International Journal of Cardiology xxx (xxxx) xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Autonomic regulation therapy in chronic heart failure with preserved/mildly reduced ejection fraction: ANTHEM-HFpEF study results

H. Uday Kumar [a,1], Bruce D. Nearing [b,1], Sanjay Mittal [c,1], Rajendra K. Premchand [d,1], Imad Libbus [e,1], Lorenzo A. DiCarlo [e,1], Badri Amurthur [e,1], Bruce H. KenKnight [e,1], Inder S. Anand [f,1], Richard L. Verrier [b,1,*]

[a] Yashoda Hospital, Secunderabad, India
[b] Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
[c] Medanta, The Medicity, Haryana, India
[d] Krishna Institute of Medical Science, Secunderabad, India
[e] LivaNova USA, Inc., Houston, TX, USA
[f] University of Minnesota, Minneapolis, MN, USA

ARTICLE INFO

Keywords:
Heart failure
Preserved ejection fraction
Mildly reduced ejection fraction
Autonomic regulation therapy
Vagus nerve stimulation
T-wave alternans

ABSTRACT

Background: Autonomic regulation therapy (ART) utilizing cervical vagus nerve stimulation (VNS) appeared to be safe and to improve autonomic tone, symptoms, and cardiac mechanical function in patients with symptomatic heart failure and reduced ejection fraction in the ANTHEM-HF Study. The ANTHEM-HFpEF Study is the first investigation to evaluate the safety and feasibility of ART in patients with symptomatic heart failure and preserved or mildly reduced ejection fraction (HFpEF, HFmrEF).

Methods: This open-label interventional study enrolled 52 patients with HFpEF or HFmrEF, NYHA Class II-III, and LVEF ≥40%, who received stable guideline-directed medical therapy. All patients were successfully implanted with LivaNova VNS Therapy® system with an electrical lead surrounding the right cervical vagus nerve.

Results: Adverse event incidence was low. At 12 months, NYHA class ($p < 0.0001$), 6-min walk distance ($p < 0.05$), and quality of life ($p < 0.0001$) were improved. Cardiac mechanical function measures were normal at baseline, except for left ventricular mass index in women and E/e' ratio in all patients, which were elevated at baseline, and were unchanged by ART. Autonomic tone and reflexes improved, indicated by 29% decrease in low-frequency/high-frequency heart rate variability to normal levels ($p = 0.028$) and by increased heart rate turbulence slope ($p = 0.047$). T-wave alternans ($p = 0.001$) and T-wave heterogeneity ($p = 0.001$) were reduced from abnormal to normal ranges. Nonsustained ventricular tachycardia incidence decreased ($p = 0.027$).

Conclusions: ART appeared well-tolerated and safe in patients with HFpEF or HFmrEF. Chronic ART did not alter mechanical function measures but was associated with improved heart failure symptoms, exercise tolerance, autonomic tone, and cardiac electrical stability.

Clinical trial registry: Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure with Preserved Ejection Fraction [ClinicalTrials.gov #NCT03163030, registered 05/22/2017].

1. Introduction

Although approximately 50% of patients with heart failure have preserved (≥50%, HFpEF) or mildly reduced (41–49%, HFmrEF) ejection fraction with or without diastolic dysfunction [1–3], diagnosis and treatment options remain elusive. HFpEF and HFmrEF are heterogeneous conditions with differing phenotypes and pathologic mechanisms [4]. Two pathophysiologic processes appear to play critical roles

* Corresponding author at: Beth Israel Deaconess Medical Center, Division of Cardiovascular Medicine, 99 Brookline Avenue, RN-301, Boston, MA 02215-3908, USA.

E-mail addresses: uday.hosad@gmail.com (H.U. Kumar), bnearing@bidmc.harvard.edu (B.D. Nearing), sanjay.mittal@medanta.org (S. Mittal), kumarpre@hotmail.com (R.K. Premchand), Imad.Libbus@livanova.com (I. Libbus), Lorenzo.DiCarlo@livanova.com (L.A. DiCarlo), Badri.Amurthur@livanova.com (B. Amurthur), Bruce.KenKnight@livanova.com (B.H. KenKnight), inder.anand001@gmail.com (I.S. Anand), rverrier@bidmc.harvard.edu (R.L. Verrier).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcard.2023.03.030
Received 10 February 2023; Received in revised form 8 March 2023; Accepted 13 March 2023
Available online 17 March 2023

across the HFpEF and HFmrEF spectra. The first is a systemic pro-inflammatory state akin to cardiometabolic syndrome [4,5] that results from comorbidities including diabetes, obesity, and ageing. Low-level transcutaneous vagus nerve stimulation (VNS) has recently been shown to exert multiple beneficial effects in patients with HFpEF including improvement in global longitudinal strain, reduction of inflammatory cytokines, and improvement in quality of life [6]. The second pathophysiologic process that has been recurrently invoked in HFpEF is altered autonomic tone with decreased parasympathetic activity and enhanced sympathetic drive to the heart [7,8].

A rationale for investigating autonomic regulation therapy (ART) using cervical VNS as a potential mitigation strategy is based upon findings from the multicenter, open-label, interventional Autonomic Regulation Therapy in Heart Failure with Reduced Ejection Fraction (ANTHEM-HF) Study, which evaluated the effects of ART utilizing cervical VNS in symptomatic patients with HFrEF [9,10]. VNS was titrated on a neurophysiologic basis, appeared to be safe, and was associated with a significant decrease in C-reactive protein and with clinically meaningful and significant improvements in left ventricular mechanical function, exercise capacity, and heart failure symptoms at 6 months after titration. Measures of autonomic tone (heart rate and heart rate variability, HRV) and reflexes (heart rate turbulence, HRT) and cardiac electrical stability (T-wave alternans, TWA; and T-wave heterogeneity, TWH) also improved significantly at 12 months [11], continuing to 24 and 36 months [12]. Nonsustained ventricular arrhythmia incidence was favorably affected. Beneficial symptomatic and functional effects were observed for up to 42 months in a cohort of the original study population [13,14].

