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

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Aim	The neural cardiac therapy for heart failure (NECTAR-HF) was a randomized sham-controlled trial designed to evaluate whether a single dose of vagal nerve stimulation (VNS) would attenuate cardiac remodelling, improve cardiac function and increase exercise capacity in symptomatic heart failure patients with severe left ventricular (LV) systolic dysfunction despite guideline recommended medical therapy.
Methods	Patients were randomized in a 2 : 1 ratio to receive therapy (VNS ON) or control (VNS OFF) for a 6-month period. The primary endpoint was the change in LV end systolic diameter (LVESD) at 6 months for control vs. therapy, with secondary endpoints of other echocardiography measurements, exercise capacity, quality-of-life assessments, 24-h Holter, and circulating biomarkers.
Results	Of the 96 implanted patients, 87 had paired datasets for the primary endpoint. Change in LVESD from baseline to 6 months was -0.04 ± 0.25 cm in the therapy group compared with -0.08 ± 0.32 cm in the control group ($P = 0.60$). Additional echocardiographic parameters of LV end diastolic dimension, LV end systolic volume, left ventricular end diastolic volume, LV ejection fraction, peak VO_2, and N-terminal pro-hormone brain natriuretic peptide failed to show superiority compared to the control group. However, there were statistically significant improvements in quality of life for the Minnesota Living with Heart Failure Questionnaire ($P = 0.049$), New York Heart Association class ($P = 0.032$), and the SF-36 Physical Component ($P = 0.016$) in the therapy group.
Conclusion	Vagal nerve stimulation as delivered in the NECTAR-HF trial failed to demonstrate a significant effect on primary and secondary endpoint measures of cardiac remodelling and functional capacity in symptomatic heart failure patients, but quality-of-life measures showed significant improvement.
Keywords	Vagal stimulation • Heart failure • Autonomic nervous system

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Introduction

Increased sympathetic activation and reduced parasympathetic tone, as reflected by reduced baroreflex sensitivity and/or decreased heart rate variability, are potentially important pathophysiological contributors to the progression of heart failure (HF) irrespective of aetiology, and are associated with poor outcome.[1,2] Experimental augmentation of parasympathetic tone has recently emerged as a potential therapeutic approach to normalizing autonomic imbalance and inhibiting the progression of HF.[3,4] The effect of enhancing parasympathetic tone via direct vagal nerve stimulation (VNS) was recently assessed in a non-randomized observational study of 32 HF patients with left ventricular (LV) systolic dysfunction, with results suggesting that vagal stimulation favourably influenced quality of life, exercise capacity, and LV remodelling.[5,6]

The neural cardiac therapy for heart failure (NECTAR-HF) trial (www.clinicaltrials.gov, NCT01385176) is the first randomized sham-controlled trial designed to evaluate whether right cervical VNS is safe and might attenuate cardiac remodelling, improve cardiac function, increase exercise capacity, enhance quality of life, and favourably impact circulating biomarkers in symptomatic HF patients with severe LV systolic dysfunction receiving guideline recommended medical therapy.[7]

Methods

The NECTAR-HF study design has been published previously.[8] The complete protocol can be viewed in the Supplementary materials online that accompany this manuscript. Twenty-seven centres across Western Europe were approved for participation in the study by the appropriate ethics committees and regulatory agencies. The study was conducted in accordance with the Declaration of Helsinki, ISO 14155: 2011 and all other applicable regulations as determined by the country of submission. Participants provided written informed consent prior to enrolment.

Patient eligibility criteria

Patients were required to have a documented LV ejection fraction (LVEF) of $\leq 35\%$, an LV end diastolic dimension (LVEDD) of ≥ 55 mm, and a New York Heart Association (NYHA) classification of II or III. Patients also had to be treated with medical therapy per European heart failure guidelines[7] for at least 30 days prior to enrolment. Key exclusion criteria included persistent or permanent atrial fibrillation, cardiac resynchronization (CRT) for <1 year or a QRS of >130 ms without CRT, type I diabetes, type II diabetes for >5 years, sleep disordered breathing that had been treated for <6 months, a surgically correctable cause of HF, recent HF hospitalization, or myocardial infarction (30 or 90 days, respectively), or an indication for dialysis.

Therapy

In all patients, implantation of the VNS system was performed within 45 days of the pre-implant screening period. *Figure 1* shows the implanted system. A self-sizing bipolar helical lead was implanted around the right vagus nerve in the cervical region and the lead body was tunnelled over the clavicle. The terminal end was connected to the pulse generator that was implanted in a subcutaneous pectoral pocket. During the implant procedure, the NECTAR-HF system was tested for system integrity and to verify effective stimulation. Prior to discharge from the hospital, patients were instructed to charge their implanted device once a week for an hour by placing the wireless external charger over the generator. Patients returned to the clinic 14 ± 5 days after the implant for

baseline assessment. At the completion of baseline testing, patients were randomized in a 2 : 1 block permuted manner to either therapy or control.

