.1	<0.001
Hospitalization days for worsening HF (days/patient/year)[b]	0.63 ± 1.5−0.14 ± 0.5	0.36 ± 1.1−0.31 ± 0.97	0.08[a]
NT pro-BNP (pg/ml) median	−69.0 pg/ml interquartile range: −504 to 198 pg/ml	129.5 pg/ml interquartile range: −67 to 619 pg/ml	0.02

6MHD, 6-min hall distance; MLWHF QoL, Minnessota living with heart failure quality-of-life score; NT pro-BNP, N-terminal probrain natriuretic peptide; NYHA F. Cl, New York Heart Association Functional Class. Reproduced with permission.[27] [a] Difference between the two groups. [b] Change from 6 months pre to 6 months postenrollment.

Efficacy trials

Efficacy of BAT was recently evaluated in a randomized controlled trial in 140 New York Heart Association (NYHA) class III with reduced ejection fraction heart failure patients receiving guideline-directed medical therapy alone (N=69) or guideline-directed medical therapy and BAT (N=71).[27] The purpose of this clinical investigation was to evaluate the efficacy on surrogate endpoints and safety of the CVRx Barostim Neo System in the treatment of patients with heart failure (ClinicalTrials.gov Identifier: NCT01471860). Patients assigned to BAT, compared with control group patients, experienced improvements in the distance walked in 6 min (59.6 ± 14 vs. 1.5 ± 13.2 m; P=0.004), Minnesota quality-of-life score (−17.4 ± 2.8 vs. 2.1 ± 3.1 points; P<0.001), and NYHA functional class ranking (P=0.002 for change in distribution). BAT significantly reduced N-terminal probrain natriuretic peptide (P=0.02) and was associated with a trend toward fewer in-hospital days for heart failure worsening (P=0.08; Table 1). Despite the absence of an evident effect on LVEF, BAT also significantly increased SBP and pulse pressure (Fig. 2).

It should be noted that the magnitude of SBP and pulse pressure changes observed in the BAT controlled trial are not trivial and carry potential implications for outcomes in heart failure. In the comparison of medical therapy, pacing, and defibrillation in heart failure trial, median changes in SBP from baseline to 3, 6, and 12 months in the two groups did not exceed 4 mm Hg.[28] In the BAT trial treatment arm, the mean change in SBP was 8.5 ± 3.8 mmHg higher than that of the control arm (P=0.03).

The data carry clinical relevance in view of the mechanistic studies demonstrating that the sympathovagal balance mediated by carotid baroreceptor activation is impaired even in mild heart failure, leading to increased sympathetic activity and decreased parasympathetic activity. This imbalance affects control of blood pressure (BP), peripheral vascular resistance, and the cardiopulmonary receptor's ability to modulate sympathetic activity. All this represents a primary mechanism of ventriculoarterial coupling loss and the consequent decline in heart function.[29,30] Proof of this concept is evident from experiments in which intravenous infusions

Fig. 2
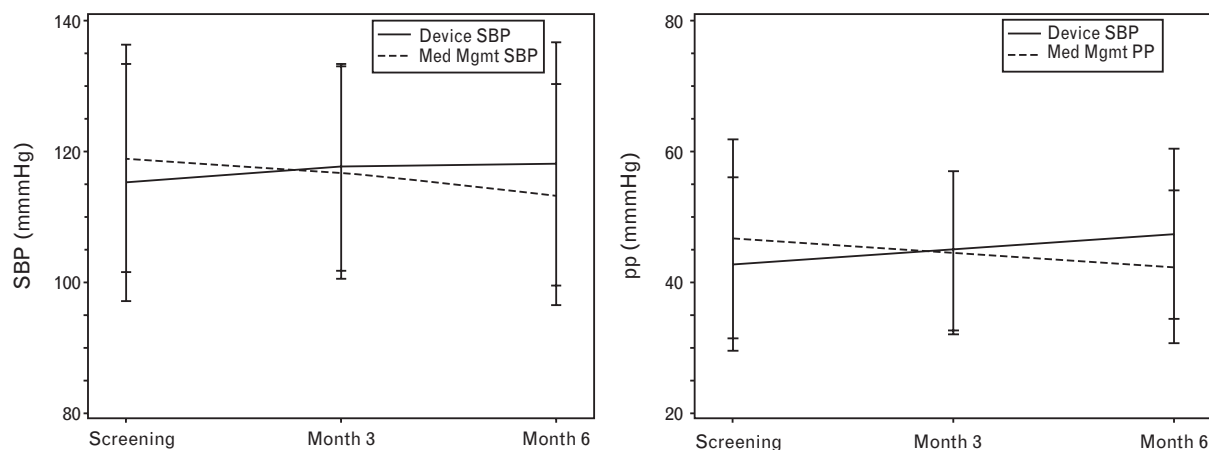
Effect of BAT on blood pressure. BAT significantly increased SBP (P=0.03) (a) and pulse pressure (P=0.004) (b), compared with the medical management control group which displayed decreasing trends in blood pressure. BAT, baroreflex activation therapy; Med Mgmt, medical management; PP, pulse pressure. Reproduced with permission[27].