The favorable results from the ANTHEM-HF Study when compared to the previous NECTAR-HF [15] and INOVATE-HF [16] studies appear to be attributable in part to differences in VNS administration and ensuing engagement of the autonomic nervous system [17]. In the ANTHEM-HF Study, and in the current investigation, each patient's stimulation parameters were individually optimized during the VNS titration phase by making use of the "neural fulcrum," which is the neurophysiological operating point of balance in vagal control of cardiac function. This fulcral operating point was identifiable at the bedside utilizing changes in heart rate dynamics as VNS intensity was increased [18].

The present study was conducted to evaluate whether ART using cervical VNS may have a role in treatment of patients with HFpEF or HFmrEF.

2. Methods

2.1. Study objectives

The multi-center, open-label, interventional, single-arm Autonomic Regulation Therapy in Heart Failure With Preserved Ejection Fraction (ANTHEM-HFpEF) Study was designed to evaluate the feasibility, tolerability, and safety of ART using VNS for the treatment of patients with HFpEF and HFmrEF [19]. Feasibility was defined as the proportion of study subjects successfully implanted with the VNS Therapy system lead and pulse generator, based upon implant attempt. Tolerability was defined as the percentage of study subjects who continued ART throughout the 12-month follow-up period that began after completion of post-implantation titration of VNS. Safety was defined in terms of the incidence of procedure- and device-related adverse events.

This study also evaluated cardiovascular and functional responses to ART in this population. Efficacy measurements were made at baseline and at each 3-month follow-up visit: vital and health status, echocardiographic assessment of cardiac structure and mechanical function that included left atrial volume index (LAVI), left ventricular mass index, left ventricular end systolic volume (LVESV), index (LVESVi), and diameter (LVESD), functional status indicators such as New York Heart Association (NYHA) class, quality of life (Minnesota Living With Heart Failure Questionnaire, MLHFQ), 6-min walk test (6MWT) and plasma biomarkers, including N-terminal pro-BNP, hs-C-reactive protein, and creatinine.

Electrocardiographic analyses included arrhythmia incidence, autonomic tone and reflexes, and cardiac electrical instability. TWA [20] and TWH [21,22] are measures of cardiac electrical instability associated with increased risk for cardiovascular mortality and sudden cardiac death. TWH measured from resting 12-lead electrocardiograms (ECGs) predicted sudden cardiac death in the 5600-subject Health Survey 2000 [23]. In patients with ischemic and nonischemic cardiomyopathies, TWH monitored prior to electrophysiologic testing predicted sustained ventricular arrhythmia, appropriate implantable cardioverter defibrillator therapies, and arrhythmic death or cardiac arrest during followup [24].

2.2. Study design

The study enrolled 52 symptomatic, adult subjects with NYHA class II-III heart failure and LVEF $\geq$40% on stable guideline-directed pharmacologic therapy [19]. Only 23% of patients had LVEF 41–49% (HFmrEF), while 77% had LVEF $\geq$50% (HFpEF); no patient had LVEF = 40%. Other inclusion criteria were: Physically capable and willing to perform repeated 6MWT and achieve a baseline distance of 150 to 425 m limited by symptoms due to heart failure; controlled systolic blood pressure; plasma NT-proBNP $\geq$220 pg/mL; and ratio of mitral inflow velocity to early diastolic velocity of the mitral annulus (E/e' ratio) >15, or >8 with left atrial enlargement (LAVI $\geq$29 mL/m^2).

Exclusion criteria were: heart failure due to congenital heart disease; hypertrophic, infiltrative, or restrictive cardiomyopathy; recent hospitalization for heart failure or intravenous therapy for heart failure in the past 30 days; therapeutic cardiovascular intervention or surgery within the past 2 months or planned within the next 6 months; chronic atrial fibrillation (lasting >1 week or requiring cardioversion or pharmacologic conversion) in the past 2 months, or atrial fibrillation with a resting ventricular rate >120 bpm; implanted pacemaker or cardioverter-defibrillator; participation in another investigational drug or device trial; and medical or surgical condition that could reduce life expectancy or present an unacceptable risk from ART system implantation or stimulation.

All subjects received VNS Therapy System implant (Demipulse® Model 103 pulse generator and PerenniaFLEX® Model 304 lead, LivaNova, Houston TX, USA) with lead placement on the right cervical vagus nerve. During titration, the VNS parameters were kept within the neural fulcrum, determined as frequency, amplitude, and pulse width parameters in which a minimum heart rate response was produced during the "on" phase of VNS. Specifically, VNS was systematically titrated over 10 weeks to a maximum tolerated amplitude (2.4 $\pm$ 0.5 mA) at a pulse width of 250 μs and a pulse frequency of 5 Hz, near the natural frequency of discharge of cardiac vagal fibers during physiological reflex activation, based on transient modulation of heart rate and guided by the "neural fulcrum," as described by Ardell et al [11]. VNS parameters were maintained unchanged for 12 months with follow-up visits every 3 months.

The study complied with the 1975 Declaration of Helsinki, as reflected in a priori approval of the protocol by local ethics committees at all sites. All patients gave written informed consent in local languages. An independent Data Safety and Monitoring Committee oversaw the study, and all adverse events were adjudicated by a Clinical Events Adjudication Committee.

2.3. Data analysis

All transthoracic echocardiographic recordings and blood samples were deidentified of patient and sample source prior to being sent to core laboratories for interpretation by blinded experts. Effects were compared to normal ranges, namely, for LVEF: 52–72% for men,

Table 1
Baseline characteristics of enrolled patients.