During therapy titration, the stimulation amplitude was increased until patients either experienced side effects that were unpleasant (e.g. neck pain or coughing), or the maximum allowed current for chronic stimulation was reached (4 mA). The recommended settings were 20 Hz, with 10 s on, 50 s off, and a pulse width of 300 µs. So as to maintain blinding, regardless of group randomization, all patients underwent therapy titration until first detectable level of stimulation, such as a tickling sensation in the throat, coughing, or voice alteration, but in the control group stimulation was turned off at the end of the visit.

Following the baseline visit, all patients returned for three stimulation titrations within the next 30 days. After the final titration, the 6-month time window began. Therapy patients received active stimulation; control patients' devices remained off. Additional follow-up visits were performed at 3 and 6 months for device checks, adverse event reporting, and/or endpoint assessments. Patients who had a defibrillator underwent routine device checks to assess for possible system interference.

Blinding

Programming of the generator was performed by a physician un-blinded to treatment assignment, while all other investigators and site study staff involved in endpoint data collection were blinded to randomization. Before and after titrations, a standard statement was read to patients informing them that they may feel sensations during titrations, or on a chronic basis, but that these sensations were not indicative that they were receiving therapeutic stimulation. At scheduled visits, patients were queried on whether they believed they were assigned to the therapy or control group. To assess the degree to which patients were blinded to treatment assignment, a blinding index analysis was performed. A detailed description of the analysis has been described elsewhere.[9]

At the end of 6 months, all patients in the control group had their devices turned ON to receive active therapy. Additional follow-up visits occur every 3 months through 18 month. Because NECTAR-HF is an on-going trial, the present report is limited to the results of the 6 month randomized and controlled phase.

Endpoints and sample size

The change in left ventricular end systolic diameter (LVESD) from baseline (randomization visit) to 6 months was selected as primary efficacy endpoint. Echocardiography exams were performed by treatment-blinded sonographers who were certified by the echocardiography core lab (Brigham and Women's Hospital, Boston, MA, USA). Details of the echocardiography views and analysis can be found in the Supplementary materials online.

Secondary endpoints included LV end systolic volume (LVESV), LVEF, peak VO_2, N-terminal pro-hormone brain natriuretic peptide (NT-proBNP), Holter derived indices of autonomic nerve modulation (standard deviation of normal to normal beats, SDNN; standard deviation of the average normal to normal beats, SDANN; root mean square of successive differences, RMSSD), Minnesota Living with Heart Failure Questionnaire © (MLHFQ),[9] the Short Form 36 Health Survey (SF-36)[10] and NYHA functional class. All procedures for echocardiography, cardiopulmonary exercise testing, quality-of-life and plasma collection are described in the main design paper.[8] NT-proBNP (Roche Elecsys ECLIA) was quantified at the Clinical Reference Laboratory (Lenexa, KS, USA) and the 45-biomarker Human Inflammation-MAP® v. 1.0 (multiplexed immunoassay) was performed at Myriad RBM (Austin, TX, USA).

