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Neuromodulation devices for heart failure

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Autonomic imbalance with a sympathetic dominance is acknowledged to be a critical determinant of the pathophysiology of chronic heart failure with reduced ejection fraction (HFrEF), regardless of the etiology. Consequently, therapeutic interventions directly targeting the cardiac autonomic nervous system, generally referred to as neuromodulation strategies, have gained increasing interest and have been intensively studied at both the pre-clinical level and the clinical level. This review will focus on device-based neuromodulation in the setting of HFrEF. It will first provide some general principles about electrical neuromodulation and discuss specifically the complex issue of dose-response with this therapeutic approach. The paper will thereafter summarize the rationale, the pre-clinical and the clinical data, as well as the future prospectives of the three most studied form of device-based neuromodulation in HFrEF. These include cervical vagal nerve stimulation (cVNS), baroreflex activation therapy (BAT), and spinal cord stimulation (SCS). BAT has been approved by the Food and Drug Administration for use in patients with HfrEF, while the other two approaches are still considered investigational; VNS is currently being investigated in a large phase III Study.

Introduction

In the last decades, a consistent body of pre-clinical as well as clinical evidence, clearly demonstrated that sympathetic overactivation, always combined to different degrees of vagal withdrawn, plays a major role in the pathophysiology of chronic heart failure (HF) with reduced ejection fraction (HFrEF), regardless of the aetiology.[1] As a logical consequence, unravelling invasive and even better non-invasive markers of this autonomic imbalance, as well as therapeutic interventions aimed at reducing and potentially correcting it, have become a main goal in experimental and clinical HFrEF research. Interventions directly targeting the autonomic nervous system (ANS) are generally referred to as neuromodulation or autonomic regulation therapy (ART). ART can be either performed using pharmacological or surgical interventions that directly target the ANS, or using electrical devices aimed at modulating the autonomic balance by means of the direct delivery of electrical energy to affect neural processes (neuronal stimulation or inhibition, or a combination of both). The possibility of treating diseases through electrical neuromodulation has led to a new area of therapeutic treatment, known as electroceuticals or bio-electronic medicine[2] (*Figure 1*). This review will focus on the three most studied device-based ART modalities in the setting of HFrEF: cervical vagal nerve stimulation (cVNS), baroreflex activation therapy (BAT), and spinal cord stimulation (SCS).

Principles of electrical neuromodulation: the dose-response issue

The two essential components of an electrical neuromodulation system are the generator of the electrical current and the electrode (or the electrodes) that delivers

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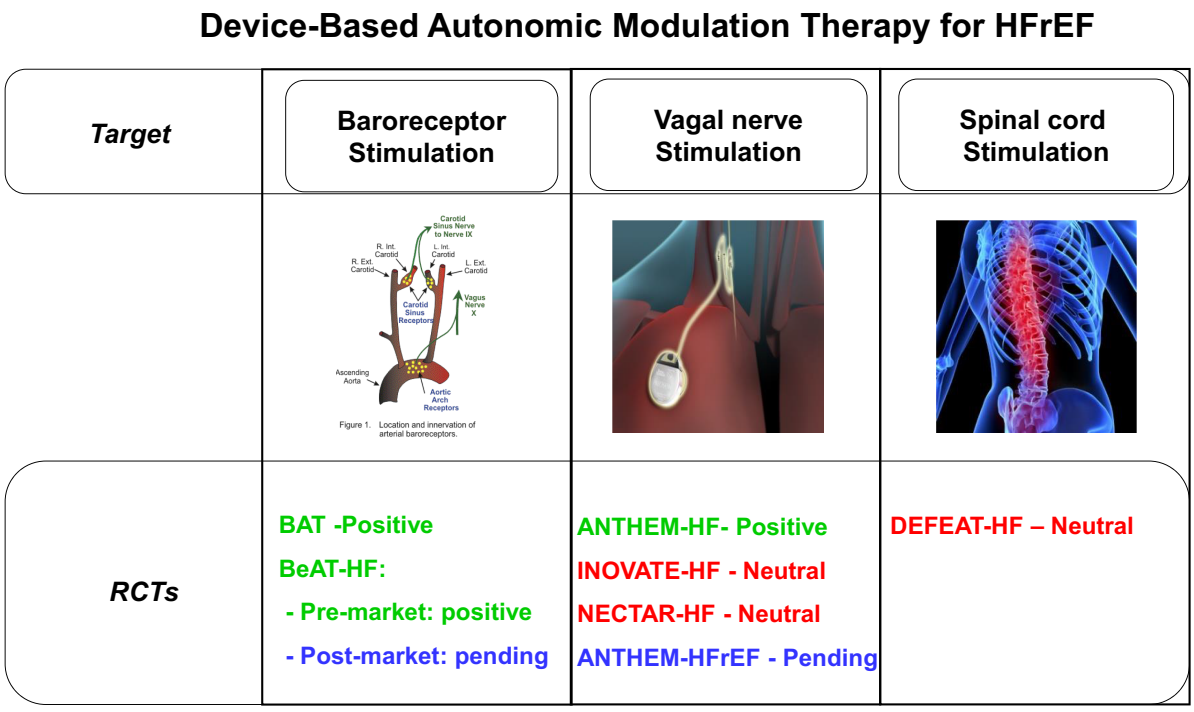


Figure 1 Device-based autonomic modulation (electroceutical) therapy for heart failure and a reduced ejection fraction. RCTs, randomized clinical trials.

Table 1 Parameters that can be modified in the setting of electrical neuromodulation

Electrodes and current-related parameters	Stimulation modalities related parameters	For closed loop systems: safety parameters
Electrode and waveform configuration	Right vs. left vs. bilateral stimulation	Limits for stimulation withdrawal (e.g. low heart rate)
Current amplitude, frequency, and duty cycle (duration on the on/off cycles)	Bidirectional efferent and afferent (technically easier) vs. preferential efferent or preferential afferent stimulation (technically more complex) Continuous stimulation vs. respiratory and/or pulse-synchronous stimulation With pulse-synchronous stimulation: delay from the R-wave (or other trigger) and number of pulses per cycle Open-loop vs. closed loop stimulation Titration protocols	

Modified from De Ferrari GM. Vagal stimulation in heart failure. *J Cardiovasc Transl Res* 2014;7(3):310–320. doi:10.1007/s12265-014-9540-1.[4]

the current to the target. A first important distinction is between open-loop and closed loop systems. In open-loop systems, the stimulation protocol is intrinsically independent on the evoked biological response and/or the biological demand, although some kind of 'adaptation' can be implemented, for instance by progressively modifying some parameters over time based on pre-acquired knowledge of the physiological responses to electrical neuronal stimulation and/or by programming a pre-defined response to an external input. In closed loop systems, at least one biomarker is continuously monitored, and algorithms can be implemented to decide the timing (when) and the strength (how much) of the electrical stimulation, while monitoring the marker of interest. The latter are conceived to mimic, albeit with an obviously minor degree of integration, the principle of functioning of an animal or human feedback neuronal network, including biomarkers, sensors, and data-processing algorithms. Conventional biomarkers for closed loop neuromodulation include electrical neural signals and non-neuronal biomarkers such as electrocardiography (ECG). Recently, closed loop implantable therapeutic neuromodulation systems based on

neurochemical monitoring have also been developed outside the cardiovascular arena.[3]

The concept of 'dose' for electrical therapies is by far more complex than for pharmacological therapies, since there are more than 10 different parameters that can be modified simultaneously (also depending on the specific type of stimulation), with hundreds of possible combinations. *Table 1* summarizes the most relevant. For simplicity purposes, these parameters can be divided into electrode and current-related parameters, stimulation modality-related parameters, and safety parameters (namely parameters used in closed loop systems to actively and continuously modify the stimulation modality according to the response).

Such complexity reflects the highly integrated and extremely dynamic behaviour of the therapeutic target, namely the ANS, both in physiological and in pathological conditions, that is still far from being completely unravelled.[5] A huge amount of pre-clinical and clinical studies with hundreds of subjects would be required to address the issue of the most suitable stimulation protocol in different settings, with obvious ethical concerns. Computational model strategies combined to artificial intelligence techniques are expected to complement the classical translational approach based on animal models and provide an important drive in the clinical implementation of electrical neuromodulation in the next future.[6] Indeed, the final biological response to electrical neuromodulation reflects our capability to comprehend and to modify, the outcome of advanced mathematical operations performed by complex neuronal networks. These operations can be simulated through the implementation of artificial representations of neuronal networks and of their interactions with neuromodulation technologies. This kind of approach has already been implemented, for instance, to unravel the interactions between SCS and the dynamics of spinal circuits for the design of the most suitable stimulation protocol to reduce chronic pain[7] and to improve motor control in people with spinal cord injury.[8] Computational modelling has also been successfully used in the field of deep brain stimulation.[9]

At present, clinical use and technological innovations, such as novel waveforms, advanced stimulator capabilities and lead designs, largely outrun our scientific understanding of the dose-response relationship of this therapeutic option, as will become clear in the text sessions.

Cervical vagal nerve stimulation

The vagus nerve (VN) contains approximately 80% of afferent and 20% of efferent neuronal projections. The latter are pre-ganglionic fibres directed towards post-ganglionic neuronal stations embedded within several peripheral organs in addition to the heart, including upper and lower respiratory organs, gastrointestinal organs, and ovaries. The spectrum of VN fibres, classified according to diameter and conduction velocity, ranges from Aα, the largest and fastest, to unmyelinated C-fibres, the smallest and slowest. Cardiac vagal control in mammalians relies on B-type (efferent) and C-type fibres (afferent and efferent). Notably, the distribution of the right and left VN fibres on post-ganglionic parasympathetic neurons located within epicardial fat pads is not symmetrical: the right VN has a larger influence on the sinus node activity, whereas the left VN has a predominant control over the atrioventricular node function. Both affect atrial and ventricular cardiomyocytes.

