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Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure

Gaetano M. De Ferrari[1]*, Harry J.G.M. Crijns[2], Martin Borggrefe[3], Goran Milasinovic[4], Jan Smid[5], Markus Zabel[6], Antonello Gavazzi[7], Antonio Sanzo[1], Robert Dennert[3], Juergen Kuschyk[4], Srdjan Raspopovic[5], Helmut Klein[6,8], Karl Swedberg[9], and Peter J. Schwartz[1,10,11,12,13], for the CardioFit Multicenter Trial Investigators

[1]Department of Cardiology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [2]University Hospital Maastricht, Maastricht, The Netherlands; [3]Ruprechts-Karl University Hospital at Mannheim, Mannheim, Germany; [4]Clinical Center of Serbia, Belgrade, Serbia; [5]Otto von Guericke University Hospital, Magdeburg, Germany; [6]Georg-August University Hospital, Göttingen, Germany; [7]Cardiovascular Department, Ospedali Riuniti, Bergamo, Italy; [8]Rochester University Hospital, Rochester, NY, USA; [9]Department of Emergency and Cardiovascular Medicine, University of Göteborg, Göteborg, Sweden; [10]Department of Internal Medicine, University of Pavia, Pavia, Italy; [11]Laboratory of Cardiovascular Genetics, IRCCS Istituto Auxologico Italiano, Milan, Italy; [12]Chair of Sudden Death, Department of Family and Community Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia; and [13]Cardiovascular Genetics Laboratory, Hatter Institute for Cardiovascular Research, Department of Medicine, University of Cape Town, South Africa

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Aims In chronic heart failure (CHF), reduced vagal activity correlates with increased mortality and acute decompensation. Experimentally, chronic vagus nerve stimulation (VNS) improved left ventricular (LV) function and survival; clinically, it is used for the treatment of drug-refractory epilepsy. We assessed safety and tolerability of chronic VNS in symptomatic CHF patients, using a novel implantable nerve stimulation system. The secondary goal was to obtain preliminary data on clinical efficacy.

Methods and results This multi-centre, open-label phase II, two-staged study (8-patient feasibility phase plus 24-patient safety and tolerability phase) enrolled 32 New York Heart Association (NYHA) class II–IV patients [age 56 ± 11 years, LV ejection fraction (LVEF) 23 ± 8%]. Right cervical VNS with CardioFit (BioControl Medical) implantable system started 2–4 weeks after implant, slowly raising intensity; patients were followed 3 and 6 months thereafter with optional 1-year follow-up. Overall, 26 serious adverse events (SAEs) occurred in 13 of 32 patients (40.6%), including three deaths and two clearly device-related AEs (post-operative pulmonary oedema, need of surgical revision). Expected non-serious device-related AEs (cough, dysphonia, and stimulation-related pain) occurred early but were reduced and disappeared after stimulation intensity adjustment. There were significant improvements ($P < 0.001$) in NYHA class quality of life, 6-minute walk test (from 411 ± 76 to 471 ± 111 m), LVEF (from 22 ± 7 to 29 ± 8%), and LV systolic volumes ($P = 0.02$). These improvements were maintained at 1 year.

Conclusions This open-label study shows that chronic VNS in CHF patients with severe systolic dysfunction may be safe and tolerable and may improve quality of life and LV function. A controlled clinical trial appears warranted.

Keywords Heart failure • Autonomic nervous system • Non-pharmacologic therapy

Introduction

Heart failure (HF) is characterized by an autonomic imbalance with withdrawal of vagal activity and increased sympathetic activity. Whereas cardiac adrenergic drive initially supports the performance of the failing heart, long-term activation of the sympathetic nervous system is deleterious and, accordingly, beta-adrenergic blocker treatment is beneficial.[1]

A wealth of experimental and clinical studies suggested that reduced or increased vagal activity could modify the risk for

* Corresponding author. Tel: +39 0382 503715, Fax: +39 0382 503161, Email: g.deferrari@smatteo.pv.it

ischaemia-related mortality.[2–6] Reduced vagal activity is associated with increased mortality also in chronic heart failure (CHF) patients[7] and further vagal withdrawal precedes acute decompensation.[8] In three different experimental models of HF, chronic vagus nerve stimulation (VNS) significantly improved left ventricular (LV) haemodynamics,[9–11] and decreased mortality.[9] Clinically, VNS is used in drug-refractory epilepsy[12,13] and, more recently, depression.[14]

The primary goal of the present study was to assess safety and tolerability of chronic VNS in symptomatic CHF patients with severe LV systolic dysfunction, using a novel implantable nerve stimulation system. The secondary objective was to obtain preliminary data on clinical efficacy.