Figure 1 Consort diagram for neural cardiac therapy for heart failure.
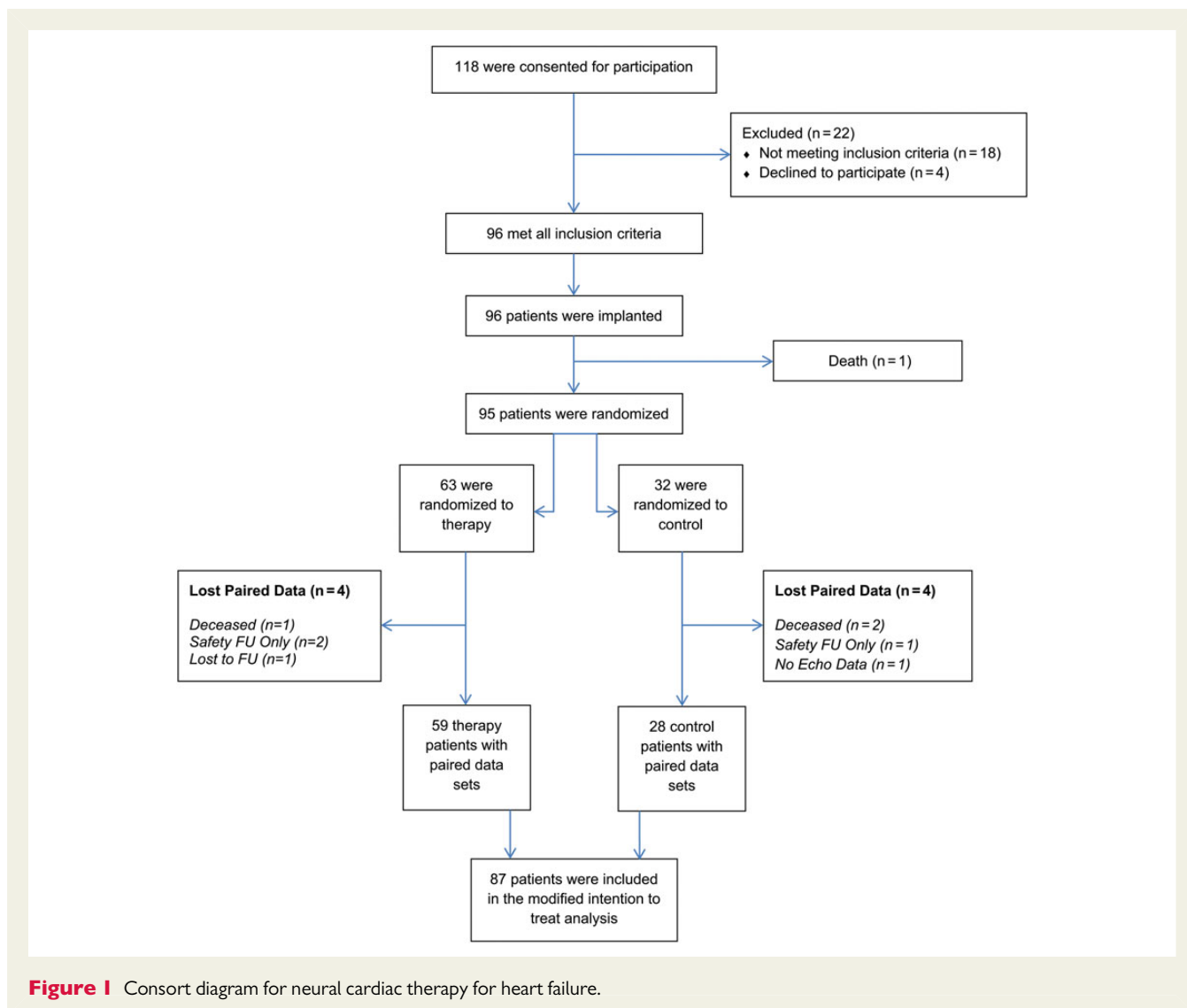
Statistical analysis

The primary endpoint of LVESD was analysed using a modified intention to treat analysis on the final dataset, where only patients with paired datasets from baseline and 6 months were included in the analysis. Sample size calculation and the statistical analysis plan have been described elsewhere (Supplementary materials online),[8] but was estimated that the 96 patients study was powered to detect a 5 ± 6 mm difference in LVESD between groups using a 2 : 1 randomization, assuming 40% data attrition.

An as-treated sub-analysis was performed including only patients who received per-protocol therapy for at least 85% of the randomization period. The primary endpoint of LVESD was tested using a general linear model, with LVESD as the outcome and randomization group, and baseline LVESD as a covariate in the model. Statistical testing was performed at a significance level of 5%.

Testing of all secondary outcomes, except NYHA, was performed using the same methodology that was used for the primary endpoint. NYHA was assessed using a Cochran-Armitage test for trend, in which the number of NYHA classes changed from baseline to 6 months was compared between the randomization groups. Exploratory analyses were performed on pre-specified endpoints and subgroups as defined in the Statistical Analysis Plan (see Supplementary materials online). All-cause mortality will be further formally evaluated as the primary safety endpoint at 18 months as specified in the protocol.

Results

Of the 118 patients enrolled, 96 were found to be eligible and were implanted across 24 centres (7 sites with 5–10 implants, 1 site with 13 implants). As shown in *Figure 2*, 87 patients completed the 6-month study having paired echocardiography exams. In addition, 86 patients had paired blood samples, and 83 had paired exercise tests available.