	HFpEF ($n = 40$) LVEF ≥50%	HFmrEF ($n = 12$) LVEF 41–49%	Combined ($n = 52$)
Demographics			
Age (years)	59 ± 10	55 ± 11	57 ± 10
Female (%)	31 (78%)	5 (42%)	36 (69%)
Medical History			
Hypertension	26 (65%)	6 (50%)	32 (64%)
Coronary Artery Disease	7 (18%)	0	7 (14%)
Clinical Examination			
NYHA Class II/III	23/17 (58%/42%)	8/4 (67%/33%)	31/21 (60%/40%)
Body mass index (kg/m^2)	26 ± 5	25 ± 5	26 ± 5
Heart rate (bpm)	76 ± 11	74 ± 4.1	74 ± 1.3
Systolic blood pressure (mmHg)	134 ± 16	116 ± 15	129 ± 16
Diastolic blood pressure (mmHg)	81 ± 8	76 ± 9	80 ± 8
Heart Failure Drug Treatment (%)			
β-blocker	50%	58%	52%
ACE-I or ARB	78%	83%	79%
Aldosterone antagonist	55%	50%	54%
Digoxin	5%	25%	10%
Loop diuretics	100%	100%	100%
ICD Implantation	0	0	0

Key: NYHA, New York Heart Association; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICD, implantable cardioverter defibrillator. Data are presented as means ± standard deviation.

54–74% for women; for LVESV: 21–61 mL for men, 14–42 mL for women; for LVESD: 25–40 mm for men, 22–35 mm for women; for LAVI: 16–34 mL/m^2 for both men and women; for left ventricular mass index: 49–115 g/m^2 for men, 43–95 g/m^2 for women; and for E/e' ratio: <6.0 for both men and women [25].

Arrhythmia incidence, autonomic tone, and cardiac electrical instability were calculated from ambulatory ECGs (AECGs) recorded (Digitrak XT™, Philips Medical Systems®, Best, The Netherlands) from standard precordial leads V_1 and V_5 and aVF at baseline and follow up when the VNS device was operating at clinically defined treatment settings. Measurements of heart rate, HRV, HRT, TWA, and non-sustained ventricular tachycardia (NSVT) incidence were performed at a core lab by an investigator (B.D.N.) who was blinded to clinical status, using FDA-cleared commercial software running on the MARS Ambulatory ECG Analysis System™ (GE Healthcare®, Milwaukee WI, USA). TWH was analyzed using proprietary software on MARS Ambulatory ECG Analysis System.™

HRV was analyzed in the frequency domain using the fast Fourier spectral transform method. The beat stream of the normal-to-normal interval series was transformed to compute high-frequency (HF) power within the frequency band 0.150–0.400 Hz and low-frequency (LF) power within the frequency band 0.040–0.150 Hz. HRV was analyzed during 5-min ECG segments throughout the recordings. LF is abnormal when >1170 ± 416 m^2; HF is abnormal when <975 ± 203 ms^2 (means ±SD). The LF/HF ratio, a unitless measure of autonomic tone and balance, calculated as LF divided by HF, is abnormal when >1.5–2.0 [26]. In the time domain, the square root of the mean squared differences of successive normal-to-normal intervals (rMSSD) and the standard deviation of the normal-to-normal intervals (SDNN) were also calculated. Abnormal rMSSD was defined as <27 ± 12 ms and abnormal SDNN as <141 ± 39 ms [26].

HRT onset, which calculates the initial brief acceleration of sinus rate after a premature ventricular contraction, and HRT slope, which characterizes the subsequent heart rate deceleration, were evaluated as continuous variables to characterize baroreceptor sensitivity [27]. HRT onset ≥0% and HRT slope ≤ 2.5 ms/RR interval were defined as abnormal [27].

TWA was quantified by Modified Moving Average analysis, which employs the noise-rejection principle of recursive averaging, as previously described [20]. Maximum TWA across 24 hours was reported. The TWA cutpoint ≥47 μV was considered abnormal and ≥ 60 μV severely abnormal. TWH was quantified by second central moment analysis from 10-s segments of the AECG recordings, as previously described [21,22]. A TWH cutpoint ≥80 μV was considered abnormal [24].

2.4. Statistical methods

As this was an open-label interventional study, the sample size was not statistically derived. Data from all investigational sites were pooled for analysis. Coefficient of variation correction was applied to left ventricular mass index data. Effects of VNS on heart rate, HRV, HRT, TWA, TWH and NSVT incidence were analyzed with paired *t*-tests, and Bonferroni correction for multiple comparisons was employed. Fisher exact test was used to compare arrhythmia count. Efficacy data are reported as means ± standard deviation (SD) while electrocardiographic data are presented as means ± standard error of the mean (SEM). Statistical significance testing was performed at the 0.05 level.

3. Results

3.1. Baseline characteristics of patients

Consecutive patients with HFpEF ($n = 40$, 77%) or HFmrEF ($n = 12$, 23%) were enrolled (Table 1). Heart failure etiology is provided in Supplementary Table 1. Importantly, there were no significant changes in heart failure medications or side-effect related changes in VNS parameters during the 12-month study.

3.2. Feasibility, tolerability, and safety assessment

All 52 patients were successfully implanted with the lead and pulse generator and titrated to a maximum tolerable intensity. Two patients withdrew from the study after device implantation; one patient was lost to followup, and two patients died after the 6-month followup (CONSORT diagram, Supplementary Fig. 1).

All serious adverse events (SAEs) were formally adjudicated (Supplementary Table 2). There were two device-related SAEs: an implant-related infection that was treated with oral and intravenous antibiotics and did not require device replacement; and a transient bradycardia event with hypoxia. SAEs unrelated to the device ($n = 21$) included two deaths: one hemorrhagic stroke and one acute coronary syndrome with complete heart block. There were no sudden cardiac deaths, ventricular