Most of pre-clinical evidence suggests an organotopic or function-specific organization of neural fibres within the VN.[10] Several factors affect neuronal fibres engagement during electrical stimulation, including distance from the stimulation electrode, local electric field strength, and fibre diameter—with A-fibres being recruited first and C-fibres last. Accordingly, the possibility of achieving a selective VNS to limit off targets' side effect while increasing the effective dose to the therapeutic target (e.g. cardiac fibres) has been extensively studied in recent years.[11] Several key paradigms have been developed including spatial selectivity, fibre selectivity, anodal block, neural titration, and kilohertz electrical stimulation block, as well as various stimulation pulse parameters and electrode array geometries.[12] Recently direct neuronal recordings of VN activity in humans using ultrasound-guided microneurography have been performed.[13]

Historically, cVNS was first studied as an antiarrhythmic intervention. More than 100 years after the landmark observation of Einbrodt on the protective effect of VNS from the deadly effects of direct electrical current delivery to the heart, several studies in anaesthetized animals described the antiarrhythmic effect of cVNS during acute myocardial ischaemia.[14-17] The conclusive demonstration came in 1991 from a conscious canine model of sudden death during acute myocardial ischaemia; approximately 50% of the anti-fibrillatory effect of right cVNS was related to heart rate (HR) reduction,[18] suggesting the existence of other protective pathways. Vagal nerve stimulation exerts anti-apoptotic effects through the same protective pathways of ischaemic pre-conditioning,[19-21] and anti-inflammatory effects through the cholinergic anti-inflammatory pathway, a neural mechanism inhibiting pro-inflammatory cytokine release through the activation of cholinergic nicotinic receptors on macrophages and other immunocompetent cells. This mechanism was first described by Tracey at hepatic level,[22] and then confirmed at cardiac level, where nicotinic receptors were proved to be crucial for the HR-independent protective effect of cVNS leading to infarct size reduction in ischaemia/reperfusion rat models.[23]

The first experimental data on the efficacy of chronic cVNS in HFrEF were reported in 2004.[24] Rats with a previous 14-day-old large anterior myocardial infarction (MI) leading to HFrEF were randomized to sham stimulation or active cVNS (10 s on/50 s off), at 20 Hz, with 0.2 ms pulses. A 20–30 b.p.m. HR reduction (starting value around 360 b.p.m.) was used as target to adjust cVNS stimulation amplitude. A 6-week therapy duration significantly improved LV function, biventricular weight, norepinephrine and B-type natriuretic peptide (BNP)

Table 2 Study comparison: trial characteristics and stimulation protocols of the main cervical vagal nerve stimulation, baroreflex activation therapy, and spinal cord stimulation studies

Parameter	CARDIOFIT (2011)	ANTHEM-HF (2014)	NECTAR-HF (2014)	INOVATE-HF (2016)	ANTHEM-HFrEF Pivotal Study (ongoing)	BAT (2015)	BeAT-HF (2020)	SCS HEART (2015)	DEFEAT-HF (2016)
Trial characteristics									
Phase	I and II	I and II	II	III	III	II	III	I and II	II
Stimulation side	R	R vs. L	R	R	R	R	R	Spinal cord	Spinal cord
Control group	None	R vs. L	Stimulation off	GDMT	GDMT	GDMT	GDMT	Patients not fulfilling inclusion criteria	Stimulation off
Primary endpoint	Safety	LVESV; LVESD, LVEF	LVESD	Composite of death and HF hospitalization	Composite of cardiovascular death, or first HF hospitalization	Efficacy: changes in NYHA class, QoL score, and 6MWT. Safety: system- and procedure-related MANCE	Efficacy: change from baseline to 6 months in 6MWT, QoL, NT-proBNP levels. Safety: system- and procedure-related MANCE	Safety	LVESVi
Exclusion criteria for diabetic patients	Insulin-dependent diabetes mellitus or diabetic neuropathy	Autonomic or sensory neuropathy of any cause; HbA1C>8% in the past 60 days	Type I diabetes, Type II diabetes for over 5 years	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
NYHA Class	II-IV	II and III	II and III	III	III stable-II unstable	III	III stable-II unstable	III	III
LVEF, LVEDD	≤35%	≤40%, LVEDD 50-80 mm	≤35%, LVEDD > 55 mm	≤40%, LVEDD 50-80 mm	≤35%, LVEDD < 80 mm	≤35%	≤35%	20–35%	≤35%, LVEDD 55-80 mm
Rhythm, QRS duration (ms)	SR, QRS NA	SR, QRS ≤150	SR, QRS <130	SR, QRS NA	Both SR an AF, QRS not specified	Both SR an AF/AFL, QRS not specified	Both SR an AF/AFL, QRS not specified	SR or not persistent AF, QRS NA	Not specified, QRS < 120 ms
NT-proBNP levels (pg/mL)	Not specified	Not specified	Not specified	Not specified	≥800 for patients in SR ≥1200 for patients in AF	Not specified	Not specified	Not specified	Not specified
6MWT (m)	>300	150-425	Not specified	Not specified	150-450	150-450	150-450	Not specified	Not specified
Stimulation protocols									
Implantable pulse generator	CardioFit, BioControl Medical	Cyberonic IPG: Model 103	Precision, Boston Scientific	CardioFit, BioControl Medical	VITARIA System (LivaNova)	BAROSTIM NEO System, CVRx	BAROSTIM NEO System, CVRx	Eon Mini Neurostimulation System, St Jude Medical	Medtronic Prime ADVANCED Neurostimulator Model 37702
Electrode lead	Asymmetric bipolar multi-contact cuff	Helical bipolar	Helical bipolar	Asymmetric bipolar multi-contact cuff	Helical bipolar	Oxide-coated platinum-iridium disk electrode	Oxide-coated platinum-iridium disk electrode	Octrode percutaneous leads (eight electrodes each, St Jude Medical)	Medtronic Model 3777/3877
Asymmetric stimulation	Yes (afferent block above 4 mA)	No	No	Yes (afferent block above 4 mA)	No	Not applicable	Not applicable	Not applicable	Not applicable
ECG Synch[a]	Yes	No	No	Yes	No	No	No	No	No
Current amplitude (mA)	4.1 ± 1.2 (range 1.1-5.5)	2.0 ± 0.6 (maximum 3)	1.3 ± 0.8 (range 0.3-3.5)	3.9 ± 1.0 mA at 6 months target 3.5-5.5	NA	6.8 ± 2.4	8.3 ± 2.4	1-15 mA	90% of paraesthesia threshold
Frequency (Hz)	1-3	10	20	1-2	NA	61.9 ± 20.8	43.6 ± 12.2	50 Hz	50 Hz
Duty cycle (%)	21	17.5	17	≤ 25%	NA	Not applicable	Not applicable	Not applicable	Not applicable
On/off (s)	Variable	14/66	10/50	Variable	NA	Not applicable	Not applicable	1440/0	720/720

SCS HEART, Thoracic Spinal Cord Stimulation for Heart Failure as a Restorative Treatment. Modified from Dusi V, De Ferrari GM. Vagal stimulation in heart failure. *Herz* 2021;46(6):541-549.[29]

AF, atrial fibrillation; ANTHEM-HF, Autonomic Regulation Therapy via Left or Right Cervical Vagus Nerve Stimulation in Patients With Chronic Heart Failure; ANTHEM-HFrEF, Autonomic Regulation Therapy to Enhance Myocardial Function and Reduce Progression of Heart Failure with Reduced Ejection Fraction; BAT, baroreflex activation therapy; BeAT-HF, Baroreflex Activation Therapy for Heart Failure; DEFEAT-HF, Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure; GDMT, guideline-directed medical treatment; HF, heart failure; INOVATE-HF, Increase of Vagal Tone in Heart Failure; L, left; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MANCE: system- and procedure-related major adverse neurological and cardiovascular events, 6-MWT, 6-min walking test, NA, not available; NECTAR-HF, Neural Cardiac Therapy for Heart Failure; NYHA, New York Heart Association class; R, right, S, sinus rhythm, SCS, spinal cord stimulation.

[a]Synch, synchronization.

Table 3 Studies comparison: basal characteristics and 6 months results of the main cervical vagal nerve stimulation, baroreflex activation therapy, and spinal cord stimulation studies

Parameter	CARDIOFIT (2011)	ANTHEM-HF (2014)	NECTAR-HF (2014)	INOVATE-HF (2016)	BAT (2015)	BeAT-HF (2020)	SCS HEART[a] (2015)	DEFEAT-HF (2016)
Patients' characteristics								
No. of patients (male, %)	32 (30, 94)	60 (52, 87)	96, 87 paired	707 (558, 79)	140 (120, 86)	264 (211, 80)	17 (17, 100)	66 (52, 79)
Age (years)	56 ± 11	51 ± 12	59 ± 11	61 ± 10	65 ± 12	62 ± 11	63 ± 10	61 ± 12
Type II diabetes (%)	NA	NA	26	36	35	NA	47	NA
NYHA II/III/IV	47/47/6	57/43/0	16/84/0	0/100/0	1/99/0	6/94/0	0/100/0	0/100/0
Ischaemic HF (%)	62	75	67	60	67	NA	65	56
AF (%)	0	0	0	0	44	36	47	24
LVEF (%)	23 ± 8	32 ± 7	30 ± 6	25 ± 7	25 ± 7	27 ± 6	25 ± 6	29 ± 5
Basal LVESV	185 ± 63 mL	108 ± 40 mL	155 ± 58 mL	103 ± 41 mL/m^2	NA	NA	174 ± 57 mL	57 ± 17 mL/m^2
HR (b.p.m.)	82 ± 13	78 ± 10	69 ± 13	72 ± 12	74 ± 12	75 ± 11	NA	NA
ICD/CRT/none (%)	59/0/41	0/0/100	76/10/14	48/34/28	87/32/0	78/0/22	100/47/0	74/0/26
NT-proBNP (pg/mL)	1316 (227-1997)	868 (322-1875)	879 (370-1843)	NA	1422 (455-4559) BAT 1172 (548-2558) controls	743 (477-1031)	2364 ± 2303	NA
hsCRP (mg/dL)	NA	1.7 (0.9-6.0)	0.18 (0.10-0.36)	NA	NA	NA	NA	NA
BB (%)	97	100	94	94	86	95	88	96
ACEi/ARB (%)	97	85	ACEi 78, ARB 25	89	79	58	94	91
ARNI (%)	0	0	0	0	0	29	0	0
MRA (%)	97	75	70	58	54	45	41	NA
Digoxin (%)	28	32	NA	NA	16	16	29	NA
6-month results								
Δ Mean HR (Holter)	0	−3.9	+0.5	NA	NA	NA	NA	NA
Δ LVEF (%)	+6.4	+4.5	+0.9	0	+2.5 ($P = 0.15$)	NA	+12	NA
Δ LVESV (mL)	−25	−4.1	0	−3.7	NA but reported NS	NA	−37	+2.8
Δ QoL	−17 (MLHF)	−18 (MLHF)	−8 (MLHF)	+5 (KCCQ)	−20 (MLHF)	−14 (MLHF)	−15 (MLHF)	−12 (MLHF)
Δ NYHA increase (%)	59	77	17	13	55		77	58
Δ 6MWT (m)	+60	+56	pVO_2 + 0.7	+33	+58	+60	NA	+16
Δ NT-proBNP (pg/ml)	−594 ($P = 0.06$)	+140	+93	NA	NA	-25%	NS	-32 ± 994

Modified from Dusi V, De Ferrari GM. Vagal stimulation in heart failure. *Herz* 2021;46(6):541-549.

ACEi, angiotensin-converting-enzyme inhibitor; ANTHEM-HF, Autonomic Regulation Therapy via Left or Right Cervical Vagus Nerve Stimulation in Patients With Chronic Heart Failure; ANTHEM-HFrEF, Autonomic Regulation Therapy to Enhance Myocardial Function and Reduce Progression of Heart Failure with Reduced Ejection Fraction; ARB, angiotensin II receptor blocker; BAT, baroreflex activation therapy; BeAT-HF, Baroreflex Activation Therapy for Heart Failure; BB, beta-blocker; CRP, C-reactive protein; CRT, cardiac resynchronization therapy; DEFEAT-HF, Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure; HF, heart failure; ICD, implantable cardioverter defibrillator; INOVATE-HF, Increase of Vagal Tone in Heart Failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MLHF, Minnesota living with heart failure; 6-MWT, 6-min walking test; MRA, mineralocorticoid receptor antagonist; NA, not available; NECTAR-HF, Neural Cardiac Therapy for Heart Failure; NYHA, New York Heart Association class; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; NS, not significant.