Patient characteristics

Table 1 summarizes the patient characteristics. Body mass index was significantly greater and diuretic usage higher in the control group, while statin usage was statistically higher in the therapy group. No patients were treated with ivabradine. All other variables, including efficacy endpoints, were balanced between the therapy and control groups. The median pre-implant NT-proBNP was 882 pg/ml
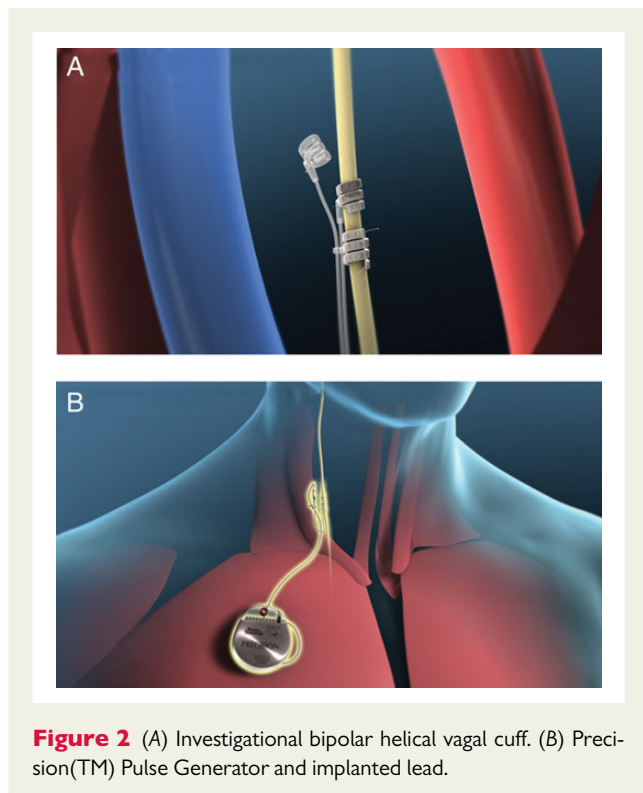
Figure 2 (*A*) Investigational bipolar helical vagal cuff. (*B*) Precision(TM) Pulse Generator and implanted lead.

Table I Baseline patient characteristics at enrolment for the therapy and control groups

	Therapy (*N* = 63)	Control (*N* = 32)	*P*-value
Demographics			
Gender: male, *n* (%)	56 (89)	26 (81)	0.31
Age	59.8 ± 12.2	59.3 ± 10.1	0.87
Body mass index	28.6 ± 5.9	31.2 ± 5.1	0.02
NYHA II/III	7/51	7/22	0.22
ICD/CRT-D/No device	51/5/7	22/4/6	0.68
Resting heart rate (bpm)	68.2 ± 13.2	71.3 ± 12.9	0.24
Blood pressure (mmHg)			
Systolic	118 ± 17	115 ± 16	0.39
Diastolic	73 ± 10	73 ± 13	0.98
Clinical history			
Ischaemic heart failure, *n* (%)	44 (70)	20 (63)	0.47
Hypertension, *n* (%)	29 (46)	21 (66)	0.07
Renal disease *n* (%)	12 (19)	9 (28)	0.31
Heart failure hospitalization past 6 months, *n* (%)	8 (13)	4 (13)	0.98
Previous myocardial infarction, *n* (%)	42 (67)	19 (59)	0.48
Non-insulin dependent diabetes, *n* (%)	14 (22)	9 (28)	0.53
Sleep apnoea, *n* (%)	9 (14)	3 (9)	0.50
Cardiovascular medications			
B-blockers, *n* (%)	59 (94)	30 (94)	0.99
Angiotensin converting enzyme inhibitor, *n* (%)	51 (81)	24 (75)	0.50
Angiotensin receptor blocker, *n* (%)	17 (27)	7 (22)	0.59
Mineralocorticoid receptor antagonist, *n* (%)	43 (68)	23 (72)	0.72
Loop diuretics, *n* (%)	54 (86)	32 (100)	0.02
Statin, *n* (%)	50 (79)	19 (59)	0.04

(inter-quartile range, IQR: 488−1926) and 879 (IQR: 370−1843) for control and therapy patients, respectively. The median pre-implant CRP levels were 2.6 µg/mL (IQR: 1.9−12.0) and 2.1 µg/mL (IQR: 1.0−4.7) for control and therapy patients, respectively.

Therapy

The mean stimulation amplitude for the therapy patients at the end of the 3rd titration was 1.24 ± 0.74 mA, and 1.42 ± 0.80 mA after the 3-month follow-up visit. The self-reported threshold for activating the laryngeal fibres at the 3rd titration visit was 0.99 ± 0.67 mA, and 1.17 ± 0.74 mA at the 3-month follow-up visit. During the full 6-month randomization period, there were 10 patients that were defined as having lost therapy due to magnet reset of the device (six patients), failure to adequately re-charge the stimulator (two patients), system explant due to infection (one patient), and elective deactivation of the device (one patient).

Blinding

Table 2 shows the results of a blinding assessment that was performed at the 6-month follow-up visit. The blinding index ranged from 0.31 in the inactive therapy group to 0.70 in the active therapy arm.