Table 2

A. Cardiac mechanical function efficacy and echocardiographic measures.

	Baseline (n = 52)	6 Months (*n* = 49)	12 Months (*n* = 47)	*p*-value 0-12 M
LVEF (%)	60.4 ± 12.5	60 ± 13.8	59.2 ± 12.7	0.428
LVESV (mL)	34.6 ± 28.2	36.3 ± 30.3	35.8 ± 29.0	0.967
LVESVi (mL/m^2)	22.4 ± 2.6	23.4 ± 3.0	22.8 ± 2.9	0.79
LVESD (mm)	34 ± 8	34 ± 10	34 ± 9	0.806
LAVI (mL/m^2)	32.3 ± 8.5	31.1 ± 10.0	32.8 ± 11.4	0.527
Left Ventricular Mass Index (g/m^2), male	75.6 ± 22.0	97.3 ± 38.7	103.4 ± 33.4	0.07
Left Ventricular Mass Index (g/m^2) after correction for >25% CoV, male	84.4 ± 21.2	79.4 ± 15.5	79.2 ± 26.8	0.675
Left Ventricular Mass Index (g/m^2), female	80.6 ± 49.2	95.5 ± 39.7	110.4 ± 36.6	<0.001
Left Ventricular Mass Index (g/m^2) after correction for >25% CoV, female	131.7 ± 51.5	114.3 ± 23.5	129.0 ± 43.9	0.803
E/E' Ratio	15.3 ± 5.5	15.7 ± 5.9	16.1 ± 8.2	0.633
NYHA Class (I/II/III/IV)	0/30/22/0	19/26/4/0	18/22/7/0	<0.0001
6MWT (meters)	288 ± 78	304 ± 79	300 ± 71	<0.05
MLHFQ score	33.7 ± 12.0	19.3 ± 9.6	20.2 ± 12.6	<0.0001

B. Electrocardiographic Measures

	Baseline (n = 52)	6 Months (n = 49)	12 Months (n = 47)	p-value 0-12 M
24-h heart rate (beats/min)	74 ± 1.3	76 ± 1.5	76 ± 1.5	0.724
SDNN (ms)	104 ± 5.6	107 ± 6.2	124 ± 17.4	0.185
rMSSD-HRV (ms)	29 ± 2.3	31 ± 2.7	31 ± 2.6	0.546
LF (ms^2)	935 ± 296	587 ± 172	292 ± 53	0.024
HF (ms^2)	286 ± 64	221 ± 53	139 ± 22	0.020
LF/HF Ratio	2.8 ± 0.2	2.3 ± 0.2	2.0 ± 0.2	0.028
HRT onset (%)	−0.81 ± 0.28	−0.71 ± 0.32	−1.67 ± 0.30	0.082
HRT slope (ms/RR interval)	4.06 ± 0.62	7.11 ± 1.19	6.29 ± 0.65	0.047
TWA (μV)	69 ± 2.4	48 ± 1.2	42 ± 1.3	0.001
TWH (μV)	88 ± 4.5	59 ± 3.4	40 ± 2.8	0.001
# Patients with NSVT >4 beats, n (%)	7 (13.5%)	1 (1.9%)	1 (1.9%)	0.027

Key: CoV, coefficient of variance; E/E', ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity; HF, high frequency; HRT, heart rate turbulence; HRV, heart rate variability; LAVI, left atrial volume index; LF, low frequency; LF/HF ratio, low- to high-frequency HRV ratio; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic dimension; LVESV, left ventricular end systolic volume; LVESVi, left ventricular end systolic volume index; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; rMSSD, square root of the mean squared differences of successive normal-to-normal intervals; SDNN, standard deviation of normal to normal intervals; TWA, T-wave alternans; TWH, T-wave heterogeneity. 6MWT, 6-min walk test. Efficacy data are presented as means ± SD. Electrocardiographic data are presented as means ± SEM.

fibrillation events, or sustained ventricular arrhythmias during the course of the study.

All non-serious adverse events (AEs) ($n = 79$) adjudicated to be device- or therapy-related were transient and were resolved without sequelae. These included implant site pain (22 cases), oropharyngeal pain (10 cases), voice alteration (9 cases), and cough (6 cases). There were no device-related malfunctions and no unexpected device-related adverse events.

3.3. Efficacy assessments

There was a clinically meaningful and significant improvement from baseline in heart failure symptoms and quality of life, and a small but significant improvement in exercise tolerance at 12 months (Table 2). NYHA Class improved in 55% of patients (26 of 47) at 12 months ($p < 0.0001$). At 6 and 12 months, LVEF remained preserved or mildly reduced; LVESV, LVESVi, LVESD and LAVI remained normal; and E/e' ratio remained high. Left ventricular mass index data were highly variable due in part to difficulties in acquiring anatomically correct apical views [28]. When patients with a coefficient of variation (CoV, calculated as standard deviation/mean) >25% were excluded, no increase in this measure was evident: left ventricular mass index remained normal in men and remained elevated in women. There were no significant changes in N-terminal pro-BNP (716 ± 187 vs 743 ± 162 pg/mL, $p = 0.21$), hs-C-reactive protein (5.9 ± 0.7 vs 8.2 ± 2.1 mg/dL, $p = 0.28$), or creatinine (0.99 ± 0.05 to 0.94 ± 0.04 mg/dL, $p = 0.33$).

3.4. Electrocardiographic analysis

Heart rate and time-domain HRV measures were normal at baseline and were unchanged after initiation of VNS (Table 2). LF/HF ratio, a frequency-domain indicator of sympathetic predominance over vagal tone, decreased by 29% ($p = 0.028$) to normal levels at 12 months. The baroreceptor sensitivity measure HRT slope was elevated in the normal range at baseline and showed significant enhancement at 12 months ($p < 0.001$).

Maximum TWA was severely abnormal at baseline, as 98% of patients exceeded the abnormal ≥47-μV cutpoint and 73% of patients exceeded the severely abnormal ≥60-μV cutpoint (Fig. 1, Table 2). VNS reduced the maximum TWA level by 30% ($p = 0.001$) at 6 months and by 39% at 12 months ($p = 0.001$) to normal levels. The percentage of patients with abnormal TWA levels decreased to 43% at 6 months and to 26% at 12 months, while the percentage of patients with severely abnormal TWA levels decreased to 12% at 6 months and to 0 at 12 months (Table 2).

TWH was also abnormal at baseline with reference to the ≥80 μV cutpoint of abnormality (Fig. 1, Table 2). VNS reduced TWH by 33% ($p = 0.001$) at 6 months, reaching normal levels in 87% of patients, and by 55% at 12 months ($p = 0.001$), reaching normal levels in 94% of patients.

VNS significantly reduced the number of patients with NSVT ≥4 beats from seven at baseline to one at 6 and 12 months (both, $p = 0.027$).