Methods

This single-arm, open-label interventional phase II study, followed a two-staged approach: a first, single-centre feasibility phase, already reported,[15] followed by an international multicentre phase assessing safety and tolerability of chronic VNS with the CardioFit™ system in patients with symptomatic CHF. The protocol was approved by all Ethics Committees and every patient signed an informed consent.

Inclusion and exclusion criteria

Patients with a history of CHF, age 18–75 years, and New York Heart Association (NYHA) functional class II–III were eligible. Main inclusion criteria were presence of sinus rhythm with a 24-h Holter heart rate (HR) of 60–110 b.p.m., optimal medical treatment with no change in the previous 3 months, LV ejection fraction (LVEF) $\leq$35%, and capability to perform a 6-minute walk test. Exclusion criteria included: acute coronary syndrome, coronary re-vascularization or an episode of NYHA class IV CHF in the previous 3 months; previous stroke; history of acute myocarditis, haemodynamically significant valve disease; severe renal or hepatic failure, insulin-dependent diabetes mellitus or diabetic neuropathy; previous neck surgery; active peptic disease or history of upper gastrointestinal bleeding; asthma or severe chronic obstructive pulmonary disease; PR interval $>$240 ms, second or third degree atrioventricular block; atrial fibrillation or flutter in the previous 3 months; or candidacy for cardiac resynchronization device implantation.

Vagus nerve stimulation system

The CardioFit™ system (BioControl Medical Ltd, Yehud, Israel) is an implantable vagal neurostimulator system delivering low current electrical pulses, remotely programmable using a dedicated wireless communication system, designed to sense HR (via a standard intracardiac electrode) and deliver stimulation at a variable delay (70–325 ms) from the R-wave. A bradycardia limit causing interruption of vagal stimulation was set at 55 b.p.m.

The stimulation lead is an asymmetric bipolar multi-contact cuff electrode specifically designed for cathodic induction of action potentials, while simultaneously applying asymmetrical anodal blocks expected to lead to preferential, but not exclusive, activation of vagal efferent fibres. Electrode size can be tailored to each patient choosing from five different internal diameters of 2.25–3.25 mm.

CardioFit implantation procedure

The implantation procedure has been described.[15] Following positioning under local anaesthesia of an intracardiac sensing electrode, the right vagus was exposed through a latero-cervical incision under general anaesthesia, the appropriate size of the cuff electrode was determined and the cuff positioned. The stimulation lead was then tunnelled and connected with the intracardiac sensing electrode to a subcutaneous stimulator in the right subclavicular region. Prior to closure, a continuity test and HR reduction by stimulation test were performed to ensure proper device functioning.

Stimulation protocol

Approximately 3 weeks after implantation, the device was first activated. Stimulation started with an amplitude of 0.5 mA at a frequency of one stimulation pulse per heart beat given for 2 s ("ON time") and paused for 6 s ("OFF time"). During the 3-week up-titration phase, patients underwent 3 sessions/week; in each session, amplitude was raised in steps of 0.2 mA by a maximum of 1 mA. Increase in amplitude was achieved according to the subject sensations, so that if the patient felt stimulations and experienced discomfort at a certain amplitude, the current was not further increased in that session and the stimulation was left at a level just below that amplitude. Concomitantly, the ON and OFF times were progressively prolonged to a maximum time of 10 and 30 s, respectively. As with current amplitude, prolongation of ON/OFF times also was based upon the patient sensations. The duty cycle was defined as the percentage of time the stimulation was ON. For instance, a sequence of 8 s (2 s ON, 6 s OFF) would represent a duty cycle of 25% (2/8). To ensure that the duty cycle would not exceed the pre-specified target of 25%, prolonged periods with no stimulation were entered after a certain sequence of ON-OFF repetitions. For instance, after 20 repetitions of the 10 s ON 20 s OFF sequence, (600 s) a pause of 200 s would allow an overall duty cycle of 25% (200 s stimulation/800 s time). Targets were the attainment of either 5.5 mA, HR reduction of 5–10 beats, or onset of side-effects. Stimulation parameters were further fine-tuned during follow-up visits in case of significant side-effects, or sub-optimal HR reductions.