[a]Data for the treated group.

levels, and survival compared with sham-operated animals. Subsequently, between 2005 and 2013, the effects of right cVNS were evaluated on a canine model of chronic HFrEF induced by coronary microembolizations.

In the first two studies,[25] right cVNS was delivered by a closed loop system, namely the CardioFit system, that uses an intracardiac sensing lead to synchronize the stimulation to the cardiac cycle and to modulate VNS intensity, targeted at 10% HR reduction during stimulation. Compared with sham-operation, 3 months of cVNS had a favourable effect on LV haemodynamics, tumour necrosis factor-α and interleukin-6 levels (reduced), nitric oxide synthase expression and Connexin 43 expression (increased), without affecting nerve structure. These favourable effects were additional to those achieved with metoprolol alone. In the third study,[26] the same group proved that the beneficial effects of cVNS were still significant when the stimulation was performed using a different, open-loop, cVNS system (Boston Scientific Corporation), with no acute impact on HR. Finally, cVNS (Cyberonics system, at 20 Hz) was also studied, in comparison with sham controls, in a canine model of 8 weeks high-rate ventricular pacing-induced HF, confirming previous findings. Vagal nerve stimulation intensity was adjusted before the beginning of pacing to reduce HR by ~20%.

Chronic left-sided (to avoid effects on HR) cVNS use was first reported in humans for the management of drug-refractory epilepsy,[27] obtaining Food and Drug Administration (FDA) approval in 1997, then for resistant depression,[28] with hundreds of thousands of devices implanted all over the word and a very good safety profile.

Table 2 lists the main clinical studies of cVNS (four published, one ongoing), BAT, and SCS in HFrEF, showing their main inclusion/exclusion criteria, their objectives, and their stimulation protocols. *Table 3* shows patients' characteristics and 6-month results of the same studies.

The first human single-centre study of right cVNS in HFrEF showed favourable results[30] and was extended to a multi-centre Phase II study, the European Multicentre CardioFit Study, including 32 patients with advanced HFrEF [New York Heart Association (NYHA) Classes II–IV, left ventricular ejection fraction (LVEF) $\leq$ 35%], and using the CardioFit 5000 device[31] already tested in animals, and including an intracardiac sensing lead sense to provide a pulse-synchronous (1–3 pulses per each cardiac cycle) cVNS. The electrode design aimed to achieve a preferential stimulation of efferent fibres, by means of anodal block and to minimize the off-target recruitment of A-type fibre by means of a multi-contact cuff design. Vagal nerve stimulation was delivered at 1–3 Hz, with 10 s on/30 s off, and an HR safety boundary (leading to temporary VNS stop) that was initially set at 55 b.p.m. Vagal nerve stimulation intensity was up titrated in five to six visits to reach a mean level of 4.1 $\pm$ 1.2 mA; a further increase was mostly limited by hoarseness and jaw pain. Notably, the acute on-phase HR lowering was modest (around 1.5 b.p.m.) but consistent across patients, with few exceptions showing as much as 10 b.p.m. acute decrease. At 6 months, HR from resting ECG decreased from 82 $\pm$ 13 to 76 $\pm$ 13 b.p.m., while data from 24-Holter ECG recording showed no changes in the mean HR, paired with a significant increase in heart rate variability (HRV) as assessed by pNN50. Notably, changes in time-domain HRV indices not associated with changes in mean HR are strongly suggestive of an improved cardiac vagal output, as opposed to changes in both parameters.[32,33] Accordingly, 6 months efficacy data showed a significant improvement in quality of life (QoL) scores, functional capacity, and LV volumes and function (LVEF from 22 $\pm$ 7 to 29 $\pm$ 8%), which were maintained at 1- and 2-year follow-up, with no major safety concerns.[34]

The Autonomic Regulation Therapy for the Improvement of Left Ventricular Function and Heart Failure Symptoms (ANTHEM-HF) study[35] compared right (n = 29) and left (n = 31) cVNSs performed using the open-loop cyberonics system, in a multi-centre, open-label, Phase II, randomized clinical trial with no control arm, performed in India and enrolling patient with an NYHA Classes II and III and LVEF $\leq$ 40%. None of the subjects had implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT). The stimulation system had already been approved for drug-refractory epilepsy. Vagal nerve stimulation was delivered at 10 Hz, with a 14 s on/66 s off stimulation protocol, using a vagal electrode not designed for asymmetric stimulation and reaching a mean output current of 2.0 $\pm$ 0.6 mA at the end of the 10-week up-titration period. At 6 months, a significant (+4.5% in absolute values) increase in LVEF was observed in the entire study population, combined to a non-significant decrease of left ventricular end-systolic volume (LVESV; co-primary endpoints) and a significant improvement in QoL, 6 min walking test (6MWT) and NYHA class; these effects were maintained at 12 months,[36] and until 42 months.[37] The benefit tended to be greater for right cVNS compared with left cVNS at 6 months, while no side differences were observed thereafter, although with the limitation of a smaller sample size. The long-lasting protective effects of cVNS were confirmed by the analysis of markers of autonomic tone (HRV) and reflexes (HR turbulence) and of cardiac electrical stability (T-wave alternans, R-wave, and T-wave heterogeneity) and by assessing the burden of non-sustained ventricular tachycardia episodes.[38] Interestingly, the beneficial effects of cVNS in ANTHEM-HF were found to be independent form baseline *N*-terminal pro-BNP (NT-proBNP) levels.[39]

The Neuronal Cardiac Therapy for Heart Failure (NECTAR-HF) study was a Phase II, multi-centre sham-controlled study enrolling 96 patients (NYHA Classes II and III, LVEF $\leq$ 35%) randomized 2:1 to active cVNS or sham treatment for the first 6 months; subsequently, cVNS was turned on in all patients.[40] Most (76%) had an ICD, 9% CRT. The stimulation system (Boston Scientific, MN, USA) provided an open-loop cVNS aiming at both central and peripheral targets and obtained through a rechargeable generator already approved for chronic pain therapy (Precision™) and an investigational helical bipolar vagal electrode relatively similar to that used in ANTHEM-HF. Stimulation was delivered at 20 Hz, and at the relatively low mean amplitude of 1.4 $\pm$ 0.8 mA.

Notably, the maximum tolerated current amplitude *in vivo* is inversely related to the pulse frequency,[41] explaining why in most of the patients in the NECTAR-HF cVNS up-titration was limited by off-target effects. Left ventricular end-systolic diameter (LVESD, primary efficacy endpoint) at 6 months was not changed, as well LVEDD, LVESV, LVEF, peak VO_2 at cardiopulmonary exercise test and NT-proBNP levels (all additional secondary endpoints), but a significant improvement in QoL and in NYHA class was observed. These findings were substantially confirmed at 18 months (with all patients on active cVNS), except for the QoL improvement, that was no longer observed. Mean HR at 24 h Holter ECG did not change, as well as standard deviation of the intervals between normal beats (SDNN) and root mean square of successive normal to nomal interval differences (RMSSD), while a slight improvement was observed in another time-domain marker of HRV, namely standard deviation of the average normal to normal intervals for each 5 minutes segment of a 24 hours HRV recording (SDANN). A subsequent subanalysis of the study, using tridimensional heat maps applied to 6 and 12 months 24 h Holter ECG, was able to detect subtle VNS-evoked HR changes only in 12% of the treated patients (vs. 0% in the sham arm),[42] suggesting less efferent fibre recruitment compared with pre-clinical studies using the same device, possibly related to the lower stimulation amplitude. Yet, a positive heat maps response was not associated with any difference in conventional measures of frequency and time-domain HR variability, further complicating the puzzle. Notably, most of the patients enrolled were able to properly guess their randomization group.

The largest clinical trial of cVNS in HFrEF completed so far is the Increase of Vagal Tone in Heart Failure (INOVATE-HF), a Phase III international, multi-centre, randomized trial assessing the efficacy and safety of right-sided cVNS with the CardioFit system[43] (*Figure 2*). A total of 707 patients (NYHA Class III, LVEF $\leq$40%) were enrolled, mostly in the USA, and 3:2 randomized to cVNS plus guideline directed medical therapy (GDMT) or continuation of GDMT alone. At baseline, a slightly lower LVEF in the cVNS arm was the only difference between the two groups. Most patients (88%) had a cardiac device, including 34% with CRT. A composite of all-cause mortality or unplanned HF hospitalization equivalent was used as primary efficacy endpoint, while 90 days freedom from procedure and system-related complications and number of patients with death for any cause or complications at 12 months were the two co-primary safety endpoints. The second interim analysis led to study discontinuation for futility in December 2015, after a mean follow-up of 16 months (range: 0.1–52). Mean current amplitude was 3.9 ± 1.0 mA, with 73% of patients achieving the goal of >3.5 mA. Among the secondary endpoints, LVESV index did not change, while QoL, NYHA class, and 6MWT significantly improved with cVNS. Age, 6MWT distance at baseline, HF aetiology, diabetes, and CRT were not found to affect the primary outcome in the subgroup analysis. Yet, in a post-hoc exploratory analysis of the INOVATE-HF restricted to patients with no CRT, a QRS interval duration <130 ms and a baseline ability to walk >300 m (the inclusion criteria used in CardioFit), showed a weak favourable trend vs. reverse LV remodelling.

Very recently, the symptomatic and functional responses to cVNS in the three completed randomized trial, namely the ANTHEM-HF (overall population), INOVATE-HF, and NECTAR-HF were compared in a post-hoc analysis.[44] SDNN, LVEF, and Minnesota living with HF mean scores at 6 months were significantly more improved in ANTHEM-HF compared with NECTAR-HF. Patients enrolled in the ANTHEM-HF also obtained a greater improvement in 6MWT compared with those of the INOVATE-HF.

Finally, based on the favourable results of the ANTHEM-HF, an open-label, randomized, study, the ANTHEM-HFrEF, is currently ongoing.[45] The study is randomizing patients with a 2:1 ratio to cVNS plus GDMT or GDMT alone, with an estimated completion date of December 2024. Stimulation is delivered using the VITARIA System (LivaNova) and according to the same stimulation principles of the ANTHEM-HF study, namely a closed loop afferent and efferent stimulation, not pursuing acute HR changes. The rationale for this kind of stimulation has been recently explored in a conscious canine model specifically assessing the contribution of afferent vs. efferent VN activation to the acute HR responses elicited during the active phase of chronic right VNS.[46] Based on frequency–amplitude–pulse width, the authors were able to identify an operating point, defined as the neuronal fulcrum, in which the HR response was null, transitioning from positive to negative. They also proved that only when the neuronal fulcrum constrains were implemented in the setting of chronic cVNS, the circadian control of HRV could be preserved. ANTHEM-HFrEF utilizes an innovative adaptive design as allowed by the new FDA breakthrough device programme: the primary outcome will be a composite of cardiovascular death, or first HF hospitalization traditionally assessed, yet the sample size determination will be performed using a Bayesian adaptive approach.