3.5. Subgroup analysis of the effects of VNS in HFmrEF and HFpEF patients

While significant changes in LVEF did not occur in either the HFpEF ($p = 0.19$) or HFmrEF groups ($p = 0.61$) at 12 months, a significant improvement in NYHA Class was observed in both groups ($p < 0.001$ in HFpEF; $p = 0.05$ in HFmrEF) (Table 3). Improvements in TWA and TWH were substantial and highly significant in both HFpEF and HFmrEF groups (all, $p < 0.002$). The reduction in NSVT was observed in the HFmrEF group ($p = 0.0434$).

3.6. Clinical outcomes

While the study was not designed to evaluate mortality, the mortality rate of 13.6 deaths/1000 patient-years compares favorably with the mortality rate of 121 deaths/1000 patient-years reported in the general HFpEF and HFmrEF populations [29].

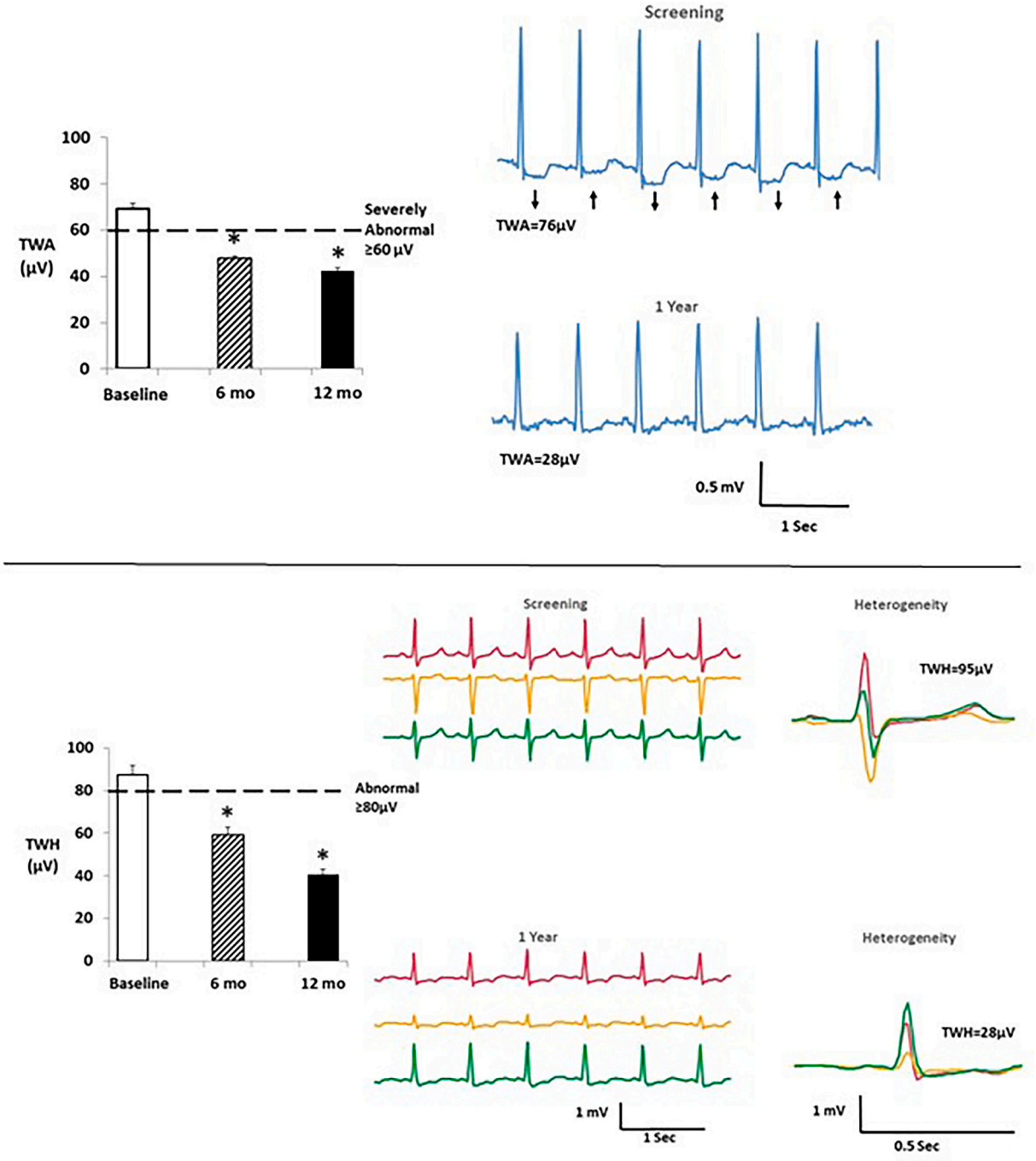

Fig. 1. Upper left panel: Progressive reduction in T-wave alternans (TWA) during 12 months of chronic autonomic regulation therapy (ART) relative to the 60-μV cutpoint of severe abnormality (dashed line). Data are presented as means ± SEM. Upper right panel: ECG tracings from a representative patient showing the effects of chronic ART on TWA.
Lower left panel: Progressive decrease in T-wave heterogeneity (TWH) during 12 months of chronic ART relative to the 80-μV cutpoint of abnormality (dashed line). Data are presented as means ± SEM. Lower right panel: ECG tracings from a representative patient showing the effects of chronic ART on TWH. *$p = 0.001$.

4. Discussion

4.1. Main findings

ANTHEM-HFpEF Study is the first investigation to evaluate the effects of chronic VNS in patients with HFpEF or HFmrEF. ART using VNS appeared to be feasible and tolerable in the patient population studied. There were clinically meaningful and significant improvements in heart failure symptoms and quality of life. The rate of all-cause mortality was low, and there was a low incidence of device-related adverse events. The overall safety profile was similar to that of ART in HFrEF in the ANTHEM-HF Study [9,13,14]. Cardiac mechanical function was unchanged, and heart failure symptoms were improved.