Table 2 Vagal nerve stimulation studies

Clinical trial	Study design	Inclusion criteria	Number of patients	Stimulation amplitude (mA)	Outcomes	Results
CardioFit[4] (NCT00461019)	Nonrandomized Open label	NYHA f. cl. II–III, EF <35%	32	4.1	Occurrence at 6 months of all system and/or procedure-related adverse events 2. NYHA f. cl., 6MWD, LVESV, MLHFQ QoL scores	1. No significant adverse events 2. Significant improvement in NYHA f. cl 6MWD, LVESV, QoL scores
NECTAR-HF[6] (NCT01385176)	Randomized Double blind	NYHA f. cl. II -III, EF 35%, LVESD >5.5 cm, QRS <130 ms	96	1.2	1. LVESD (6 months) 2. NYHA functional class, VO2 max, SF-36 and MLHFQ QoL scores, pro-BNP	1. No significant change in LVESD 2. Significant improvement in NYHA f. Cl. and QoL scores
ANTHEM-HF[5] (NCT01823887)	Randomized Open label Right vs. Left Cervical Vagus	NYHA f. Cl. II–III, EF ≤40%, QRS <150 ms	60	2.2	1. Change in EF and LVESV (6 months) 2. NYHA f. Cl., 6MWD, MLHFQ QoL scores, LVESD, HRV, BNP	1. Significant increase in EF (4.5%); no change in LVESV 2. Significant improvement in NYHA f. cl. and QoL scores
INOVATE-HF[21] (NCT01303718)	Randomized Open label	NYHA f. Cl. III EF ≤40 LVESD 5–8 cm	730	3.9 3.5 (73% of cases)	1. Composite all-cause mortality/HF hospitalizations (end of study); freedom from procedure-/system-related complications (90 days); all cause death or complications (12 months) 2. LVESV index, 6MWD, KCCQ QoL scores, hospitalization-free days	1. No significant difference in all-cause mortality and HF hospitalizations 2. Significant improvement in 6MWD, KCCQ QoL; no safety issues identified

6MWD, 6-min walk distance; ANTHEM-HF, Autonomic Regulation Therapy via Left or Right Cervical Vagus Nerve Stimulation in Patients With Chronic Heart Failure; BNP, B-type natriuretic peptide; CardioFit, CardioFit for the Treatment of Heart Failure; EF, ejection fraction; HF, heart failure; HRV, heart rate variability; INOVATE-HF, INcrease of VAgal TonE in Heart Failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MLHFQ, Minnesota Living With Heart Failure Questionnaire; NECTAR-HF, Neural Cardiac Therapy for Heart Failure; NYHA f. cl, New York Heart Association functional class; QoL, quality of life; SF-36, Short Form 36 Questionnaire; VO2 max, maximum volume of oxygen consumed.

of phenylephrine restore sympathovagal balance and reinstate the basic ventriculoarterial coupling relation as expressed by heart rate decrease and BP increase.[31]

These studies support the hypothesis that restoration of BRS provided by BAT can lead to a more efficient ventriculoarterial coupling resulting in arterial BP amelioration. The trend toward declining pressure observed in the control arm of the BAT controlled trial[27] likely mirrors a progression of heart failure worsening that, in this study, was prevented in the BAT treated arm.

The BP increase resulting from BAT also underscores its complementary value to medical therapy including β-blockade, which has been shown to provide benefit independently of BP.[32] Indeed, although medical therapies address end-organ consequences of the hyperadrenergic state of heart failure, the added treatment benefit observed with BAT exploits additional therapeutic pathways.