Baroreflex activation therapy

Arterial baroreceptors are stretch receptors that form a branching network in the adventitial–medial layers of the carotid sinus and the aortic arch walls.

Nerve impulses from baroreceptors are tonically active; increases in blood pressure (BP) lead to increased rate of impulse firing, increased stimulation of the nucleus tractus solitarius, and increased inhibition of the tonically active sympathetic outflow to the heart and peripheral vasculature. Decreased mean and pulsatile BP, lead to decreased nerve firing, reduced stimulation of the nucleus tractus solitarius, and reduced inhibition of sympathetic outflow, which is thus increased.

These inputs from baroreceptors are continuously integrated and balanced at the central level with afferent excitatory inputs from skeletal muscle, kidney, cardiac mechanoreceptors, and chemoreceptors, which inhibit vagal outflow and enhance sympathetic output. Even in advanced HFrEF, carotid baroreflex circuits are not

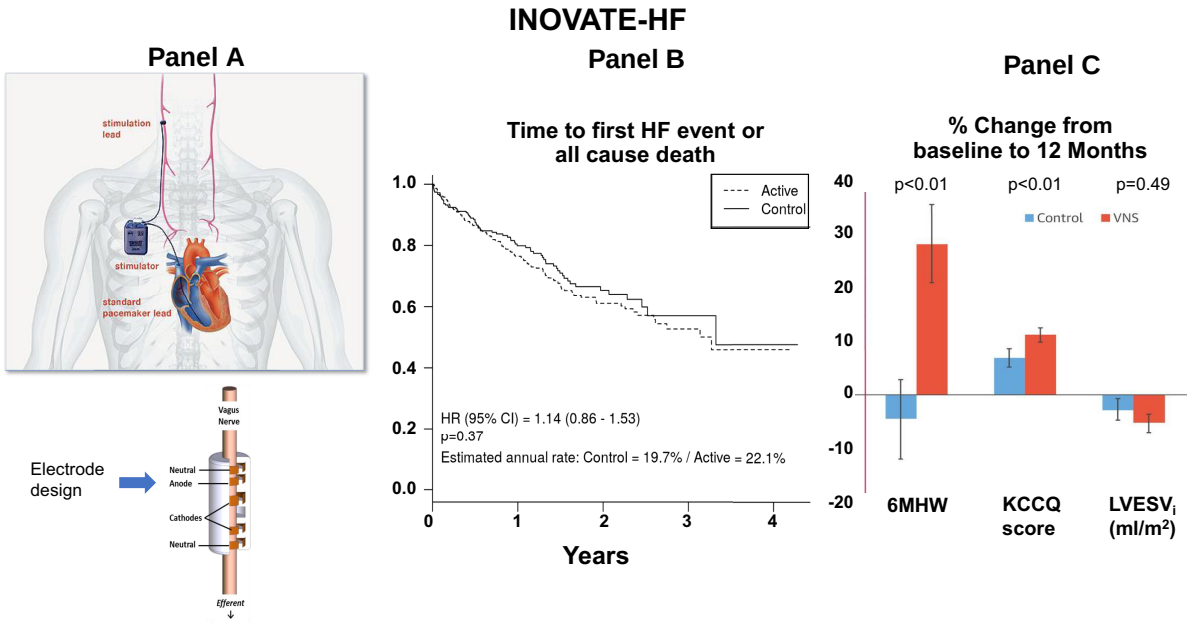


Figure 2 Summary of results from the INOVATE-HF study using vagal nerve stimulation. (*A*) Schematic showing the proposed neuromodulation pathways and the stimulation device design. (*B*) Kaplan-Meier curves plotting the time to first HF event or all-cause death in the control and treatment groups. Vagal nerve stimulation did not have a statistically significant effect. (*C*) Data examining change from baseline to 12 months in control group vs. treatment group. There was a significant treatment based increase in 6-min hall walk distance and Kansas city quality of life score but no significant change in left ventricular end-systolic volume index. LVESVi, left ventricular end-systolic volume index, KCCQ, Kansas city quality of life score; 6MHW, 6-min hall walk.

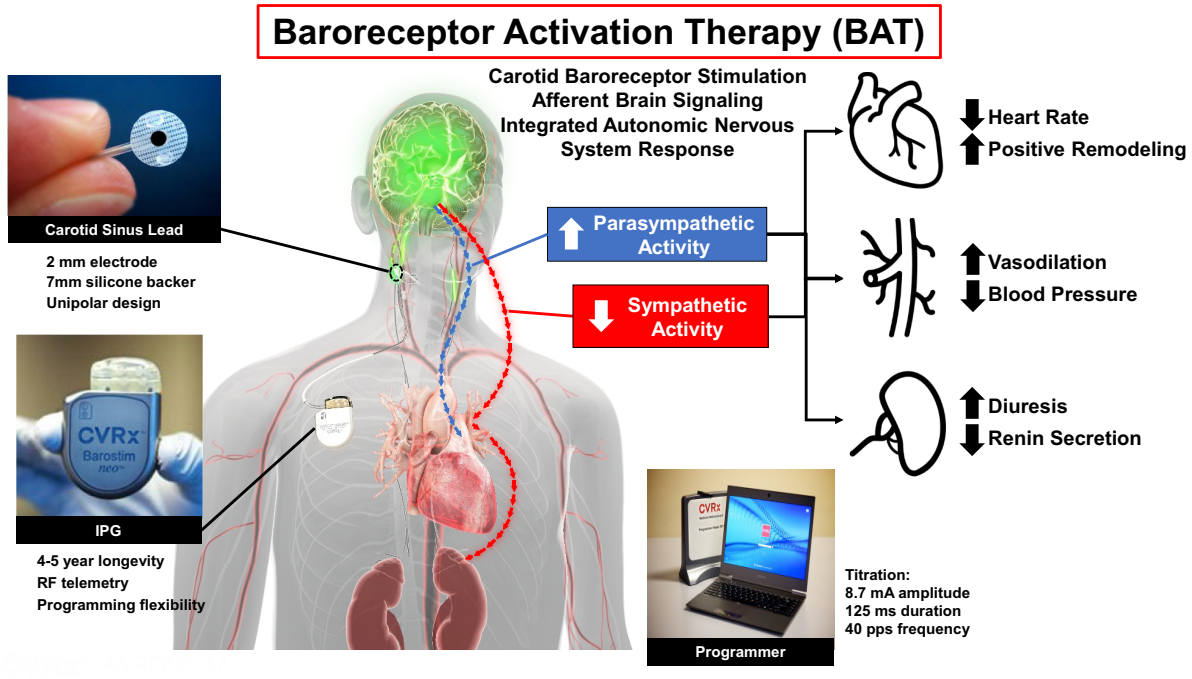


Figure 3 Schematic representation of the baroreceptor activation therapy device components and the mechanisms of action of baroreceptor activation therapy and their effects on advanced heart failure with a reduced ejection fraction-associated changes in autonomic function.

intrinsically malfunctioning.[47] After cardiac (and renal) damage, the autonomic balance shifts towards a sympathetic predominance due to the offset of the baroreflex control by increased afferent pathological signalling from the other receptors. The functional baroreceptor impairment can be further enhanced because of baroreceptor unloading in case of reduced cardiac output, concurring to support the strong rationale for BAT in

HFrEF. The BAT device components and the mechanisms of action of BAT and their effects on advanced HFrEF-associated changes in autonomic function are shown schematically in *Figure 3*.

The best location for the BAT electrode in the carotid sinus and the efficacy of stimulation are confirmed at the time of surgery by acute stimulation showing a BP and HR drop.

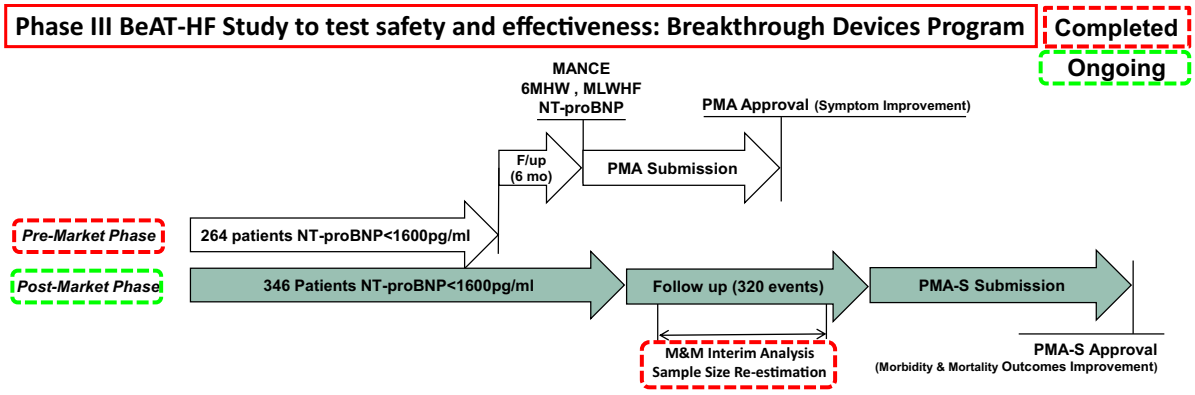
Chronic BAT proved to be very promising in animal models of HFrEF of different aetiologies. Zucker *et al.*[48] demonstrated for the first time in a canine model of pacing induced HFrEF, that continuous bilateral BAT (50–100 Hz, 0.5–1 ms^2, 2.5–7.5 V, duty cycle 90%) performed using the Rheos system (CVRx, Inc., Minneapolis, MN, USA) improved survival and suppressed neurohormonal activation as assessed by plasma norepinephrine and angiotensin II levels, despite ongoing pacing for the entire study length and no differences in arterial BP, resting HR, and LV pressure. Few years later, the group of Hani Sabbah showed in a canine model of coronary microembolization-induced HFrEF (mean LVEF around 25%) that chronic bilateral BAT using the same system and parameters, improved LV function and LV remodelling. It also reduced plasma norepinephrine levels, interstitial fibrosis, and cardiomyocyte hypertrophy and normalized expression of cardiac β_1-adrenergic receptors, β-adrenergic receptor kinase, and nitric oxide synthase.[49]