Efficacy endpoints

Table 3 shows a summary of the primary and secondary endpoint outcomes. Analysis of the primary endpoint of LVESD revealed comparable changes from baseline to 6 months in the therapy and control groups. Other echocardiographic endpoints (LVEDD, LVESV, left ventricular end diastolic volume, and LVEF) and the additional endpoints of exercise capacity (peak VO$_2$) and NT-proBNP

likewise showed comparable changes in the two groups. Analysis of MLHFQ and SF-36 demonstrated statistically significant improvement with VNS treatment when compared with control. *Figure 3* displays the NYHA results, showing that 62% of patients in the therapy group improved their functional class at least one point compared with only 45% of control patients (*P* = 0.032). Additional analyses, performed using pure intention to treat (imputed missing data), failed to show significance in echocardiography related measures. An as-treated analysis, excluding patients defined as having lost therapy (described above) did not alter the results of the primary or secondary endpoint outcomes. Finally, indexing the echocardiography analysis to body surface area did not impact the results.

Table 2 At the 6-month follow-up visit, patients were asked what to which group they believed they were randomized

6 months

Randomization group	Patients' response to blinding			Blinding Index (95% CI)
	On	Off	Did not know	
Off	7 (24.1%)	16 (55.2%)	6 (20.7%)	0.31 (0.08, 0.54)
On	44 (77.2%)	4 (7.0%)	9 (15.8%)	0.70 (0.48, 0.92)

Data are presented as N (%). A blinding index of 0 means blinding was perfect, and score of 1 would be completely un-blinded.

Table 3 Changes in primary and secondary efficacy endpoints from baseline to 6 months for therapy and control patients

Endpoint	N	Therapy		Control		P-value[a]
		Baseline	6-month	Baseline	6-month	
LVESD (cm)	86	4.9 ± 0.9	4.9 ± 0.8	5.2 ± 0.7	5.1 ± 0.8	0.60
LVEDD (cm)	86	5.9 ± 0.7	5.8 ± 0.7	6.0 ± 0.6	6.0 ± 0.7	0.84
LVEDV (ml)	86	218.3 ± 67.1	207.4 ± 68.5	235.4 ± 46.7	221.3 ± 49.3	0.36
LVESV (ml)	86	154.7 ± 58.5	142.5 ± 57.1	164.0 ± 39.2	152.1 ± 43.8	0.86
LVEF (%)	86	30.5 ± 6.0	32.7 ± 6.4	30.8 ± 4.2	32.1 ± 5.6	0.27
Peak VO$_2$ (ml/kg/min)	83	15.6 ± 3.9	15.8 ± 4.4	15.2 ± 3.3	14.7 ± 3.6	0.26
MLHFQ score	87	44.4 ± 22.2	35.8 ± 20.8	42.8 ± 25.1	41.8 ± 24.3	0.049
SF-36 physical	85	36.3 ± 7.6	41.2 ± 7.9	37.7 ± 7.9	38.4 ± 8.4	0.02
SF-36 mental	85	41.2 ± 7.9	43.8 ± 10.8	40.7 ± 10.9	41.1 ± 10.7	0.24
NT-proBNP	84	879 (370−1843)	930 (409−1938)	882 (488−1926)	839 (302−1847)	0.41

LVESD, left ventricular end systolic diameter; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire.
Data presented as mean $\pm$ SD for all values except NT-proBNP which is median (inter-quartile range). MLWHFQ intergroup difference, 95% confidence interval = −7.7 (−14.3, −0.03); SF-36 intergroup difference (95% confidence interval) = 3.7 (0.7, −6.7).
[a]Comparing the therapy and control deltas from baseline to 6 months.

24-h Holter

As shown in *Table 4*, analysis of the 24-h Holter data did not reveal statistically significant differences in the changes from baseline to 6 months for minimum, maximum, or mean HR. Time domain measures of heart rate variability showed that SDANN was statistically increased in the active treatment group when compared with the control group, but not for RMSSD, SDNN, and the traditional frequency domain parameters.

Safety

Table 5 shows adverse events for the control and therapy groups. One patient died pre-randomization from 4 days post-operatively from a pulmonary embolism. There were three patient deaths that occurred between randomization and 6 months; two patients randomized to the control group died from heart failure complications 40 and 124 days after VNS implant, and one patient randomized to therapy died 127 days after VNS implant from worsening heart failure.

An overall infection rate of 7.4% (7 infections) associated with the implanted system occurred in the entire cohort of 95 patients; three infections resulted in explant of the VNS system (two control, one

therapy). Four infections were managed with antibiotics. One patient needed a pulse generator pocket revision because of problems recharging the device, and another patient underwent lead revision due to inappropriate lead movement. There were no significant differences in the occurrence of ICD shock delivery and/or anti-tachycardia pacing between the two groups (VNS-therapy 9.5%, control 6.5%; $P = 0.71$). All ICD shocks and anti-tachycardia pacing were adjudicated and determined not to be associated with interference from the investigational system.