Evaluation and follow-up

Follow-up visits were conducted 1, 3, and 6 months after the optimization period. The patients were examined for physical signs and asked for any symptoms or adverse events (AEs). Investigation performed at baseline, 3, and 6 months included clinical findings, 12-lead electrocardiogram (ECG), QoL questionnaire (The Minnesota Living with Heart Failure® Questionnaire, MLwHF) a 6-minute walk test, blood tests, echocardiography, and 24-h Holter recording. Echocardiograms were digitally recorded for subsequent off-line blinded evaluation in a core laboratory. Measurements were performed in triplicate and averaged. The following indices of time domain HR variability were derived from the Holter recording read blindly in a core laboratory: standard deviation of the normal to normal interval (SDNN), mean squared successive difference (MSSD), and percentage of normal to normal intervals differing $>$50 ms from the previous one (pNN50). At the end of the 6-month follow-up period, patients were offered the choice of entering an optional extended follow-up phase with repetition of the full set of investigation at 12 months.

Endpoints and sample size

The primary endpoint of the study was the occurrence of all system and procedure-related AEs. The AE-related case report forms were subjected to careful independent monitoring and queries were issued to clarify all aspects that were not sufficiently described or were ambiguous. After all queries were cleared and a consensus was reached between the investigator and the monitor, the AEs were further evaluated and validated by members of the Steering Committee.

The secondary endpoints were the changes between baseline and the 6-month follow-up visit in: NYHA class, quality of life (MLwHF®), 6-minute walk test, LVEF, LV end-diastolic and end-systolic volumes. The sample size was based on the change between baseline and 6 months in MLwHF® quality of life. Anticipating a baseline value of 50 ± 15 points, thirty patients allowed 80% power to detect a 12 point difference with alpha = 0.05 (two-tailed).

Statistical analysis

Since the primary endpoint of the study was safety (the occurrence of all system and procedure-related side-effects), we considered appropriate to report, as main result, the combined analysis of the two phases of the study. Regarding efficacy, separate data on the second set of patients ($n = 24$) are also provided. Finally, all data available for the 1-year follow-up are reported.

Data are expressed as mean ± SD or median and inter-quartile range for normal and non-normal distributions, respectively. Data on variables explored at baseline, 3, and 6-month follow-up were analysed with repeated measures ANOVA followed by Bonferroni multiple comparison test or Kruskal–Wallis ANOVA followed by Wilcoxon signed rank test. One year data were compared with baseline data with paired *t*-test or Mann–Whitney test, as appropriate. A *P*-value of 0.05 was considered the limit for significance. All *P*-values reported are corrected for multiple comparisons, unless otherwise specified. Statistical analysis was performed with MedCalc 10.1.3 for PC.

Results

Thirty-two patients were enrolled (*Table 1* shows their main baseline clinical characteristics). Two NYHA class IV patients were enrolled following agreement by the local Ethics Committee and the Sponsor given the absence, in these patients, of any possible alternative treatment.

Surgery and hospitalization

The CardioFit implantation procedure lasted an overall average of 144 min (46 min intracardiac sensing lead implantation, 68 min cervical vagus stimulation lead implantation, 30 min battery connection, and implantation). Implant success rate was 100% and no implantation failure occurred. Acutely, patients responded to VNS with a HR reduction of 7 ± 2 b.p.m. Patients were discharged from hospital a median of 4 days (range 2–13) after the intervention on their usual treatment.

Up-titration of vagus nerve stimulation

The intensity of stimulation reached at the end of the titration phase was 4.1 ± 1.2 mA (range 1.1–5.5 mA). The up-titration was limited by patient's discomfort or pain in the majority of patients (23/32, 72%), by attainment of an amplitude of 5.5 mA in six patients (19%), by the attainment of an acute HR decrease >5 b.p.m. in one patient (3%), and by the attainment of both an amplitude of 5.5 mA and an acute HR decrease >5 b.p.m. in two patients (6%). The average duty cycle (percent of active stimulation) was 21 ± 5%.