The first human study of chronic BAT in HFrEF was reported in 2014 as a single-centre, open-label experience, including 11 patients with advanced HF (67 ± 9 years, all in NYHA Class III, LVEF 31 ± 7%, 46% with chronic renal disease) despite optimized medical treatment, ineligible for CRT. Patients underwent unilateral BAT (right sided in 10 patients) for 6 months using the Barostim™ *neo*™ system (CVRx Inc.). The decision to perform unilateral rather than bilateral BAT was largely due to safety concerns based on previous clinical experience with bilateral BAT performed using the larger stimulating electrodes of the Rheos system in the setting of arterial hypertension.[50] Also, in patients with resistant hypertension unilateral and mostly right-sided BAT had a more profound effect on BP than bilateral or left-sided BAT.[51] In patients with HFrEF, a 30% drop in muscle sympathetic nerve activity (MSNA) was observed after only 3 months of BAT and was subsequently maintained at 6 months. Baroreflex sensitivity (BRS) also improved at 3 months, with a further increase at 6 months. MSNA reduction and BRS increase were accompanied by a significant improvement in NYHA class, QoL scores, and 6MWT, and by a consistent LV reverse remodelling, as assessed by 3D echocardiography, despite no changes in HR. These findings persisted after 21 months of follow-up and were associated with a significant reduction in hospitalizations and emergency department visits compared with the year before BAT.[52]

The efficacy and safety of BAT were then evaluated in a 1:1 randomized trial including 140 patients with NYHA Class III and LVEF ≤ 35%, (32% had a CRT), receiving GDMT alone or GDMT plus BAT performed using the CVRx Barostim Neo System.[53] Baroreflex activation therapy significantly improved NYHA class, QoL score, 6MWT (primary efficacy endpoints), and NT-proBNP and showed a trend toward fewer in-hospital days for HF. Notably, despite no evident changes in LVEF, BAT also significantly increased systolic BP and pulse pressure. A subsequent subanalysis of the study showed that the beneficial effects of BAT were more pronounced among patients with no CRT.[54] One proposed explanation for this phenomenon is that CRT, by improving electromechanical dyssynchrony, not only increases cardiac output, but also reduces abnormal afferent sympathetic signalling from both cardiac mechanoreceptors and carotid baroreceptors, therefore reducing sympathovagal imbalance and limiting the benefits of BAT.

Based on the favourable results of the previous trial, a larger randomized study including 408 patients, the Baroreflex Activation Therapy for Heart Failure (BeAT-HF) trial, was conducted, enrolling patients on GMDT for HFrEF for at least 4 weeks, with NYHA Class III or II (with recent deterioration in Class III), LVEF $\leq$ 35%, 6MWT between 150 and 400 m, and no Class I indication for CRT.[55] Patients were randomized 1:1 to receive either GMDT alone or GDMT plus unilateral BAT. The trial was designed in collaboration with the FDA breakthrough device programme and had a complex, interactive and adaptive design. The BeAT-HF study was divided into two phases: pre-market phase and post-market phase. The details and status of the BeAT-HF study are presented in *Figure 4*. In the completed pre-market phase, the population intended for use was represented by the 264 patients fulfilling the enrolment criteria plus NT-proBNP levels below 1600 pg/mL. In this group, a significant 6-month decrease of all the components of the primary efficacy endpoint (6MWT, NT-proBNP levels, and QoL) was observed, combined to a 97% free rate from major adverse neurological or cardiovascular system or procedure-related events (primary safety endpoint). These data are summarized in *Table 3* and *Figure 5*. No data were provided about the impact of BAT on LVEF or LV volumes. Also, when compared with the previous randomized trial of BAT, no significant changes were detected in BP or HR. The restriction to patients with lower NT-proBNP levels was based on a preliminary analysis of the first 271 subjects, enrolled without NT-proBNP level limitations, showing a lower efficacy of BAT among patients with NT-proBNP >1600 pg/mL (no significant impact either on 6MHW or on NT-proBNP level). In the intended for use population, additional benefits were observed, such as lower need for additional drugs compared with controls (mostly ARNI), significant improvement of the EuroQoL-5 Dimensions (EQ-5D) index, and a 51% reduction in the cardiovascular serious adverse event rate (non-HF-related events). Based on the data of the entire BeAT-HF population, on August 2019, the FDA approved BAT for the intended use population.

A subsequent subanalysis of the BeAT-HF assessing potential differences in BAT response according to sex,[56] showed that woman (20% of the intended for use population of 264 subjects), despite a poorer baseline QoL compared with men, had similar improvements with BAT in 6-minute hall walk (6MHW), QoL, and NYHA class. Notably,



	Sample Size	Analysis Timing	Clinical Evidence
Pre-Market Phase	N = 264 randomized subjects	N = 264 complete 6 months follow-up	Safety evaluation (MANCE) NT-proBNP Six-minute hallwalk Minnesota living with heart failure (QOL)
Post-Market Phase	N = 346 randomized subjects (N=264 subjects from Pre-Market Phase + additional N=82 new subjects)	Sufficient morbidity and mortality data collected on all subjects (320 events collected)	• Full morbidity and mortality • Heart Failure Hospitalization • CV Death • Totality of evidence

Figure 4 Baroreflex Activation Therapy for Heart Failure trial design. Baroreflex Activation Therapy for Heart Failure was designed in collaboration with the FDA breakthrough device programme and was divided into two phases: pre-market phase and post-market phase. The details and status of the Baroreflex Activation Therapy for Heart Failure study are represented. MANCE, major adverse neurological and cardiovascular events; MLWHF, Minnesota living with heart failure; 6MHW, 6 minutes hallwalk; PMA, premarket approval.

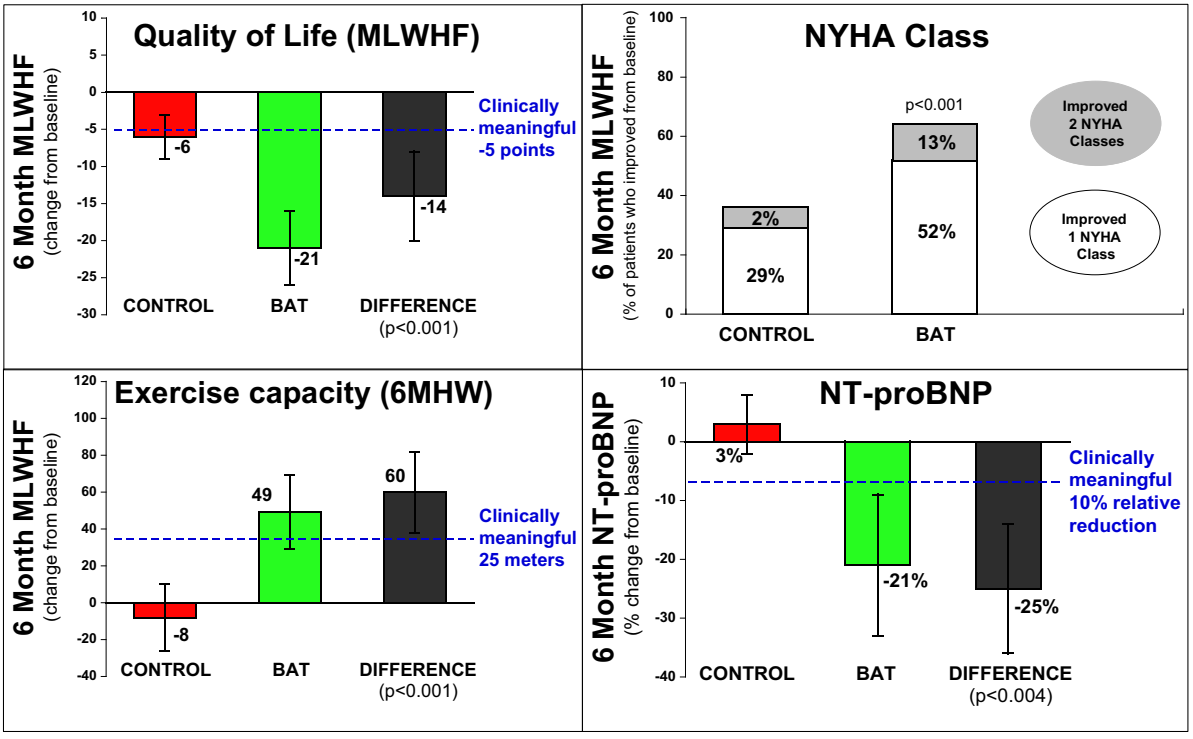


Figure 5 Primary efficacy endpoints in the Baroreflex Activation Therapy for Heart Failure trial pre-market phase. There were significant improvements in quality of life score using the Minnesota living with heart failure questionnaire, exercise capacity measured using the 6-min hall walk test, New York Heart Association class, and *N*-terminal pro-B-type natriuretic peptide levels. MLWHF, Minnesota living with heart failure questionnaire; 6MHW, 6-min hall walk.

women had a highly significant improvement in NT-proBNP levels (−43 vs. 7% with GDMT alone; $P<0.01$), whereas only a trend for significance was found in men (−15 vs. 2% with GDMT; $P=0.08$), with an interaction P-value of 0.05. These preliminary findings are in agreement with what already observed in CRT studies[57]