On top of these positive cardiovascular actions, BAT has been successfully tested in refractory hypertensive patients, providing effective BP reduction in long-term follow-up.[33] The highly significant decrease in BP translated to an 18% reduction of LV mass.[34] The impressive physiological changes in hypertension, reinforced by confirmation of an impact on ventricular hypertrophy, suggest that BAT could be effective in the treatment of heart failure patients, as many peripheral mechanisms are common to hypertension and heart failure.

On the vagal stimulation side, heart failure studies have generated somewhat conflicting results (Table 2), with the recently published INOVATE-heart failure study results providing the most substantiated evidence.[21] INOVATE-heart failure was a multicenter (involving 85 centers), randomized trial in patients with chronic heart failure, ejection fraction less than 40%, and NYHA class III symptoms that, for the first time in the neurostimulation field, challenged a combined endpoint including hospitalization for worsening heart failure and mortality. Patients were assigned to device implantation to provide VNS (active) or continued medical therapy (control) in a 3 : 2 ratio.

The mean stimulation current was 3.9 ± 1.0 mA at the 6-month follow-up visit [inferior only to the stimulation current in the CardioFit study (4.2 ± 1.2 mA)],[3] with 73% of patients achieving the goal of more than 3.5 mA. The INOVATE-heart failure study primary endpoint was the composite of death from any cause or first event for worsening heart failure.

The study enrolled, randomized and followed 707 patients for a mean of 16 months. The primary efficacy outcome occurred in 132 of 436 patients in the VNS group, compared with 70 of 271 in the control group (30.3 vs. 25.8%; hazard ratio, 1.14; 95% confidence interval, 0.86–1.53; $P = 0.37$). Estimated annual mortality rates were 9.3 and 7.1%, respectively ($P = 0.19$) and LV end-systolic volume index were not different ($P = 0.49$)

between the study groups. Similarly, hospitalization rate was identical in the two groups: 44/271 in the control group vs. 70/436 in the treatment arm (16% for both). Only quality of life, NYHA functional class and 6-min walking distance were favorably affected by VNS ($P < 0.05$).

Intriguing subgroup analyses [presented at the 2016 American College of Cardiology (ACC) meeting but not detailed in the INOVATE-heart failure manuscript] displayed some unexpected results. The study outcome was, at least partly, affected by the fact that women in the active arm had a significantly lower 6-min walking distance ($P < 0.03$) and LVEF ($P < 0.01$) at baseline in comparison with the control arm. Also, the female control arm had a better outcome in comparison with the global male population and to the female treated arm. Overall, these unexpected differences in the study populations might have negatively affected the trial outcome.

Also of interest is the fact that the subgroup without CRT, presenting with a QRS width less than 130 ms and the ability to walk at least 300 m, showed a better outcome with a nonstatistically significant 20% primary outcome event decrease in the active arm. Notably, the LV end-systolic and end-diastolic volumes also decreased, although the change was not statistically significant. These data (also not reported in the published manuscript, but presented at the 2016 ACC meeting) are similar to the results of the Barostim controlled trial post hoc analysis where only no-CRT patients displayed a significant increase of LVEF in the treated arm.[35] On the other hand, the lack of efficacy of VNS and BAT in CRT nonresponders might suggest that this is a patient subset in which the disease severity has reached an irreversible stage.

Overall, neither VNS nor BAT are considered effective heart failure treatments in the European Society of Cardiology heart failure association guidelines. However, BAT efficacy is supported by a specific proof of concept study where MSNA decline after BAT in NYHA class III patients was coupled with a consistent drop in heart failure hospital admissions,[25] and both effects were proven to persist throughout long-term follow-up.[26] In the treated arm of the larger controlled study, reduction of hospital resource utilization was confirmed and associated with a decline in N-terminal probrain natriuretic peptide and an increase in SBP and pulse pressure,[27] suggesting that the restraining action on sympathetic activity observed in the proof of concept study does translate to a significant clinical advantage.

Who can be a candidate for baroreflex activation therapy?

Defining the optimal patient population for BAT and, in general, for neuromodulation, is a challenging priority.[36] Heart failure progression is characterized by relapsing and recurrent hospitalizations,[8] coupled with progressive deterioration and increased mortality, despite optimal evidence-based, guideline-directed therapy. This negative progression is accompanied by persistent baroreflex impairment.[37] Worsening heart failure is also detected by an increasing need to pharmacologically induce diuresis.[9]

The kidney is robustly innervated by both afferent and efferent sympathetic fibers, and their activity, as quantified by norepinephrine spillover, is a powerful predictor of survival in heart failure.[38] Increased renal sympathetic tone enhances tubular sodium reuptake, thus decreasing natriuresis during daily physical activity and blunting the response to diuretics.[39] These actions are key mechanisms underlying heart failure symptoms.