Safety evaluation

During the 6-month duration of the study, the overall number of serious AEs (SAEs) was 26, occurring in 13 of 32 patients (40.6%, *Table 2* for full disclosure of SAEs). Two SAEs (in 2 of 32 patients, 6.2%) were clearly related to the procedure: one episode of acute pulmonary oedema occurring after the surgical implantation and treated with i.v. diuretics and one case of surgical revision of the device consisting in opening the generator pocket and tightening a loose electrode connector. Atrial fibrillation in one patient leading to electrical cardioversion was considered to be possibly related to the experimental treatment similarly to an episode of ulcer bleeding in a patient with *Helicobacter pylori* positive tests. The investigators considered expected and likely unrelated to the investigational procedure the following SAEs: three cases of death, all occurring before the third month and due to intractable HF (in two class III and one class IV patient); eight episodes of cardiac decompensation observed in five patients, one pleural effusion in one and a sequence of five appropriate implantable cardioverter-defibrillator (ICD) shocks leading to hospitalization in one patient.

Table 1 Baseline characteristics of enrolled patients

Male gender	30/32 (94%)
Age (years)	56 ± 11
Ischaemic heart failure	20/32 (62%)
NYHA II/III/IV	15/15/2
Duration of HF prior to enrolment (years)	4.3 ± 2.8
Left ventricular ejection fraction (%)	23.1 ± 7.6
Treatment with:	
β-blockers	31/32 (97%)
ACE-I or ARB	31/32 (97%)
Digoxin	9/32 (28%)
Loop diuretics	31/32 (97%)
Anti-aldosterone agents	17/32 (53%)
Previous ICD implantation	19/32 (59%)

ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association.

The following non-SAEs were considered to be related to the investigational device: pain at stimulation site in six patients, cough in five, dysphonia in four, mandibular pain in three, and stimulus artefact on ECG in one patient. These side effects were expected on the basis of the previous experience with VNS for drug-resistant epilepsy. They were reduced and eventually disappeared after fine-tuning of the stimulation intensity. There were also 11 AEs considered by the local investigator not to be related to the investigational device.

No interaction was noticed between the investigational device and the ICD, implanted in 19 out of 32 patients; no episodes of oversensing possibly related to VNS were identified. No blood pressure, PR, QRS, QT intervals, or standard blood tests changes were observed. No difference was found throughout the study in the occurrence of ventricular tachycardia observed at Holter recording.

At the end of the 6-month period, 28 out of 29 patients agreed to continue treatment with an extended follow-up. During the subsequent 6-month period, one patient had the opportunity for heart transplantation and accepted, two patients died, one stopped stimulation following gastric ulcer, and one stopped