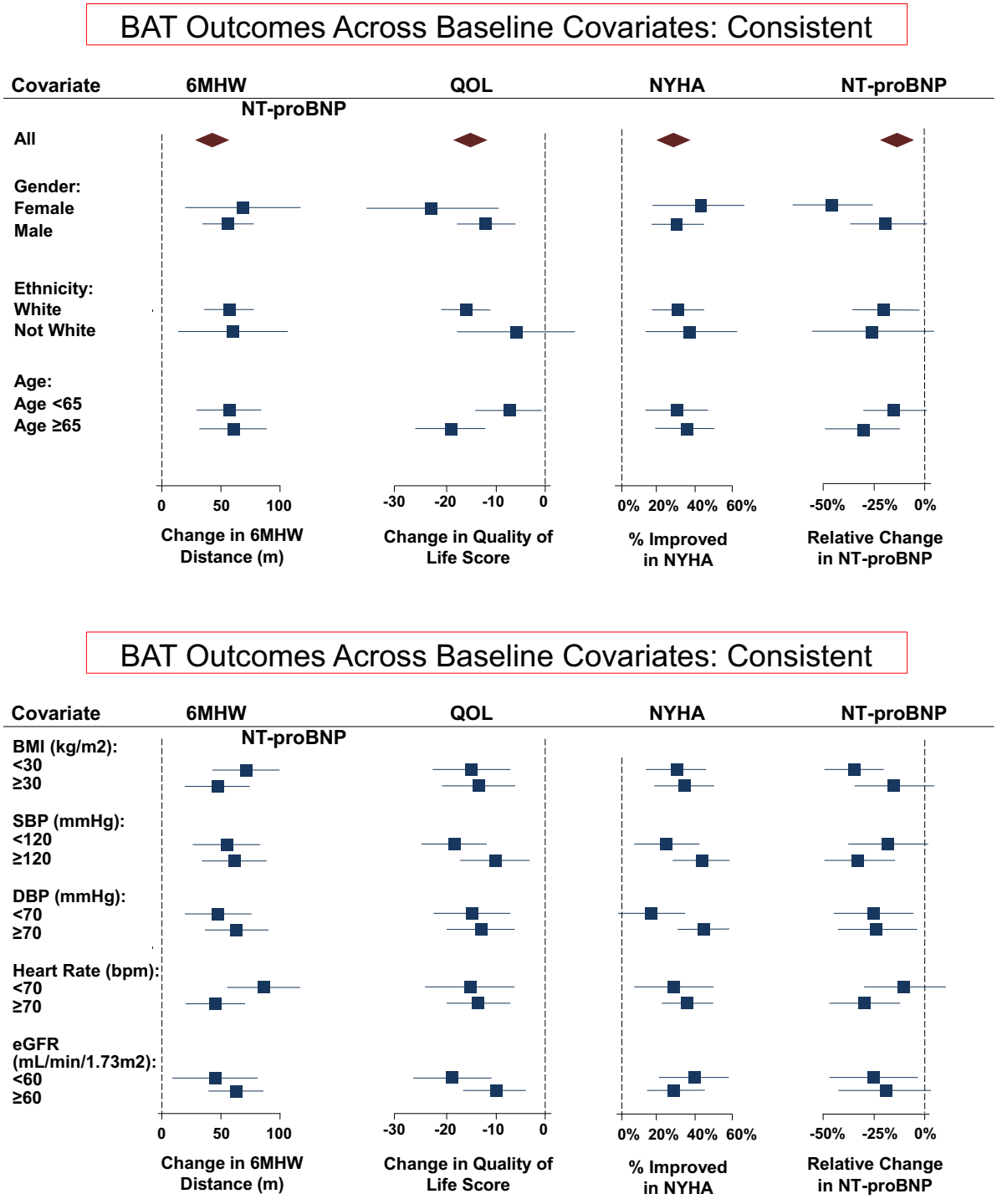


Figure 6 The effects of baroreceptor activation therapy across all baseline covariates examined in the Baroreflex Activation Therapy for Heart Failure study were very consistent for all four primary endpoints: quality of life score using the Minnesota living with heart failure questionnaire, exercise capacity measured using the 6-min hall walk test, New York Heart Association class, and *N*-terminal pro-B-type natriuretic peptide levels. MLWHF, Minnesota living with heart failure questionnaire; 6MHW, 6-min hall walk.

Continued

and suggest that women are likely to benefit from BAT at least as much as men, if not more.

In addition to examining the effects of sex on the effectiveness of BAT, *Figure 6* demonstrates the very consistent effects of BAT across all baseline covariates examined in the BeAT-HF study. Two cost-effectiveness analyses, one performed in Germany[58] and the other simulated based 6-month data from

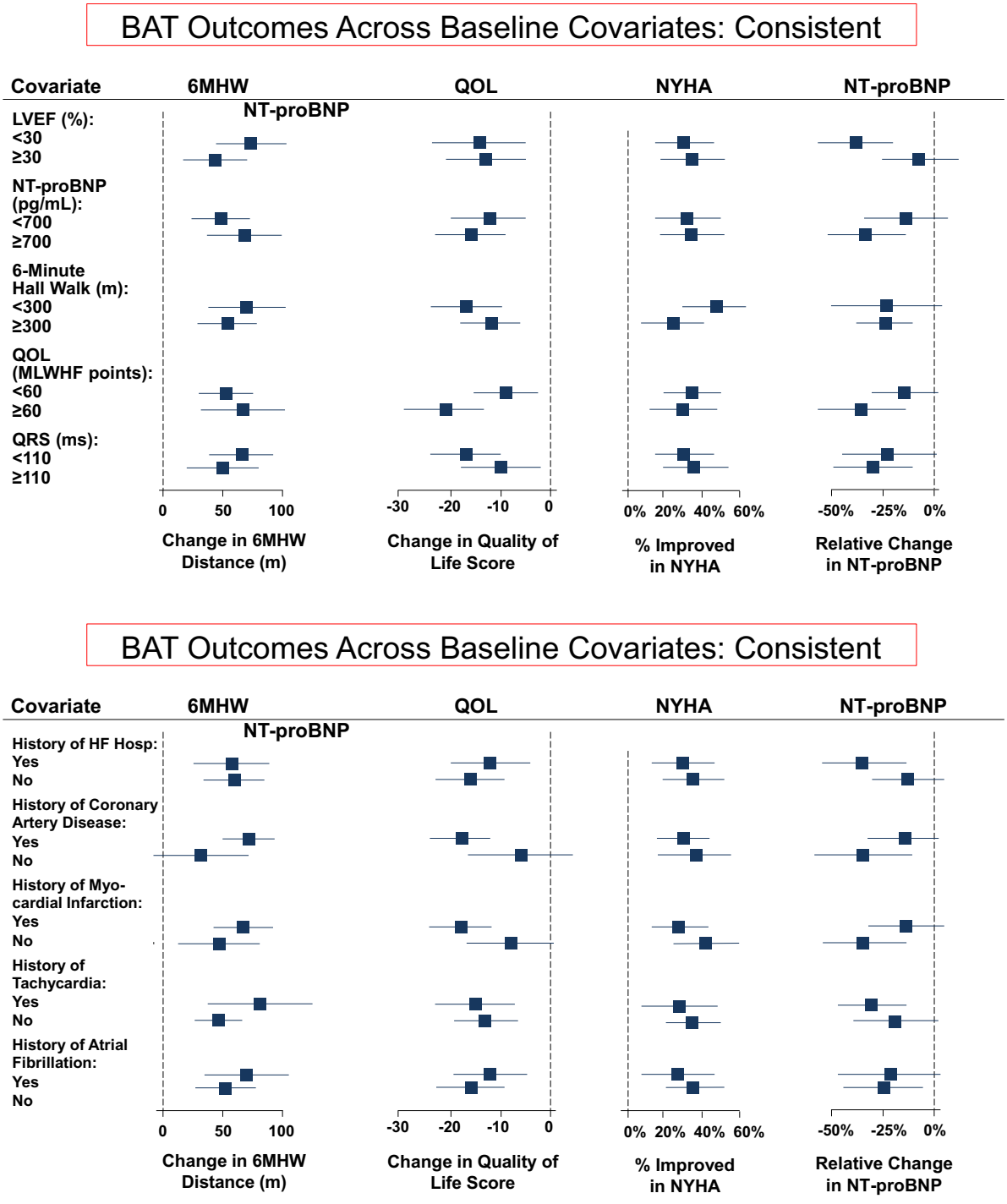


Figure 6 Continued

the BeAT-HF trial and the existing literature,[59] suggest that BAT can be cost-effective for HFrEF patients not eligible for cardiac resynchronization therapy.

Spinal cord stimulation

Albeit the precise mechanisms underlying SCS efficacy are multifactorial and not completely unravelled yet,[60] the rational for its first applications lays its foundations on the seminal works of Melzack and Wall[61] and Wall and Sweet[62] on the gate-control theory of pain, which assumed that stimulation of large diameter Aβ-type afferent fibres could reduce pain through the indirect inhibition of afferent small C-fibre-mediated signalling. Several pre-clinical studies proved that SCS can blunt sympathetic reflex responses to cardiac stressors by

modulation of both sympathetic and parasympathetic cardiac output. Southerland *et al.*[63] demonstrated in a rabbit model that the reduction in infarct size promoted by SCS was counteracted by α- or β-adrenergic blockade, while Olgin *et al.*[64] showed an increase in RR and AH intervals and a significant reduction in ventricular arrhythmias triggered by MI following SCS. These favourable effects are due to a stabilizing impact of SCS on sympathetic reflex arches occurring at lower levels, namely within extracardiac sympathetic ganglia[65] and within the intrinsic cardiac ganglionated plexus,[66] leading as a final result to a blunted neuronal cardiac release of norepinephrine.[67]

Spinal cord stimulation was the first neuromodulation strategy to be explored in humans, first in the 1960s for cancer pain relief,[68] later to treat refractory neuropathic pain syndromes[69] and refractory angina pectoris, proving to be effective and safe.[70] Notably, a reduced LV deterioration was noted during adenosine-provoked ischaemia.[71]

In a canine HF model induced by anterior MI and rapid pacing, SCS delivered at the T4–T5 spinal level for 2 hours three times a day, significantly improved LVEF from 18 to 47% and reduced ventricular arrhythmias.[72] Similarly, in a porcine model of ischaemic HF, SCS at a higher level (T1–T2) improved LV function and decreased myocardial oxygen consumption.[73]

Following these promising pre-clinical results, two small trials were performed in humans with HFrEF, showing a possible benefit of SCS. In a prospective, randomized, double-blind, crossover study,[74] nine NYHA Class III patients, with LVEF $\leq$ 30% and an ICD (CRT-D in 6), were randomized to active or inactive SCS for 3 months, with subsequent crossover. Spinal cord stimulation was delivered using an eight-electrode epidural single lead (Octrode; St Jude Medical) at the T1–T4 level, active three times daily for 2 h, at 90% of the paraesthesia threshold (PT). Spinal cord stimulation proved to be safe, free from ICD interferences, and effective in improving symptoms; LV function and BNP levels were unchanged. Notably, most patients correctly identified their active or inactive randomization periods afterwards; this was at least partially attributed to variation of the PT over time.

The Spinal Cord Stimulation for Heart Failure (SCS HEART) study enrolled with an open design of 17 patients with NYHA Class III, LVEF 20–35% and ICD carriers (including 47% with CRT-D) to be implanted with dual eight electrodes thoracic SCS leads (Octrode; St Jude Medical) at the T1–T3 levels, programmed to provide SCS for 24 h/day (50 Hz, 200 μs) at 90–110% of the PT[75]; four patients not fulfilling the study criteria served as non-treated controls. After 6 months of treatment, there were no deaths or ICD interactions, but three patients needed device reprogramming due to back or neck discomfort, two patients suffered ventricular tachyarrhythmias requiring intervention, and two were hospitalized for HF. As opposed to controls, NHYA class, QoL, peak VO_2 consumption, LVEF, and LVESV significantly improved in SCS treated patients, despite unchanged NT-proBNP levels.

The largest trial on SCS in HFrEF patients is the Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure (DEFEAT-HF) trial,[76] which randomized in a single-blind 3:2 fashion 66 NYHA Class III HF patients with a mean LVEF of 29 ± 5% (76% with an ICD, none with CRT), to SCS or sham stimulation with control crossing over to active SCS after 6 months. An eight-electrode single lead (Medtronic Model 3777/3877) was inserted in the epidural space at T2–T4 levels and stimulation was programmed for 12 hours/day (50 Hz, 200 μs). At 6 months, LVESV index (primary endpoint), peak VO_2 consumption, and NT-proBNP levels (secondary endpoints) were unchanged, as well as HR, QoL, functional capacity, and ventricular arrhythmias burden. The same findings were confirmed at the 12-month extended longitudinal analysis.

The discordant results of the last two trials must be interpreted considering some important differences in both electrode positioning (two eight-electrode leads at T1–T3 vs. single eight-electrode lead at T2–T4) level and stimulation protocol (continuous stimulation vs. 12 h/day). Since the protective effects of SCS can extend for up to 1 hour after SCS offset, it is likely that SCS heart patients were more protected from cardiac stressors.