Therefore, escalating diuretic requirements or worsening renal function may be the pivotal marker of heart failure progression even if classical hemodynamic or symptomatic markers such as LVEF, NYHA class, or Seattle heart failure score[40] may not provide meaningful information on the advancing of the clinical condition.

Recurrent heart failure hospitalizations are another critical clinical indicator which should lead physicians to consider novel therapies beyond guideline-based drug and device therapy and disease management.[41] A useful tool for patient clinical profile assessment might be the North American Interagency Registry for Mechanically Assisted Circulatory Support scale, where patient profiles are classified by seven heart failure severity grades on the basis of functional capacity, clinical stability, and therapy needs.[42] It is worth noting that patient profile 7 includes advanced heart failure patients that have achieved acceptable compensation with stable renal function after repeated heart failure hospitalizations. Patient profile 6 describes patients who are comfortable at rest but are significantly limited in daily activity because of high filling pressures generated by the persistence of fluid retention. Patient profile 5 addresses intolerance to exercise and profile 4 includes the presence of resting symptoms at home with oral therapy. The 'frequent flyer' definition is a common characteristic of the above detailed profiles and conveys the frequent need for hospital or emergency department admissions for worsening heart failure symptoms. The poor heart failure prognosis characterized by these heart failure profiles (Table 3) may identify candidates for baroreflex stimulation therapy.

The challenge of comorbidities in baroreflex activation therapy candidacy

Comorbidities are common in advanced heart failure[43] including diabetes,[44] chronic kidney disease,[45] respiratory sleep disorders,[46] and chronic obstructive pulmonary diseases.[47] Relevant to this is the evidence that obstructive sleep apnea independently induces sympathetic system activation which may contribute to heart failure progression.[48]

Table 3 Interagency Registry of Mechanically Assisted Circulatory Support: profiles for patient selection

Possible profile modifiers

Profile	Description	Temporary circulatory support	Arrhythmia	Frequent flyer[a]
1.	Critical cardiogenic shock	X	X	
2.	Progressive decline on inotropic support	X	X	
3.	Stable, but inotrope dependent	X (In-hospital)	X	X (if home)
4.	Resting symptoms home on oral therapy		X	X
5.	Exertion intolerant		X	X
6.	Exertion limited		X	X
7.	Advanced NYHA[b]		X	X
	Class III symptoms			

The heart failure patients 'failing' guideline-directed medical therapy may be grouped into seven general profiles, according to Interagency Registry of Mechanically Assisted Circulatory Patient profile 6 describes patients who are comfortable at rest but have significantly limited tolerance in daily activity because of the persistence of fluid retention. Patient profile 7 is consistent with heart failure patients with advanced disease that achieved acceptable compensation with stable renal function after repeated heart failure hospitalizations. The heart failure patients presenting a disease status consistent with profiles 6 and 7 are likely good candidates for baroreflex activation therapy. [a] Frequent flyers refers to patients needing frequent hospital or emergency department admissions for worsening heart failure symptoms. [b] NYHA, New York Heart Association Classification.Reproduced with permission.[42]

Among patients with many comorbidities, it may be difficult to judge which subgroup will have a net benefit from BAT. The extent of symptoms in such patients might relate more to the number of comorbidities than to heart failure itself. In such patient groups, a theoretical rationale might exist to quantify baroreflex impairment with a clinical test such as the phenylephrine test.

Many therapies may become less effective in highly diseased subpopulations, and BAT is not an exception. Patients with end-stage or unstable heart failure may be in an irreversible disease state such that BAT cannot contribute a beneficial treatment effect. Thus, patients with permanent NYHA class IV heart failure symptoms, with acute pulmonary edema or who need IV inotrope therapy are not ideal candidates for BAT. In addition, patients not yet on optimal drug and device therapy, and patients in the first few months after acute coronary syndrome or CRT where favorable remodeling may be occurring do not represent the target population at this moment but may become so in the future, once optimization of BAT is attained. Early use of BAT might indeed be superior to current therapies, because of its direct neural action in preventing negative LV remodeling during the progression of ischemic heart disease. Other groups who are not ideal candidates for BAT include those developing hypotensive intolerance to neurohormonal drugs such as β-blockers[49] and those with accelerated renal impairment.[50]

These patients may have developed irreversible deterioration and may need advanced heart failure therapies (i.e. mechanical circulatory support or cardiac transplantation) rather than BAT.