Table 2 Serious adverse events (SAE) observed during the study

Patients number	SAEs	Event	Time of event (days post-implant)	Expected	Intervention	Relatedness to procedure or system	Outcome
0001	2	Syncope facilitated by dehydration	154	N	Reduce diuretics	Possibly related	Resolved
0006	1	Cardiac decompensation due to worsening of HF	195	Y	Diuretic therapy	Probably not related	Resolved
0006	1	Cardiac decompensation due to worsening of HF	211	Y	Diuretic therapy	Probably not related	Resolved
0010	1	Re-acutization of chronic bronchitis	41	N	Hospitalization medication change including antibiotics	Probably not related. Patient had chronic bronchitis	Resolved
0010	1	Re-acutization of chronic bronchitis	190	N	Hospitalization medication change including antibiotics	Probably not related. Patient had chronic bronchitis	Resolved
0101	1	Salivary gland tumour	57	N	Complete tumour–resection	Certainly not related	Resolved
0101	1	Non persistent ST elevation myocardial infarction	118	N	Hospitalization	Probably not related	Resolved
0202	1	Pulmonary oedema after device implantation	1	Y	Medications (i.v. diuretics)	Certainly related to procedure	Resolved
0202	1	Death due to worsening of End stage HF	116	Y		Probably not related	Death
0204	1	Cardiac device revision caused by incomplete insertion of stimulation lead	129	Y	Surgery	Certainly related to procedure	Resolved
0404	1	Cardiac decompensation due to worsening of HF and depression	41	Y	Diuretics and antidepressants	Probably not related	Resolved
0404	1	Death due to worsening of end stage HF	76	Y		Probably not related	Death
0405	1	ICD shocks due to ventricular tachycardias	150	Y	Hospitalization medication change	Probably not related	Resolved
0501	1	Pleural effusion due to worsening of HF	48	Y	i.v. diuretics	Probably not related	Resolved
0502	1	Cardiac decompensation	134	Y	i.v. diuretics; hospitalization	Probably not related	Resolved
0504	1	Haemianopsy due to transient ischemic attack from left posterior cerebral artery	42	N	Hospitalization; head computerized tomography	Probably not related	Resolved
0504	1	Syncope associated with new onset atrial fibrillation and hypotension	50	N	Hospitalization	Possibly related to system (patient collapsed after removing the magnet and resumption of stimulations)	Resolved
0504	1	Cardiac decompensation due to worsening of end stage HF	115	Y	Medication change	Probably not related	Death
0505	1	Cardiac decompensation	100	Y	Hospitalization; diuretics	Probably not related	Resolved
0505	1	Cardiac decompensation	160	Y	Hospitalization	Probably not related	Resolved
0505	1	Atrial Fibrillation	167	Y	Hospitalization for cardioversion	Possibly related	Resolved

Continued

Table 2 *Continued*

Patients number	SAEs	Event	Time of event (days post-implant)	Expected	Intervention	Relatedness to procedure or system	Outcome
0505	1	Return to atrial fibrillation after conversion	168	Y	No action taken	Possibly related	Resolved
0505	1	Cardiac decompensation	190	Y	Hospitalization; diuretics	Probably not related	Resolved
0602	1	Hyperglycaemia caused by diabetes	94	N	Hospitalization; insulin	Probably not related	Resolved
0602	1	Abdominal tension associated with pre-existing Hepatopathy	155	N	Hospitalization for abdomen computerized tomography	Probably not related	Resolved

Table 3 **Serious adverse events (SAE) observed during the extended follow-up (6–12 months)**

Patients number	SAEs	Event	Time of event (days post-implant)	Expected	Intervention	Relatedness to procedure or system	Outcome
0001	1	Death due to worsening of end stage HF	267	Y		Probably not related because stimulation was stopped weeks before death	Death
0403	1	ICD shocks due to VTs associated with worsening of HF	217	Y	Hospitalization; i.v. diuretics	Probably not related	Resolved
0501	1	Ulcer bleeding associated with *Helicobacter pylori* (positivity)	246	N	Blood transfusion	Possibly related. However, patient was positive to *H. pylori*	Resolved. Stimulation stopped
0503	1	Angina pectoris	301	Y	Percutaneous coronary intervention	Probably not related. Patient was ischaemic	Resolved
0601	1	Acute myocardial infarction	247	N	Percutaneous coronary intervention and pharmacological therapy	Probably not related. Patient was ischaemic	
0601	1	Death caused by acute myocardial infarction followed by cardiogenic shock and infection	251	N		Probably not related. Patient suffered cardiogenic shock and infection	Death

stimulation following implantation of an ICD (patient # 0002). Thus, 23 patients reached the 12 month visit. Serious AEs observed during the optional extended follow-up period are listed in *Table 3*.

Clinical effects

The acute HR changes observed during vagal stimulation were modest (on the average 1.5 b.p.m. acute difference). However, baseline resting HR decreased significantly during the study as shown in *Table 4*, which also summarizes the most important efficacy variables analysed in the overall population of the study. *Figure 1* shows the NYHA class trajectory of each individual patient. Most patients improved by at least one NYHA class both at 3 months (18/32, 56%) and at 6 months (19/32, 59%). Quality of life, markedly improved at 3 months (from 49 $\pm$ 17 to 33 $\pm$ 16 MLwHF® Questionnaire), thereafter remaining almost identical at 6 months (32 $\pm$ 19). The same was found for the 6-minute walk test with an increase at 3 months from 411 $\pm$ 76 to 470 $\pm$ 99 month and subsequent stability. The blinded echocardiogram analysis disclosed a non-significant decrease in LV end-diastolic volume, a significant reduction in LV end-systolic volume, and a significant increase in LVEF (from 22 $\pm$ 7 to 29 $\pm$ 8%, *Figure 2*).