Discussion

NECTAR-HF is the first randomized controlled trial to investigate a prescribed right-sided VNS protocol in an HF population. The study failed to demonstrate an improvement in LV remodelling parameters, LV function, or circulating biomarkers following 6 months of chronic VNS at the prescribed stimulation settings. NECTAR-HF did however demonstrate significant improvements in the subjective endpoints of NYHA functional class and heart failure related quality-of-life measures, although these findings should be interpreted with caution given the imperfect patient-level blinding (*Table 2*). The safety profile for this application of
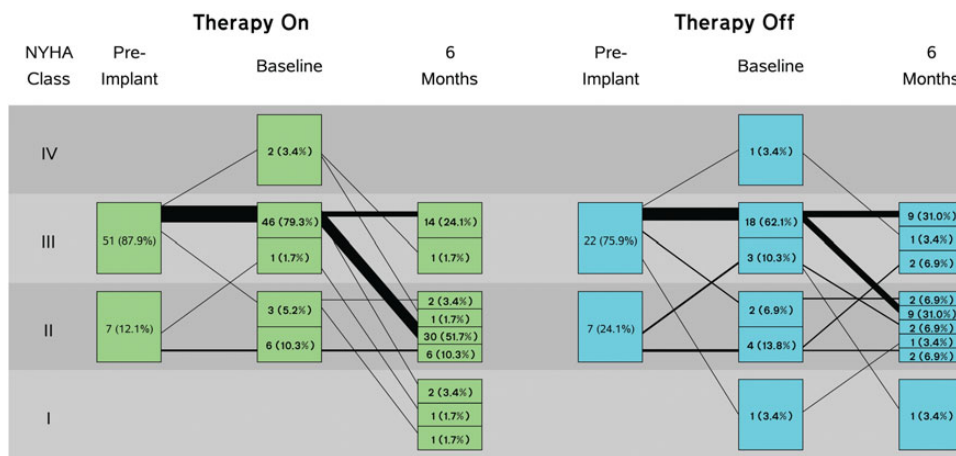
Figure 3 New York Heart Association class change from baseline to Month 6 (*P* = 0.032).

Table 4 Results of the 24-h Holter analysis

	Therapy (*N* = 55)			Control (*N* = 28)			*P*-value
	Baseline	6 months	Δ therapy	Baseline	6 months	Δ control	
RMSSD (ms ± SD)	78.8 ± 41.8	97.0 ± 40.2	18.2 ± 50.9	94.5 ± 31.5	89.9 ± 37.0	−4.7 + 45.5	0.26
SDNN (ms ± SD)	146 ± 48.3	129.7 ± 52.1	−16.3 + 60.3	146.3 ± 47.2	132.1 ± 41.3	−14.2 + 60.9	0.83
SDANN (ms ± SD)	29.1 ± 2.1	29.4 ± 2.3	0.3 ± 2.0	29.6 ± 2.5	28.8 ± 2.2	−0.8 + 2.1	0.03
Mean HR (bpm ± SD)	70.1 ± 10.4	70.7 ± 10.0	0.5 ± 8.2	69.2 ± 9.7	73.0 ± 10.7	3.8 ± 8.7	0.10
Minimum HR (bpm ± SD)	54.6 ± 9.2	53.2 ± 8.0	−1.5 + 7.6	53.4 ± 8.6	54.6 ± 10.0	1.3 ± 6.8	0.14
Maximum HR (bpm ± SD)	102.4 ± 15.7	107.4 ± 19.2	4.9 ± 19.3	101.0 ± 15.9	109.0 ± 17.9	7.9 ± 17.2	0.56

Table 5 Summary of the serious adverse events and serious adverse device effects for the control and therapy patients

	Therapy (*N* = 63)			Control (*N* = 32)		
	Events	Patients	%	Events	Patients	%
Death and/or HF hospitalization	11	7	11.1	11	5	15.6
Death	1	1	1.6	2	2	6.3
HF hospitalization	10	7	11.1	9	5	15.6
Cardiovascular−Non-HF	9	7	11.1	7	5	15.6
Non-cardiovascular	8	8	12.7	12	11	34.4
Pulmonary	0	0	0.0	3	3	9.4
Genitourinary	1	1	1.6	2	2	6.3
Other Non-cardiovascular	7	7	11.1	7	7	21.9
Investigational system related*	9	9	14.3	4	4	12.5

Data are reported for events ≥5%.
*Includes post-surgical infections of the lead and pulse generator, pulse generator failure leading to loss of therapy, and right recurrent laryngeal nerve injury.

VNS appeared acceptable, with an overall infection rate comparable with that in patients implanted with a VNS system for the treatment of epilepsy.[10] The small volume to implants per centre and the level of device implant experience likely contributed to an infection rate that was higher than is seen for other cardiac devices.