Patients with baroreflex dysfunction or autonomic neuropathy may have little chance to benefit from BAT. Implantation may be complex in patients with prior surgery, radiation, or endovascular stent placement in the carotid sinus region, which may limit the ability to place the carotid sinus lead. The likelihood of benefit may be small when symptoms are driven by serious comorbidities, such as severe asthma, chronic lung disease, or active malignancy.

For effective vagal activation, BAT should be implemented after euvolemic status has been achieved because, while central venous pressure remains elevated, the venous backpressure raises renal intraparenchymal pressure that hydrostatically elevates tension in the glomerulus, which in turn, raises sympathetic tone[51] at a point in the signaling pathway too distal for BAT to alleviate. A decision making chart for current eligibility for BAT is depicted in Fig. 3.

Future neurostimulation heart failure trials

The future of BAT and VNS is dependent on demonstrating solid clinical evidence of effectiveness in symptomatic NYHA class III heart failure with reduced ejection fraction (HFrEF) patients on appropriate heart failure guideline-directed therapy. The Barostim therapy for heart failure (BeAT-heart failure) trial is ongoing, randomizing patients in a 1 : 1 ratio to BAT or no BAT. The primary efficacy endpoint is cardiovascular mortality

Fig. 3
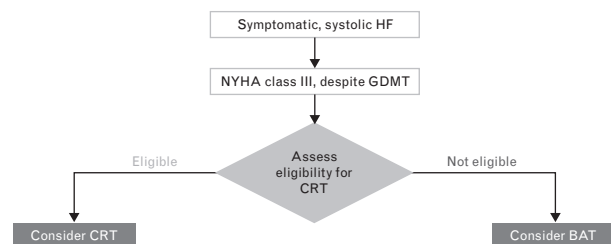
Decision making chart of eligibility for baroreflex activation therapy in patients displaying HF progression. BAT, baroreflex activation therapy; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; NYHA, New York Heart Association.

or worsening heart failure requiring hospitalization, a cardiac assist device, or a heart transplant.

The BeAT-heart failure trial began in April 2016 and is expected to close in 2021 (ClinicalTrials.Gov Identifier: NCT02627196). Should the BeAT-heart failure trial establish safety and efficacy of BAT in HFrEF, it will then be logical to study BAT in the HFpEF population in light of its efficacy in resistant hypertension.[33,34]

A conclusive take home message is that the current medical approach to heart failure has resulted in prolonged survival for patients by antagonizing the negative end-organ consequences of autonomic activation. Neural stimulation acting directly at the core of the autonomic storm might overcome the limits of currently available therapies, especially if initiated as early as possible. In this way, autonomic modulation may open new treatment opportunities for heart failure patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1   Yao Y, Zhang D, Qian J, et al. The effect of renal denervation on resistant hypertension: meta-analysis of randomized controlled clinical trials. *Clin Exp Hypertens* 2016; **38**:278–286.

2   Smith S, Rossignol P, Willis S, et al. Neural modulation for hypertension and heart failure. *Int J Cardiol* 2016; **214**:320–330.

3   Schwartz PJ, De Ferrari GM, Sanzo A, et al. Long term vagal stimulation in patients with advanced heart failure: first experience in man. *Eur J Heart Fail* 2008; **10**:884–891.

4   De Ferrari GM, Crijns HJ, Borggrefe M, et al., CardioFit Multicenter Trial Investigators. Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. *Eur Heart J* 2011; **32**:847–855.

5   Premchand RK, Sharma K, Mittal S, et al. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial. *J Card Fail* 2014; **20**:808–816.

6   Zannad F, De Ferrari GM, Tuinenburg AE, et al. Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the neural cardiac therapy for heart failure (NECTAR-HF) randomized controlled trial. *Eur Heart J* 2015; **36**:425–433.

7   Barsheshet A, Moss AJ, Eldar M, et al. Time-dependent benefit of preventive cardiac resynchronization therapy after myocardial infarction. *Eur Heart J* 2011; **32**:1614–1621.