Table 4 Main efficacy results during follow-up in the overall cohort ($n = 29$)

	Baseline	3 month	6 month	*P*-value	*P* (baseline–3 month)	*P* (baseline–6 month)	*P* (3–6 month)
NYHA (I/II/III/IV)	0/15/13/1	6/19/4/0	10/14/5/0	<0.001	0.001*	<0.001*	0.37*
6 min WT (m)	411 ± 76	470 ± 99	471 ± 111	<0.001	0.0002	0.0014	1
QoL	49 ± 17	33 ± 16	32 ± 19	<0.001	0.0001	0.0001	1
HR (b.p.m.)	82 ± 13	75 ± 11	76 ± 13	0.007	0.03	0.07	1
SBP (mmHg)	110 ± 16	110 ± 13	108 ± 19	0.84			
DBP (mmHg)	74 ± 9	73 ± 7	73 ± 11	0.96			
LVEF (%)	22.3 ± 6.9	27.1 ± 8.9	28.7 ± 8.4	<0.001	0.01	0.0003	0.78
LVEDVI (mL/m^2)	132 ± 42	127 ± 48	125 ± 46	0.44			
LVESVI (mL/m^2)	103 ± 35	94 ± 41	89 ± 38	0.02	0.35	0.02	0.69
Avg HR (b.p.m.)	78 ± 10	78 ± 10	78 ± 10	0.99			
SDNN (ms)	34 (29–45)	37 (28–47)	36 (29–52)	0.45			
MSSD (ms)	30 (20–48)	34 (29–44)	40 (27–55)	0.043	0.35*	0.08*	
pNN50 (%)	3.7 (1.8–8.4)	5.7 (2.2–10.8)	7.1 (3.1–14.7)	0.015	0.015*	0.034*	

6 min WT, 6-minute walk test; QoL, Quality of Life by Minnesota Living with Heart Failure® questionnaire; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; Avg HR, average 24-h Holter heart rate; SDNN, standard deviation of the normal to normal interval; MSSD, mean squared successive difference; pNN50, percentage of normal to normal intervals differing >50 ms from the previous one.
*P value not corrected for multiple comparison.

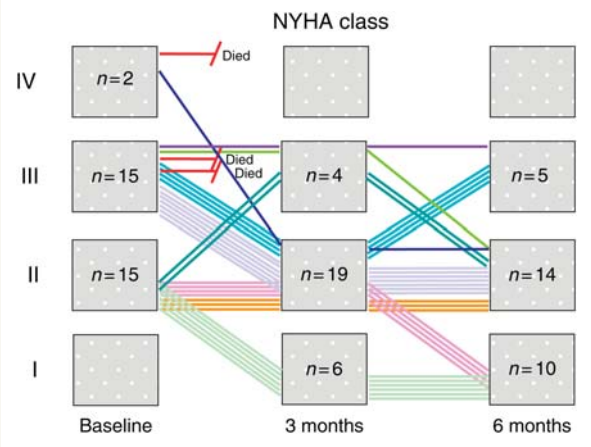

Figure 1 New York Heart Association class. Individual New York Heart Association class behaviour of each patient throughout the study. Red broken lines correspond to dead patients. Each patient is characterized by a single line.

Data limited to the 21 patients of the second phase of the study show a behaviour identical to the total cohort, but a non-significant decrease in LV systolic volume (see Supplementary material online, *Table S1*). Comparing baseline with 1-year evaluation in the 23 patients who completed this follow-up revealed maintenance and even magnification of the favourable effects of vagal stimulation (especially LVEF from 21 to 34%, *Table 5*).

Heart rate variability tended to increase during the study and the change in pNN50 was statistically significant (*Table 4*).