The present study provides evidence in patients whose heart failure status cannot be monitored by LVEF that autonomic tone, cardiac electrical stability, and freedom from arrhythmia are improved by VNS. The baseline elevations in TWA [20] and TWH [21,22], both measures of risk for cardiovascular mortality and sudden cardiac death, are consistent with the established observation that risk for sudden cardiac death is increased in this population [30]. The VNS-induced reductions

Table 3
Subgroup analysis in HFmrEF and HFpEF patients of effects of VNS on efficacy and electrocardiographic measures significant in the combined cohort.

	HFpEF (N = 40) Baseline	6 Months	12 months	p-value 0–12 months	HFmrEF (N = 12) Baseline	6 months	12 months	p-value 0–12 months
6MWT (meters)	271 ± 12	292 ± 12	295 ± 12	0.0018	344 ± 19	344 ± 24	308 ± 20	0.20
NYHA Class I/II/III/IV	0/22/18/0	13/20/5/0	13/20/4/0	<0.001	0/8/4/0	6/5/0/0	5/2/3/0	<0.05
TWA (μV)	68.2 ± 3.0	48.6 ± 1.5	43.4 ± 1.6	3.8E-10	72.8 ± 3.4	44.4 ± 1.4	38.3 ± 0.98	0.00001
TWH (μV)	88.5 ± 5.1	57.6 ± 3.6	39.7 ± 3.0	9.2E-11	84.2 ± 9.3	65.4 ± 8.7	42.6 ± 6.8	0.0017
# Patients with NSVT >4 beats, n (%)	3 (7.5%)	1 (2.5%)	1 (2.5%)	0.194	4 (33%)	0 (0%)	0 (0%)	0.0434

Key: HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; TWA = T-wave alternans; TWH = T-wave heterogeneity; 6MWT = 6-min walk test.

in TWA are particularly significant inasmuch as a decrement of ~20 μV has been shown to be associated with a >55% decrease in cardiac mortality and a >58% decrease in sudden cardiac death [20]. TWH has been shown clinically to be highly predictive of sudden cardiac death based on resting 12-lead ECGs in the 5600-subject Health Survey 2000 [23] as well as in patients with ischemic and nonischemic cardiomyopathies undergoing electrophysiologic study, in whom TWH predicted sustained ventricular arrhythmia, appropriate ICD therapies, and arrhythmic death or cardiac arrest [24]. The significant reduction in the number of HFmrEF patients with NSVT ≥4 beats is consistent with the VNS-induced reductions in TWA and TWH.

4.2. Absence of prior studies of VNS in heart failure patients with preserved or mildly reduced heart failure

The present study affirms the pioneering investigation by Schwartz and colleagues, [31] who demonstrated that chronic VNS exerts a significant cardioprotective effect in patients with impaired cardiac mechanical function. However, no prior studies of cervical VNS in patients with HFpEF or HFmrEF have been published. In a subgroup analysis (Table 3), evidence is provided that VNS can improve NYHA Class not only in patients with HFpEF but also in those with HFmrEF. Our study is now the first to demonstrate that VNS also significantly improves markers of susceptibility to VT/VF in both classifications. This finding is particularly important in light of a recent study in >13,000 patients [32], which reported that susceptibility to VT/VF is a critical marker of disease severity in HFpEF and HFmrEF.

4.3. Mechanistic basis for improvements by VNS

The central hypothesis motivating this investigation was that chronic VNS in HFpEF and HFmrEF patients would improve autonomic tone and reflexes, which would reduce cardiac electrical instability as assessed by TWA and TWH. This hypothesis appears to be supported by the findings that measures of autonomic tone (HRV) and reflexes (HRT slope) were improved by VNS. It is well established that adrenergic factors can increase TWA and TWH, and correspondingly, it was anticipated that the antiadrenergic effects of VNS would directly reduce these measures of cardiac electrical instability. The antisympathetic action of VNS has been demonstrated in epilepsy patients, in whom chronic VNS reduced skin sympathetic activity [33].

While not measured in our investigation, chronic VNS may also have an anti-inflammatory effect, as demonstrated by Stavrakis and colleagues with tragus nerve stimulation [6]. Thus, chronic VNS may confer a comprehensive beneficial action in HFpEF and HFmrEF by targeting two major pathophysiologic mechanisms: altered autonomic tone and inflammation.

4.4. Limitations

The significant improvements in several measures of heart failure symptoms and exercise tolerance, including NYHA functional class, 6MWT, and quality of life, may reflect a potential VNS impact on one or more of the peripheral disorders that have come to be associated with HFpEF [34,35]. However, this possibility is speculative and any improvements in symptoms or patient-reported outcomes from this uncontrolled study should be interpreted with caution, as these subjective measures could have been influenced by a placebo or Hawthorne effect. No control patients without implanted devices were enrolled. Any anti-inflammatory effects of chronic VNS that may contribute to the observed improvements also remain unknown. In future studies, improvements in critical measures such as baroreceptor sensitivity that do not require the occurrence of spontaneous heart beats should be utilized [36]. Additional bloodborne biohumoral markers should be included, as well as echocardiographic assessment of right ventricular function. In future studies, more sophisticated measures of cardiac mechanical function, in particular, global longitudinal strain, should be evaluated.

5. Conclusions

The ANTHEM-HFpEF Study achieved its primary objective by demonstrating that ART appears to be feasible, well tolerated, and safe in patients with HFpEF or HFmrEF. Chronic ART was associated with improved heart failure symptoms, exercise tolerance, autonomic tone, quality of life, and cardiac electrical stability and reduced NSVT incidence. The overall beneficial effects appear to apply both to the HFpEF and HFmrEF groups. The finding that VNS also significantly improves markers of susceptibility to VT/VF in both classifications is particularly important in light of recent evidence [32] that susceptibility to malignant ventricular arrhythmias is a critical marker of disease severity in heart failure with mildly reduced or preserved LVEF. The low incidence of mortality in the present study, which is only 11% that of the general HFpEF/HFmrEF population [29], is consistent with these observations.

Definitive demonstration of the clinical utility of chronic ART in patients with differing HFpEF and HFmrEF phenotypes will require further study.