Overall considerations

Despite new devices and drugs, there is still an unmet need for additional therapeutic strategies in the management of patients with advanced HFrEF.[77] In this setting, all favourable interventions act by promoting a positive ventricular reverse remodelling through several mechanisms which always include a beneficial effect on the autonomic imbalance. The autonomic imbalance that inevitably accompanies advanced HFrEF can be directly targeted through implantable devices able to modulate cardiovascular autonomic function at different levels, with the same final aim to increase cardiac vagal output and decrease the sympathetic one with an effect that is additional to that already provided by beta-blockers, angiotensin-converting-enzyme inhibitor/angiotensin II receptor blocker, and mineralocorticoid receptor antagonist. These devices have been extensively studied in the previous years at both pre-clinical and clinical level, with apparently discordant findings. It is now clear that the physiological and pathological functioning of cardiac neuraxis is extremely complex, and we are only starting to fully understand it. Electrical neuromodulation poses peculiar challenges related to the multiplicity of parameters that concur to define the therapeutic dose and to the lack of reliable means to assess a proper neuronal engagement. The conduction of clinical trials is further complicated by binding issues. Finally, our capability to properly select patients more likely to respond to electrical neuromodulation is still very limited. For instance, BAT was more effective in patients with NT-proBNP levels below 1600 pg/mL, while cVNS efficacy was suggested to be independent from NT-proBNP levels based on the ANTHEM-HF study, and the ongoing ANTHEM-HFrEF is enrolling patients with NT-proBNP levels >800 pg/mL.

At present, BAT, albeit still lacking definite survival benefit data, is the only electrical ART approved for clinical use by the FDA, while cVNS is still considered investigational.[78] A possible advantage of BAT, compared with the more complex mechanism of cVNS and SCS, is its action on a well-defined autonomic afferent pathway which is known to be functionally depressed in HFrEF and a main contributor to cardiovascular autonomic imbalance. Afferent information is then integrated with other cardiovascular inputs at the central level to promote a positive autonomic remodelling.

Conclusion

Electrical neuromodulation has a strong pathophysiological rational for the treatment of advanced HF with depressed left ventricular function but poses some unique challenges that were not properly addressed by the first human studies. This might concur to explain why the favourable effects observed in pre-clinical studies have not been confirmed in controlled clinical trials, with the only relevant exception of BAT, that is currently approved for use. A large trial of cVNS with an adaptive design and an innovative method to titrate the therapeutic dose is currently ongoing and will soon provide further insight on the effectiveness of the technique.

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Conflict of interest: None declared.

Data availability

No new data were generated or analysed in support of the present work.

References

1. Dusi V, De Ferrari GM, Schwartz PJ. There are 100 ways by which the sympathetic nervous system can trigger life-threatening arrhythmias. *Eur Heart J* 2020;**41**:2180–2182.
2. Famm K, Litt B, Tracey KJ, Boyden ES, Slaoui M. A jump-start for electroceuticals. *Nature* 2013;**496**:159–161.
3. Mirza KB, Golden CT, Nikolic K, Toumazou C. Closed-loop implantable therapeutic neuromodulation systems based on neurochemical monitoring. *Front Neurosci* 2019;**13**:808.
4. De Ferrari GM. Vagal stimulation in heart failure. *J Cardiovasc Transl Res* 2014;**7**:310–320.
5. Dusi V, De Ferrari GM, Mann DL. Cardiac Sympathetic-parasympathetic interaction. *JACC: Basic Trans Science* 2020;**5**:811–814.
6. Capogrosso M, Lempka SF. A computational outlook on neurostimulation. *Bioelectron Med* 2020;**6**:10.
7. Lempka SF, Patil PG. Innovations in spinal cord stimulation for pain. *Curr Opin Biomed Eng* 2018;**8**:51–60.
8. Capogrosso M, Wenger N, Raspopovic S, Musienko P, Beauparlant J, Bassi Luciani L, Courtine G, Micera S. A computational model for epidural electrical stimulation of spinal sensorimotor circuits. *J Neurosci* 2013;**33**:19326–19340.
9. McIntyre CC, Foutz TJ. Computational modeling of deep brain stimulation. *Handb Clin Neurol* 2013;**116**:55–61.
10. Settell ML, Pelot NA, Knudsen BE, Dingle AM, McConico AL, Nicolai EN, Trevathan JK, Ezzell JA, Ross EK, Gustafson KJ, Shoffstall AJ, Williams JC, Zeng W, Poore SO, Populin LC, Suminski AJ, Grill WM, Ludwig KA. Functional vagotopy in the cervical vagus nerve of the domestic pig: implications for the study of vagus nerve stimulation. *J Neural Eng* 2020;**17**:026022.
11. Aristovich K, Donega M, Fjordbakk C, Tarotin I, Chapman CAR, Viscasillas J, Stathopoulou TR, Crawford A, Chew D, Perkins J, Holder D. Model-based geometrical optimisation and in vivo validation of a spatially selective multielectrode cuff array for vagus nerve neuromodulation. *J Neurosci Methods* 2021;**352**:109079.
12. Fitchett A, Mastitskaya S, Aristovich K. Selective neuromodulation of the vagus nerve. *Front Neurosci* 2021;**15**:685872.
13. Ottaviani MM, Wright L, Dawood T, Macefield VG. In vivo recordings from the human vagus nerve using ultrasound-guided microneurography. *J Physiol* 2020;**598**:3569–3576.
14. Kent KM, Smith ER, Redwood DR, Epstein SE. Electrical stability of acutely ischemic myocardium. influences of heart rate and vagal stimulation. *Circulation* 1973;**47**:291–298.
15. Myers RW, Pearlman AS, Hyman RM, Goldstein RA, Kent KM, Goldstein RE, Epstein SE. Beneficial effects of vagal stimulation and bradycardia during experimental acute myocardial ischemia. *Circulation* 1974;**49**:943–947.
16. Kolman BS, Verrier RL, Lown B. The effect of vagus nerve stimulation upon vulnerability of the canine ventricle: role of sympathetic-parasympathetic interactions. *Circulation* 1975;**52**:578–585.
17. Yoon MS, Han J, Tse WW, Rogers R. Effects of vagal stimulation, atropine, and propranolol on fibrillation threshold of normal and ischemic ventricles. *Am Heart J* 1977;**93**:60–65.
18. Vanoli E, De Ferrari GM, Stramba-Badiale M, Hull SS Jr, Foreman RD, Schwartz PJ. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. *Circ Res* 1991;**68**:1471–1481.
19. Krieg T, Qin Q, Philipp S, Alexeyev MF, Cohen MV, Downey JM. Acetylcholine and bradykinin trigger preconditioning in the heart through a pathway that includes Akt and NOS. *Am J Physiol Heart Circ Physiol* 2004;**287**:H2606–H2611.
20. Kakinuma Y, Ando M, Kuwabara M, Katare RG, Okudela K, Kobayashi M, Sato T. Acetylcholine from vagal stimulation protects cardiomyocytes against ischemia and hypoxia involving additive non-hypoxic induction of HIF-1alpha. *FEBS Lett* 2005;**579**:2111–2118.
21. Katare RG, Ando M, Kakinuma Y, Arikawa M, Handa T, Yamasaki F Sato T. Vagal nerve stimulation prevents reperfusion injury through inhibition of opening of mitochondrial permeability transition pore independent of the bradycardiac effect. *J Thorac Cardiovasc Surg* 2009;**137**:223–231.
22. Tracey KJ. The inflammatory reflex. *Nature* 2002;**420**:853–859.
23. Calvillo L, Vanoli E, Andreoli E, Besana A, Omodeo E, Gnecchi M, Zerbi P, Vago G, Busca G, Schwartz PJ. 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.
24. Li M, Zheng C, Sato T, Kawada T, Sugimachi M, Sunagawa K. Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats. *Circulation* 2004;**109**:120–124.
25. Sabbah HN, Ilsar I, Zaretsky A, Rastogi S, Wang M, Gupta RC. Vagus nerve stimulation in experimental heart failure. *Heart Fail Rev* 2011;**16**:171–178.
26. Hamann JJ, Ruble SB, Stolen C, Wang M, Gupta RC, Rastogi S, Sabbah HN. Vagus nerve stimulation improves left ventricular function in a canine model of chronic heart failure. *Eur J Heart Fail* 2013;**15**:1319–1326.
27. Uthman BM, Reichl AM, Dean JC, Eisenschenk S, Gilmore R, Reid S, Roper SN, Wilder BJ. Effectiveness of vagus nerve stimulation in epilepsy patients: a 12-year observation. *Neurology* 2004;**63**:1124–1126.
28. Shuchman M. Approving the vagus-nerve stimulator for depression. *N Engl J Med* 2007;**356**:1604–1607.
29. Dusi V, De Ferrari GM. Vagal stimulation in heart failure. *Herz* 2021;**46**:541–549.
30. Schwartz PJ, De Ferrari GM, Sanzo A, Landolina M, Rordorf R, Raineri C, Campana C, Revera M, Ajmone-Marsan N, Tavazzi L, Odero A. Long term vagal stimulation in patients with advanced heart failure: first experience in man. *Eur J Heart Fail* 2008;**10**:884–891.