8   Jain P, Massie BM, Gattis WA, et al. Current medical treatment for the exacerbation of chronic heart failure resulting in hospitalization. *Am Heart J* 2003; **145 (2 Suppl)**:S3–S17.

9   Neuberg GW, Miller AB, O'Connor CM, et al., PRAISE Investigators Prospective Randomized Amlodipine Survival Evaluation. Diuretic resistance predicts mortality in patients with advanced heart failure. *Am Heart J* 2002; **144**:31–38.

10 Schwartz PJ, Priori SG, Cerrone M, et al. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long-QT syndrome. *Circulation* 2004; **109**:1826–1833.

11 De Ferrari GM, Dusi V, Spazzolini C, et al. Clinical management of catecholaminergic polymorphic ventricular tachycardia: the role of left cardiac sympathetic denervation. *Circulation* 2015; **131**:2185–2193.

12 Schwartz PJ, Vanoli E, Stramba-Badiale M, et al. Autonomic mechanisms and sudden death. New insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. *Circulation* 1988; **78**:969–979.

13 La Rovere MT, Pinna GD, Hohnloser SH, et al., ATRAMI Investigators. Autonomic Tone and Reflexes After Myocardial Infarcton. Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials. *Circulation* 2001; **103**:2072–2077.

14 La Rovere MT, Pinna GD, Maestri R, et al. Prognostic implications of baroreflex sensitivity in heart failure patients in the beta-blocking era. *J Am Coll Cardiol* 2009; **53**:193–199.

15 Fukuda H, Kanazawa H, Aizawa Y, et al. Cardiac innervation and sudden cardiac death. *Circ Res* 2015; **116**:2005–2019.

16 Tracy KJ. The inflammatory reflex. *Nature* 2002; **420**:853–859.

17 Calvillo L, Vanoli E, Andreoli E, et al. Vagal stimulation, through its nicotinic action, limits infarct size and the inflammatory response to myocardial ischemia and reperfusion. *J Cardiovasc Pharmacol* 2011; **58**:500–507.

18 Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. *J Am Coll Cardiol* 2009; **54**:375–385.

19 Jackson CE, Castagno D, Maggioni AP, et al., Meta-Analysis Global Group in Chronic Heart Failure MAGGIC. Differing prognostic value of pulse pressure in patients with heart failure with reduced or preserved ejection fraction: results from the MAGGIC individual patient meta-analysis. *Eur Heart J* 2015; **36**:1106–1114.

20 Camm AJ, Savelieva I. Vagal nerve stimulation in heart failure. *Eur Heart J* 2015; **36**:404–406.

21 Gold MR, Van Veldhuisen DJ, Hauptman PJ, et al. Vagus nerve stimulation for the treatment of heart failure: the INOVATE-HF trial. *J Am Coll Cardiol* 2016; **68**:149–158.

22 Gronda E, Vanoli E, Lovett E. Baroreflex activation therapy: a new avenue for heart failure treatment. *Clin Trials Regul Sci Cardiol* 2016; **13**:34–36.

23 Ardell JL, Rajendran PS, Nier HA, et al. Central-peripheral neural network interactions evoked by vagus nerve stimulation: functional consequences on control of cardiac function. *Am J Physiol Heart Circ Physiol* 2015; **309**:H1740–H1752.

24 Schwartz PJ, Pagani M, Lombardi F, et al. A cardiocardiac sympathovagal reflex in the cat. *Circ Res* 1973; **32**:215–220.

25 Gronda E, Seravalle G, Brambilla G, et al. Chronic baroreflex activation effects on sympathetic nerve traffic, baroreflex function, and cardiac haemodynamics in heart failure: a proof-of-concept study. *Eur J Heart Fail* 2014; **16**:977–983.

26 Gronda E, Seravalle G, Trevano FQ, et al. Long-term chronic baroreflex activation: persistent efficacy in patients with heart failure and reduced ejection fraction. *J Hypertens* 2015; **33**:1704–1708.

27 Abraham WT, Zile MR, Weaver FA, et al. Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction. *JACC Heart Fail* 2015; **3**:487–496.

28 Bristow MR, Saxon LA, Boehmer J, et al., Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; **350**:2140–2150.

29 Asanoi H, Sasayama S, Kameyama T. Ventriculoarterial coupling in normal and failing heart in humans. *Circ Res* 1989; **65**:483–493.