Funding

The ANTHEM-HFpEF Study was funded by LivaNova USA. ECG analyses were supported by a grant from LivaNova USA to Beth Israel Deaconess Medical Center.

CRediT Author statement

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be submitted.

H. Uday Kumar, M.D.: investigation; writing– original draft; writing—review and editing; Bruce D. Nearing, Ph.D.: data curation, formal analysis, methodology, software, validation; writing—review and editing; Sanjay Mittal, M.D.: investigation; writing—review and editing; Rajendra K. Premchand, M.D.: investigation; writing—review and editing; Imad Libbus, Ph.D.: conceptualization; data curation, formal analysis, methodology, project administration; validation; visualization; writing—review and editing; Lorenzo A. DiCarlo, M.D.:

conceptualization; funding acquisition; methodology; project administration; resources; validation; visualization; writing—review and editing; Badri Amurthur, M.S.: conceptualization; methodology; validation; visualization; writing—review and editing; Bruce H. KenKnight, Ph.D., conceptualization; funding acquisition; project administration; resources; validation; visualization; writing—review and editing; Inder S. Anand, M.D., F.R.C.P., D.Phil. (Oxon), conceptualization; investigation; methodology; supervision; writing—review and editing; Richard L. Verrier, Ph.D.: methodology; supervision; visualization; writing—original draft; writing—review and editing.

Declaration of Competing Interest

Drs. Kumar, Mittal, and Premchand were site investigators and Dr. Anand was Principal Investigator of the ANTHEM-HFpEF Study. Drs. Libbus, DiCarlo, and KenKnight and Mr. Amurthur are employees and shareholders in LivaNova USA. Drs. Nearing and Verrier declare no conflicts of interest.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.03.030.

References

[1] P.A. Heidenreich, B. Bozkurt, D. Aguilar, et al., 2022 AHA/ACC/HFSA guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines, J. Am. Coll. Cardiol. 79 (17) (2022 May 3) e263–e421, https://doi.org/10.1016/j.jacc.2021.12.012.

[2] T.A. McDonagh, M. Metra, M. Adamo, et al., For the ESC scientific document group. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the heart failure association (HFA) of the ESC, Eur. J. Heart Fail. 24 (1) (2022 Jan) 4–131, https://doi.org/10.1002/ejhf.2333.

[3] J.J. Hsu, B. Ziaeian, G.C. Fonarow, Heart failure with mid-range (borderline) ejection fraction: clinical implications and future directions, JACC Heart Fail 5 (2017) 763–771.

[4] J.B. Cohen, S.J. Schrauben, L. Zhao, et al., Clinical phenogroups in heart failure with preserved ejection fraction: detailed phenotypes, prognosis, and response to spironolactone, JACC Heart Fail 8 (3) (2020 Mar) 172–184, https://doi.org/10.1016/j.jchf.2019.09.009.

[5] N. Glezeva, J.A. Baugh, Role of inflammation in the pathogenesis of heart failure with preserved ejection fraction and its potential as a therapeutic target, Heart Fail. Rev. 19 (2014) 681–694, https://doi.org/10.1007/s10741-013-9405-8.

[6] S. Stavrakis, K. Elkholey, L. Morris, M. Niewiadomska, Z.U.A. Asad, M. B. Humphrey, Neuromodulation of inflammation to treat heart failure with preserved ejection fraction: a pilot randomized clinical trial, J. Am. Heart Assoc. 11 (3) (2022 Feb), e023582, https://doi.org/10.1161/JAHA.121.023582.

[7] I. Cygankiewicz, W. Zareba, R. Vazquez, et al., For the MUSIC investigators. Risk stratification of mortality in patients with heart failure and left ventricular ejection fraction >35%, Am. J. Cardiol. 103 (7) (2009 Apr 1) 1003–1010, https://doi.org/10.1016/j.amjcard.2008.11.061.

[8] J. Ksela, L. Rupert, A. Djordjevic, M. Antonic, V. Avbelj, B. Jug, Altered heart rate turbulence and variability parameters predict 1-year mortality in heart failure with preserved ejection fraction, J. Cardiovasc. Dev. Dis. 9 (7) (2022 Jul 2) 213, https://doi.org/10.3390/jcdd9070213.

[9] R.K. Premchand, K. Sharma, S. Mittal, R. Monteiro, S. Dixit, I. Libbus, 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. 20 (2014) 808–816.

[10] R.K. Premchand, K. Sharma, S. Mittal, et al., Extended follow-up of patients with heart failure receiving autonomic regulation therapy in the ANTHEM-HF study, J. Card. Fail. 22 (2016) 639–642.

[11] I. Libbus, B.D. Nearing, B. Amurthur, B.H. KenKnight, R.L. Verrier, Autonomic regulation therapy suppresses quantitative T-wave alternans and improves baroreflex sensitivity in patients with heart failure enrolled in the ANTHEM-HF study, Heart Rhythm. 13 (2016) 721–728, https://doi.org/10.1016/j.hrthm.2015.11.030.

[12] B.D. Nearing, I.S. Anand, I. Libbus, L.A. DiCarlo, B.H. KenKnight, R.L. Verrier, Vagus nerve stimulation provides multiyear improvements in autonomic function and cardiac electrical stability in the ANTHEM-HF study, J. Card. Fail. 27 (2021) 208–216, https://doi.org/10.1016/j.cardfail.2020.10.003.

[13] K. Sharma, R.K. Premchand, S. Mittal, et al., 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. 15 (323) (2021) 175–178, https://doi.org/10.1016/j.ijcard.2020.09.072.

[14] I. Libbus, R.K. Premchand, K. Sharma, S. Mittal, R. Monteiro, B. Amurthur, B. H. KenKnight, L.A. DiCarlo, I.S. Anand, Persistent autonomic engagement and cardiac control after four or more years of autonomic regulation therapy using Vagus nerve stimulation, Front. Physiol. 11 (13) (2022 Mar), 853617, https://doi.org/10.3389/fphys.2022.853617.