The lack of cardiac remodelling benefit was an unexpected finding given the results from pre-clinical experiments[3,4,11,12] and the initial open-label pilot study.[6] Several potential factors may have played a role in the apparent lack of translation from pre-clinical experiments to the randomized sham-controlled feasibility clinical study.

In the open-label pilot study of 32 systolic heart failure patients,[6] the results suggested a beneficial effect on LV remodelling, LV function, 6-min hall walk, and NYHA class. The most important distinction between the two studies is the inclusion of a sham-treated control group in NECTAR-HF, which was absent in the previous pilot study. Although difficult to implement in device trials,[13] the inclusion of a concurrent control group is of paramount importance, as recently underlined by the results of the Simplicity III trial.[14] In the current study, patients receiving therapy reported significant improvements in heart failure related quality-of-life and NYHA functional class. This may be in part due to a placebo effect. Indeed, despite efforts to keep investigators and patients blinded to the delivered therapy, more patients in the therapy group correctly guessed their randomization assignment (*Table 2*). Titrating to the highest comfortable amplitude likely resulted in some patients detecting the sensation caused by chronic VNS. Control patients experienced these sensations only during titration. Thus, an assessment of appropriate blinding is important in randomized controlled device trials where proper blinding is challenging and often under-reported.[15]

Another potential reason for the observed lack of objective benefit in NECTAR-HF may be related to an incomplete understanding of appropriate dosing of VNS in humans. There are numerous stimulation parameters that can be deployed which impact the 'dose' of VNS a patient may receive: frequency, amplitude, duty cycle, timing to the cardiac cycle, and efferent/afferent nerve activation.[16] The two parameters that are likely to be of most relevance for the activation of vagus nerves are the amplitude and the stimulation frequency. It is acknowledged from the large experience with VNS for epilepsy[17] and by the experience of De Ferrari *et al.*[6] that in most patients the titration of the stimulation to higher amplitudes is limited by side effects, which may impact the dose delivered.

The most appropriate technique of increasing 'physiologic' vagus nerve activation is still a matter of debate. In the present study, therapy patients experienced side effects (e.g. neck pain, coughing), which limited programming to low stimulation amplitudes. Since it appears that stimulation amplitude is inversely correlated with the stimulation frequency, the delivery of VNS at 20 Hz in NECTAR-HF may have reduced the maximum achievable current (mA). NECTAR-HF reached relatively low current (average 1.4 ± 0.8 mA) compared with a prior study investigating very low frequency (1–2 pulses per cardiac cycle, i.e. 1–3 Hz) that reached much higher current (4.1 ± 1.2 mA).[6] By using a lower frequency, it may be possible to attain higher amplitudes of stimulation, which in turn allows the recruitment of a greater number of vagal fibres.[18,19] However, it should be noted that pre-clinical studies in an established animal model of heart failure[20] showed robust efficacy using NECTAR-HF stimulation parameters, and provided a strong rational for the use of a low amplitude, 20 Hz stimulation.[12] Results were comparable with those using lower frequency and higher amplitudes.[4] The preferential activation of efferent vs. afferent vagal fibres has also been proposed as an important therapeutic parameter. Efferent stimulation may be beneficial because of the direct innervation of the heart. However, afferent vagal stimulation

may also contribute to the beneficial effects, leading to sympathetic withdrawal.[21] The present study employed a helical bipolar electrode known to activate the nerve bi-directionally (i.e. both afferent and efferent vagal fibres).[18] In contrast, the study by De Ferrari *et al.*[6] employed an asymmetric bipolar multi-contact cuff electrode designed for preferential, but not exclusive, activation of vagal efferent fibres. Thus, stimulation characteristics may have contributed to the lack of significant benefit in NECTAR-HF, but on-going clinical trials are investigating alternative application parameters which may provide additional information. Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure is investigating 10 Hz VNS,[22] and Increase of Vagal Tone in Chronic Heart Failure[23] is investigating an asymmetric bipolar multi-contact cuff electrode delivering 1–2 pulses per cardiac cycle. Results of these studies may further provide insight into the 'dosing' dependencies of VNS for human heart failure.

Cardiac resynchronization is one of the few implantable devices for the treatment of chronic heart failure, and has been shown to induce a robust beneficial cardiac remodelling effect in the first 6 months and beyond.[24] However, it may not be appropriate to compare CRT with VNS given the likely mechanistic differences, and thus the 6 month randomized period of this trial may have been too short to detect changes in cardiac remodelling. Remodelling will be further assessed at the scheduled 12- and 18-month follow-up visits. However, the lack of a concurrent control group after the 6-month randomization period will limit the interpretation of the findings.