31. De Ferrari GM, Crijns HJ, Borggrefe M, Milasinovic G, Smid J, Zabel M, Gavazzi A, Sanzo A, Dennert R, Kuschyk J, Raspopovic S, Klein H, Swedberg K, Schwartz PJ; 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.
32. Rocchetti M, Malfatto G, Lombardi F, Zaza A. Role of the input/output relation of sinoatrial myocytes in cholinergic modulation of heart rate variability. *J Cardiovasc Electrophysiol* 2000;**11**:522–530.
33. Zaza A, Lombardi F. Autonomic indexes based on the analysis of heart rate variability: a view from the sinus node. *Cardiovasc Res* 2001;**50**:434–442.
34. Dusi V, De Ferrari GM. Vagal stimulation in heart failure. *Herz* 2021; **46**:541–549.
35. Premchand RK, Sharma K, Mittal S, Monteiro R, Dixit S, Libbus I, DiCarlo LA, Ardell JL, Rector TS, Amurthur B, KenKnight BH, Anand IS. 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.
36. Premchand RK, Sharma K, Mittal S, Monteiro R, Dixit S, Libbus I, DiCarlo LA, Ardell JL, Rector TS, Amurthur B, KenKnight BH, Anand IS. Extended follow-up of patients with heart failure receiving autonomic regulation therapy in the ANTHEM-HF study. *J Card Fail* 2016; **22**:639–642.
37. Sharma K, Premchand RK, Mittal S, Monteiro R, Libbus I, DiCarlo LA, Ardell JL, Amurthur B, KenKnight BH, Anand IS. Long-term follow-up of patients with heart failure and reduced ejection fraction receiving autonomic regulation therapy in the ANTHEM-HF pilot study. *Int J Cardiol* 2021;**323**:175–178.
38. Nearing BD, Anand IS, Libbus I, Dicarlo LA, Kenknight BH, Verrier RL. Vagus nerve stimulation provides multiyear improvements in autonomic function and cardiac electrical stability in the ANTHEM-HF study. *J Card Fail* 2021;**27**:208–216.
39. Anand I, Ardell JL, Gregory D, Libbus I, DiCarlo L, Premchand RK, Sharma K, Mittal S, Monteiro R. Baseline NT-proBNP and responsiveness to autonomic regulation therapy in patients with heart failure and reduced ejection fraction. *Int J Cardiol Heart Vasc* 2020;**29**: 100520.
40. Zannad F, De Ferrari GM, Tuinenburg AE, Wright D, Brugada J, Butter C, Klein H, Stolen C, Meyer S, Stein KM, Ramuzat A, Schubert B, Daum D, Neuzil P, Botman C, Castel MA, D'Onofrio A, Solomon SD, Wold N, Ruble SB. 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.
41. De Ferrari GM, Dusi V. Vagus nerve stimulation for the treatment of heart failure. *Giornale italiano di cardiologia (2006)* 2015;**16**: 147–154.
42. De Ferrari GM, Stolen C, Tuinenburg AE, Wright DJ, Brugada J, Butter C, Klein H, Neuzil P, Botman C, Castel MA, D'Onofrio A, de Borst GJ, Solomon S, Stein KM, Schubert B, Stalsberg K, Wold N, Ruble S, Zannad F. Long-term vagal stimulation for heart failure: Eighteen-month results from the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) trial. *Int J Cardiol* 2017;**244**:229–234.
43. Gold MR, Van Veldhuisen DJ, Hauptman PJ, Borggrefe M, Kubo SH, Lieberman RA, Milasinovic G, Berman BJ, Djordjevic S, Neelagaru S, Schwartz PJ, Starling RC, Mann DL. Vagus nerve stimulation for the treatment of heart failure: the INOVATE-HF trial. *J Am Coll Cardiol* 2016;**68**:149–158.
44. Anand IS, Konstam MA, Klein HU, Mann DL, Ardell JL, Gregory DD, Massaro JM, Libbus I, DiCarlo LA, Udelson JJE, Butler J, Parker JD, Teerlink JR. Comparison of symptomatic and functional responses to vagus nerve stimulation in ANTHEM-HF, INOVATE-HF, and NECTAR-HF. *ESC Heart Fail* 2020;**7**:75–83.
45. Konstam MA, Udelson JE, Butler J, Klein HU, Parker JD, Teerlink JR, Wedge PM, Saville BR, Ardell JL, Libbus I, DiCarlo LA. Impact of autonomic regulation therapy in patients with heart failure: ANTHEM-HFrEF pivotal study design. *Circ Heart Fail* 2019;**12**: e005879.
46. Ardell JL, Nier H, Hammer M, Southerland EM, Ardell CL, Beaumont E, KenKnight BH, Armour A. Defining the neural fulcrum for chronic vagus nerve stimulation: implications for integrated cardiac control. *J Physiol* 2017;**595**:6887–6903.
47. Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. *J Am Coll Cardiol* 2009;**54**:375–385.
48. Zucker IH, Hackley JF, Cornish KG, Hiser BA, Anderson NR, Kieval R, Irwin ED, Serdar DJ, Peuler JD, Rossing MA. Chronic baroreceptor activation enhances survival in dogs with pacing-induced heart failure. *Hypertension* 2007;**50**:904–910.
49. Sabbah HN, Gupta RC, Imai M, Irwin ED, Rastogi S, Rossing MA, Kieval RS. Chronic electrical stimulation of the carotid sinus baroreflex improves left ventricular function and promotes reversal of ventricular remodeling in dogs with advanced heart failure. *Circ Heart Fail* 2011; **4**:65–70.
50. Bisognano JD, Bakris G, Nadim MK, Sanchez L, Kroon AA, Schafer J, de Leeuw PW, Sica DA. 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.
51. de Leeuw PW, Alnima T, Lovett E, Sica D, Bisognano J, Haller H, Kroon AA. Bilateral or unilateral stimulation for baroreflex activation therapy. *Hypertension* 2015;**65**:187–192.
52. Gronda E, Seravalle G, Trevano FQ, Costantino G, Casini A, Alsheraei A, Lovett EG, Vanoli E, Mancia G, Grassi G. Long-term chronic baroreflex activation: persistent efficacy in patients with heart failure and reduced ejection fraction. *J Hypertens* 2015;**33**:1704–1708.
53. Abraham WT, Zile MR, Weaver FA, Butter C, Ducharme A, Halbach M, Klug D, Lovett EG, Müller-Ehmsen J, Schafer JE, Senni M, Swarup V, Wachter R, Little WC. Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction. *JACC Heart Fail* 2015;**3**:487–496.
54. Zile MR, Abraham WT, Weaver FA, Butter C, Ducharme A, Halbach M, Klug D, Lovett EG, Müller-Ehmsen J, Schafer JE, Senni M, Swarup V, Wachter R, Little WC. 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.
55. Zile MR, Lindenfeld J, Weaver FA, Zannad F, Galle E, Rogers T, Abraham WT. Baroreflex activation therapy in patients with heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2020;**76**: 1–13.
56. Lindenfeld J, Gupta R, Grazette L, Ruddy JM, Tsao L, Galle E, Rogers T, Sears S, Zannad F. Response by sex in patient-centered outcomes with baroreflex activation therapy in systolic heart failure. *JACC Heart Fail* 2021;**9**:430–438.
57. Yin FH, Fan CL, Guo YY, Zhu H, Wang ZL, Fukumoto Y. The impact of gender difference on clinical and echocardiographic outcomes in patients with heart failure after cardiac resynchronization therapy: a systematic review and meta-analysis. *PLoS One* 2017;**12**:e0176248.
58. Borisenko O, Müller-Ehmsen J, Lindenfeld J, Rafflenbeul E, Hamm C. An early analysis of cost-utility of baroreflex activation therapy in advanced chronic heart failure in Germany. *BMC Cardiovasc Disord* 2018;**18**:163.
59. Bisognano J, Schneider JE, Davies S, Ohsfeldt RL, Galle E, Stojanovic I, Deering TF, Lindenfeld J, Zile MR. Cost-impact analysis of baroreflex activation therapy in chronic heart failure patients in the United States. *BMC Cardiovasc Disord* 2021;**21**:155.
60. Wu M, Linderoth B, Foreman RD. Putative mechanisms behind effects of spinal cord stimulation on vascular diseases: a review of experimental studies. *Auton Neurosci* 2008;**138**:9–23.
61. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965; **150**:971–979.
62. Wall PD, Sweet WH. Temporary abolition of pain in man. *Science* 1967;**155**:108–109.
63. Southerland EM, Milhorn DM, Foreman RD, Linderoth B, DeJongste MJL, Armour JA, Subramanian V, Singh M, Singh K, Ardell JL. Preemptive, but not reactive, spinal cord stimulation mitigates transient ischemia-induced myocardial infarction via cardiac adrenergic neurons. *Am J Physiol Heart Circ Physiol* 2007;**292**:H311–H317.
64. Olgin JE, Takahashi T, Wilson E, Vereckei A, Steinberg H, Zipes DP. Effects of thoracic spinal cord stimulation on cardiac autonomic regulation of the sinus and atrioventricular nodes. *J Cardiovasc Electrophysiol* 2002;**13**:475–481.
65. Ardell JL, Cardinal R, Vermeulen M, Armour JA. Dorsal spinal cord stimulation obtunds the capacity of intrathoracic extracardiac

neurons to transduce myocardial ischemia. *Am J Physiol Regul Integr Comp Physiol* 2009;**297**:R470–R477.
66. Armour JA, Linderoth B, Arora RC, DeJongste MJ, Ardell JL, Kingma JG Jr, Hill M, Foreman RD. Long-term modulation of the intrinsic cardiac nervous system by spinal cord neurons in normal and ischaemic hearts. *Auton Neurosci* 2002;**95**:71–79.
67. Ardell JL, Foreman RD, Armour JA, Shivkumar K. Cardiac sympathectomy and spinal cord stimulation attenuate reflex-mediated norepinephrine release during ischemia preventing ventricular fibrillation. *JCI Insight* 2019;**4**:e131648.
68. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. *Anesth Analg* 1967;**46**:489–491.
69. Fontaine D. Spinal cord stimulation for neuropathic pain. *Rev Neurol (Paris)* 2021;**177**:838–842.
70. Taylor RS, De Vries J, Buchser E, Dejongste MJ. Spinal cord stimulation in the treatment of refractory angina: systematic review and meta-analysis of randomised controlled trials. *BMC Cardiovasc Disord* 2009;**9**:13.
71. Kujacic V, Eliasson T, Mannheimer C, Jablonskiene D, Augustinsson LE, Emanuelsson H. Assessment of the influence of spinal cord stimulation on left ventricular function in patients with severe angina pectoris: an echocardiographic study. *Eur Heart J* 1993;**14**:1238–1244.
72. Lopshire JC, Zhou X, Dusa C, Ueyama T, Rosenberger J, Courtney N, Ujhelyi M, Mullen T, Das M, Zipes DP. Spinal cord stimulation improves ventricular function and reduces ventricular arrhythmias in a canine postinfarction heart failure model. *Circulation* 2009;**120**:286–294.
73. Liu Y, Yue WS, Liao SY, Zhang Y, Au KW, Shuto C, Hata C, Park E, Chen P, Siu CW, Tse HF. Thoracic spinal cord stimulation improves cardiac contractile function and myocardial oxygen consumption in a porcine model of ischemic heart failure. *J Cardiovasc Electrophysiol* 2012;**23**:534–540.
74. Torre-Amione G, Alo K, Estep JD, Valderrabano M, Khalil N, Farazi TG, Rosenberg SP, Ness L, Gill J. Spinal cord stimulation is safe and feasible in patients with advanced heart failure: early clinical experience. *Eur J Heart Fail* 2014;**16**:788–795.
75. Tse HF, Turner S, Sanders P, Okuyama Y, Fujij K, Cheung CW, Russo M, Green MDS, Yiu KH, Chen P, Shuto C, Lau EOY, Siu CW. Thoracic spinal cord stimulation for heart failure as a restorative treatment (SCS HEART study): first-in-man experience. *Heart Rhythm* 2015;**12**:588–595.
76. Zipes DP, Neuzil P, Theres H, Caraway D, Mann DL, Mannheimer C, Van Buren P, Linde C, Linderoth B, Kueffer F, Sarazin SA, DeJongste MJL; DEFEAT-HF Trial Investigators. Determining the feasibility of spinal cord neuromodulation for the treatment of chronic systolic heart failure: the DEFEAT-HF study. *JACC Heart Fail* 2016;**4**:129–136.
77. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm Michael, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–3726.
78. Fudim M, Abraham WT, von Bardeleben RS, Lindenfeld J, Ponikowski PP, Salah HM, Khan MS, Sievert H, Stone GW, Anker SD, Butler J. Device therapy in chronic heart failure: JACC state-of-the-art review. *J Am Coll Cardiol* 2021;**78**:931–956.