[15] F. Zannad, G.M. De Ferrari, A.E. Tuinenburg, 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. 36 (2015) 425–433, https://doi.org/10.1093/eurheartj/ehu345.

[16] M.R. Gold, D.J. Van Veldhuisen, P.J. Hauptman, et al., Vagus nerve stimulation for the treatment of heart failure: the INOVATE HF trial, J. Am. Coll. Cardiol. 68 (2016) 149–158, https://doi.org/10.1016/j.jacc.2016.03.525.

[17] I.S. Anand, M.A. Konstam, H.U. Klein, et al., Comparison of symptomatic and functional responses to vagus nerve stimulation in ANTHEM-HF, INOVATE-HF, and NECTAR-HF, ESC Heart Fail. 7 (1) (2020 Feb) 75–83, https://doi.org/10.1002/ehf2.12592.

[18] J.L. Ardell, H. Nier, M. Hammer, Defining the neural fulcrum for chronic vagus nerve stimulation: implications for integrated cardiac control, J. Physiol. 595 (22) (2017 Nov 15) 6887–6903, https://doi.org/10.1113/JP274678.

[19] L.A. DiCarlo, I. Libbus, H.U. Kumar, Autonomic regulation therapy to enhance myocardial function in heart failure patients: the ANTHEM-HFpEF study, ESC Heart Fail. 5 (2018) 95–100.

[20] R.L. Verrier, T. Klingenheben, M. Malik, et al., Microvolt T-wave alternans: physiological basis, methods of measurement, and clinical utility: consensus guideline by International Society for Holter and Noninvasive Electrocardiology, J. Am. Coll. Cardiol. 58 (2011) 1309–1324.

[21] R.L. Verrier, H.V. Huikuri, Tracking interlead heterogeneity of R- and T-wave morphology to disclose latent risk for sudden cardiac death, Heart Rhythm. 14 (2017) 1466–1475.

[22] R.L. Verrier, B.D. Nearing, A. D'Avila, Spectrum of clinical applications of interlead ECG heterogeneity assessment: from myocardial ischemia detection to sudden cardiac death risk stratification, Ann. Noninvasive Electrocardiol. 26 (6) (2021), e12894, https://doi.org/10.1111/anec.12894.

[23] T.V. Kenttä, B.D. Nearing, K. Porthan, J.T. Tikkanen, M. Viitasalo, M.S. Nieminen, V. Salomaa, L. Oikarinen, H.V. Huikuri, R.L. Verrier, Prediction of sudden cardiac death with automated high throughput analysis of heterogeneity in standard resting 12-lead electrocardiogram, Heart Rhythm. 13 (2016) 713–720, https://doi.org/10.1016/j.hrthm.2015.11.035.

[24] A.Y. Tan, B.D. Nearing, M. Rosenberg, R. Nezafat, M.E. Josephson, R.L. Verrier, Interlead heterogeneity of R- and T-wave morphology in standard 12-lead ECGs predicts sustained ventricular tachycardia/fibrillation and arrhythmic death in patients with cardiomyopathy, J. Cardiovasc. Electrophysiol. 28 (2017) 1324–1333.

[25] R.M. Lang, L.P. Badano, V. Mor-Avi, et al., Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, J. Am. Soc. Echocardiogr. 28 (1) (2015 Jan) 1–39.e14, https://doi.org/10.1016/j.echo.2014.10.003.

[26] Heart rate variability, Standards of measurement, physiological interpretation, and clinical use. Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, Eur. Heart J. 17 (1996) 354–381.

[27] A. Bauer, M. Malik, G. Schmidt, et al., Heart rate turbulence: standards of measurement, physiological interpretation, and clinical use: International Society for Holter and Noninvasive Electrophysiology Consensus, J. Am. Coll. Cardiol. 52 (2008) 1353–1365.

[28] V. Mor-Avi, L. Sugeng, L. Weinert, et al., Fast measurement of left ventricular mass with real-time three-dimensional echocardiography: comparison with magnetic resonance imaging, Circulation 110 (2004) 1814–1818, https://doi.org/10.1161/01.CIR.0000142670.65971.5F.

[29] Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis, Eur. Heart J. 33 (2012) 1750–1757.

[30] M. Vaduganathan, B.L. Claggett, N.A. Chatterjee, et al., Sudden death in heart failure with preserved ejection fraction: a competing risks analysis from the TOPCAT trial, JACC Heart Fail 6 (2018) 653–661.

[31] P.J. Schwartz, G.M. De Ferrari, A. Sanzo, et al., Long term vagal stimulation in patients with advanced heart failure: first experience in man, Eur. J. Heart Fail. 10 (2008) 884–891.

[32] J.P. Curtain, C. Adamson, T. Kondo, et al., Investigator-reported ventricular arrhythmias and mortality in heart failure with mildly reduced or preserved ejection fraction, Eur. Heart J. 12 (2023 Jan) ehac801, https://doi.org/10.1093/eurheartj/ehac801.

[33] Y. Yuan, J.L. Hassel, A. Doytchinova, et al., Left cervical vagal nerve stimulation reduces skin sympathetic nerve activity in patients with drug resistant epilepsy, Heart Rhythm. 14 (12) (2017 Dec) 1771–1778, https://doi.org/10.1016/j.hrthm.2017.07.035.

[34] B.A. Borlaug, Evaluation and management of heart failure with preserved ejection fraction, Nat. Rev. Cardiol. 17 (9) (2020) 559–573, https://doi.org/10.1038/s41569-020-0363-2.

[35] S.E. Kjeldsen, T.G. von Lueder, O.A. Smiseth, et al., Medical therapies for heart failure with preserved ejection fraction, Hypertension 75 (1) (2020) 23–32, https://doi.org/10.1161/HYPERTENSIONAHA.119.14057.

[36] A. Giannoni, F. Gentile, F. Buoncristiani, et al., Chemoreflex and baroreflex sensitivity hold a strong prognostic value in chronic heart failure, JACC Heart Fail. 10 (9) (2022 Sep) 662–676, https://doi.org/10.1016/j.jchf.2022.02.006.