Inappropriate patient selection may have also contributed to the neutral findings. The relatively low levels of NT-proBNP, the lack of cardiac remodelling progression, and the low levels of inflammatory markers suggest that patients were well managed and in a stabilized phase of their HF trajectory. The selection of patients with direct markers of autonomic imbalance could enhance the potential to respond to vagal stimulation. The regulation of systemic inflammation by the vagus nerve has been demonstrated in a series of acute experimental studies[25–29] and although the mechanism by which this occurs is not well understood[30] the selection of patients with markers of systemic inflammation may also be considered. Thus, compared with the pre-clinical models with active remodelling and evidence of inflammation, the relatively controlled heart failure progression in the NECTAR-HF patients may have limited the ability to demonstrate the benefit of VNS.

The importance of heart rate variability has been demonstrated previously.[31] Results of the Holter data in the present study suggest that VNS had no effect in decreasing the mean, minimum or maximum HR, but showed a modest effect in modulating HR variability through an improvement in SDANN. There was also a non-significant improvement in RMSSD. Whether the magnitude of change observed in this study has a biological significance or not is unclear.

Although robust pre-clinical data showed the benefit of VNS, the NECTAR-HF trial failed to demonstrate a successful clinical translation of VNS therapy to the primary endpoint. There were statistically significant improvements seen in the quality-of-life measures, and there were no significant safety concerns. The specified stimulation protocol of VNS used in this randomized sham-controlled clinical trial was shown to be ineffective for the treatment of heart failure. Additional clinical research still needs to be performed to determine if alternative translation methods can become an effective heart failure therapy.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Appendix

Steering committee

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Clinical events committee

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Data safety monitoring committee

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CARDIOVASCULAR FLASHLIGHT

Completely percutaneous repair of a failing surgical mitral valve repair
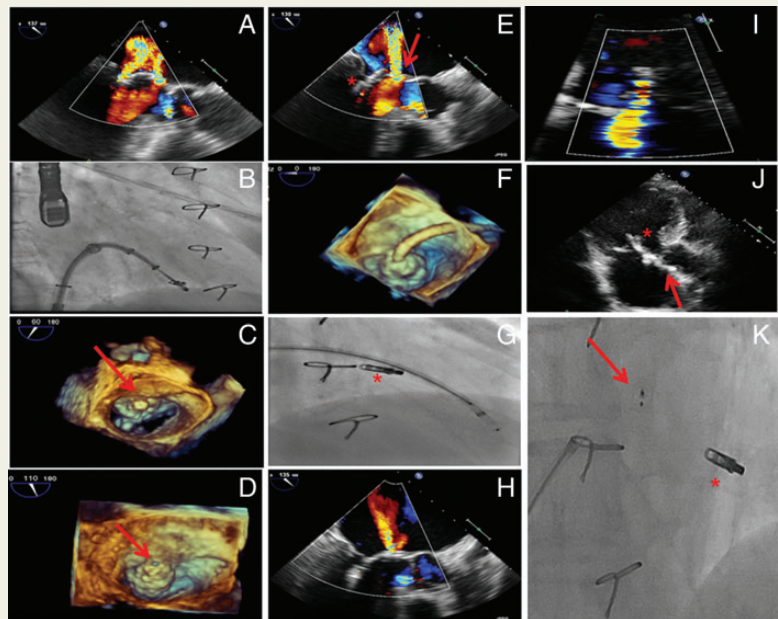
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A 70-year-old female patient with hypertrophic cardiomyopathy was admitted 18 months after surgical septal myectomy, venous bypass of the left circumflex artery, and mitral valve repair using an autologous pericardial patch extension of the anterior mitral leaflet. Echocardiogram revealed severe mitral insufficiency with a central regurgitation based on malcoaptation of the mitral leaflets and an additional leak due to a perforation in the anterior leaflet patch (Panel A). The heart team agreed upon Mitraclip implantation and plug closure of the patch perforation.

Panel B demonstrates the mitraclip opening in the left ventricle before leaflet grasping. The mitral double orifice after Mitraclip implantation as seen by three-dimensional by transoesophageal echocardiography (TOE) is shown in Panel C. Panels D and E display the residual leak through the patch (red arrow) after mitraclip (arrowhead) implantation. The patch perforation is crossed by a

6-French multipurpose diagnostic catheter (Panel F—TOE, Panel G Fluoroscopy, note mitraclip (*) in situ). A 8 × 6 mm AMPLATZER™ Duct Occluder (St Jude Medical, St Paul, MN, USA) is deployed in the patch perforation with initially mild residual patch leakage (Panel H—TOE). Transthoracic echocardiography 4 days later confirms mild central mitral regurgitation with no residual patch leakage (Panel I). Panel J (TTE) and K (fluoroscopy) illustrate the mitraclip (*) and duct occluder within the patch (arrow) in situ.

Supplementary material is available at European Heart Journal online.