30 Mancia G, Seravalle G, Giannattasio C, et al. Reflex cardiovascular control in congestive heart failure. *Am J Cardiol* 1992; **69**:17G–22G.

31 Grassi G, Seravalle G, Cattaneo BM, et al. Sympathetic activation and loss of reflex sympathetic control in mild congestive heart failure. *Circulation* 1995; **92**:3206–3211.

32 Rouleau JL, Roecker EB, Tendera M, et al., Carvedilol Prospective Randomized Cumulative Survival Study Group. Influence of pretreatment systolic blood pressure on the effect of carvedilol in patients with severe chronic heart failure: the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. *J Am Coll Cardiol* 2004; **43**:1423–1429.

33 Bisognano JD, Bakris G, Nadim MK, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled rheos pivotal trial. *J Am Coll Cardiol* 2011; **58**:765–773.

34 Bisognano JD, Kaufman CL, Bach DS, et al., DEBuT-HT and Rheos Feasibility Trial Investigators. Improved cardiac structure and function with chronic treatment using an implantable device in resistant hypertension: results from European and United States trials of the Rheos system. *J Am Coll Cardiol* 2011; **57**:1787–1788.

35 Zile MR, Abraham WT, Weaver FA, et al. 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. *Eur J Heart Fail* 2015; **17**:1066–1074.

36 Mortara A, Vanoli E. Baroreceptor activation therapy: the importance of targeting the right patient: who needs to be treated? *Eur J Heart Fail* 2015; **17**:1000–1002.

37 Mortara A, La Rovere MT, Pinna GD, *et al.* Arterial baroreflex modulation of heart rate in chronic heart failure: clinical and hemodynamic correlates and prognostic implications. *Circulation* 1997; **96**:3450–3458.

38 Petersson M, Friberg P, Eisenhofer G, *et al.* Long-term outcome in relation to renal sympathetic activity in patients with chronic heart failure. *Eur Heart J* 2005; **26**:906–913.

39 Galiwango PJ, McReynolds A, Ivano J, *et al.* Activity with ambulation attenuates diuretic responsiveness in chronic heart failure. *J Card Fail* 2011; **17**:797–803.

40 Levy WC, Mozaffarian D, Linker DT, *et al.* The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation* 2006; **113**:1424–1433.

41 Bello NA, Claggett B, Desai AS, *et al.* Influence of previous heart failure hospitalization on cardiovascular events in patients with reduced and preserved ejection fraction. *Circ Heart Fail* 2014; **7**:590–595.

42 Stevenson LW, Pagani FD, Young JB, *et al.* INTERMACS profiles of advanced heart failure: the current picture. *J Heart Lung Transplant* 2009; **28**:535–541.

43 Adler ED, Goldfinger JZ, Kalman J, *et al.* Palliative care in the treatment of advanced heart failure. *Circulation* 2009; **120**:2597–2606.

44 Nichols GA, Gullion CM, Koro CE, *et al.* The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care* 2004; **27**:1879–1884.

45 Schrier RW. Role of diminished renal function in cardiovascular mortality: marker or pathogenetic factor? *J Am Coll Cardiol* 2006; **47**:1–8.

46 Javaheri S, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. *J Am Coll Cardiol* 2007; **49**: 2028–2034.

47 Griffo R, Spanevello A, Temporelli PL, *et al.*, SUSPIRIUM Investigators. Frequent coexistence of chronic heart failure and chronic obstructive pulmonary disease in respiratory and cardiac outpatients: evidence from SUSPIRIUM, a multicentre Italian survey. *Eur J Prev Cardiol* 2017; **24**:567–576.

48 Bradley TD, Tkacova R, Hall MJ, *et al.* Augmented sympathetic neural response to simulated obstructive sleep apnoea in human heart failure. *Clin Sci (Lond)* 2003; **104**:231–238.

49 Macdonald PS, Keogh AM, Aboyoun CL, *et al.* Tolerability and efficacy of carvedilol in patients with New York Heart Association class IV heart failure. *J Am Coll Cardiol* 1999; **33**:924–931.

50 Schrier RW, De Wardener HE. Tubular reabsorption of sodium ion: influence of factors other than aldosterone and glomerular filtration rate.2. *N Engl J Med* 1971; **285**:1292–1303.

51 Kostreva DR, Seagard JL, Castaner A, Kampine JP. Reflex effects of renal afferents on the heart and kidney. *Am J Physiol* 1981; **241**:R286–R292.