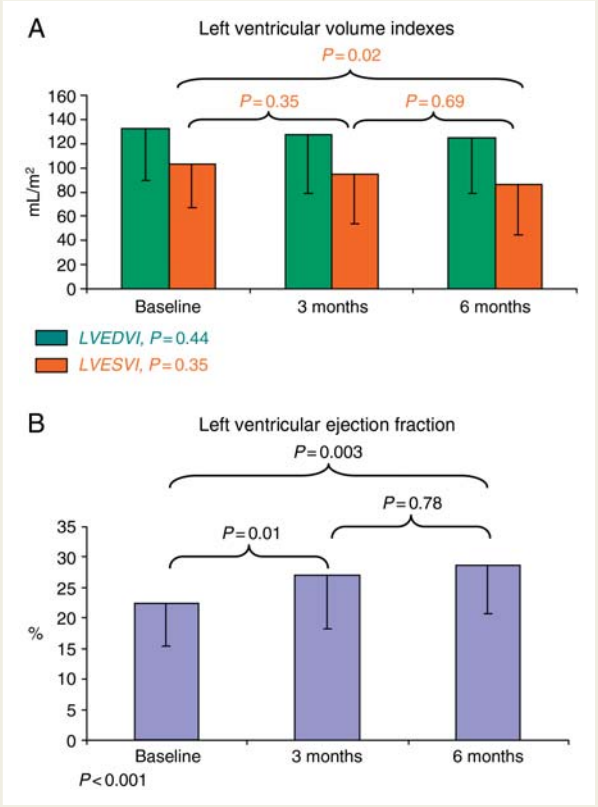

Figure 2 Echocardiographic evaluation. Left ventricular volume indexes (*A*) and ejection fraction (*B*) throughout the study. LVEDVI: left ventricular end-diastolic volume index. LVESVI: left ventricular end-systolic volume index.

Table 5 One year follow-up ($n = 23$)

	Baseline	1 year	*P*-value
NYHA (I/II/III/IV)	0/14/9/0	10/10/3/0	<0.001
6 min WT (m)	405 ± 92	472 ± 139	0.012
QoL	47 ± 19	30 ± 24	0.001
HR (b.p.m.)	85 ± 14	76 ± 11	0.003
LVEF (%)	21.1 ± 7.5	34.1 ± 12.5	<0.0001
LVEDVI (mL/m^2)	126 ± 47	118 ± 56	0.36
LVESVI (mL/m^2)	100 ± 40	80 ± 44	0.009
pNN50	4.6 (1.8–8.4)	7.4 (3.2–24.0)	0.007

For abbreviations see *Table 4*.

Discussion

This open-label study suggests that chronic vagal nerve stimulation is safe and tolerable in symptomatic congestive HF patients, and that it leads to a marked clinical subjective improvement. Compared with the previous report suggesting feasibility from a single-centre experience,[15] the present seven-centre international study on four times more patients provides significant novel data including clinical effects over a longer follow-up duration and full disclosure of AEs. Thus, the present study provides the first evidence to suggest that this new therapeutic approach may produce favourable and long-lasting effects on LV function. The preservation of these effects at 1-year follow-up strongly argues against a major role of a possible placebo effect.

Background of chronic vagus nerve stimulation

Several concepts regarding the beneficial role of parasympathetic activity originate from an animal model for post-infarction sudden cardiac death[2–4] in which effective vagal reflexes protected from ventricular fibrillation,[4] and baroreflex sensitivity, a marker of vagal reflexes, was a powerful risk predictor for sudden and non-sudden cardiac death, a finding[2] confirmed in prospective clinical studies.[5,16] In this model, we demonstrated that vagal activation induced pharmacologically,[17] by electrical VNS,[3] or by exercise training,[18] exerted a marked beneficial effect.

The hypothesis that VNS may benefit CHF patients was derived from the combined observations that the prognostic value of depressed baroreflex sensitivity was present also in CHF[7] and that vagal withdrawal precedes acute decompensation[8] and supported by a growing number of experimental studies.[9–11] In a murine model of HF, VNS significantly improved LV haemodynamics and decreased mortality from 50 to 14%.[9] In dogs with microembolization-induced HF, VNS when combined with chronic beta-blockade improved LV function and caused reverse remodelling.[10] In a pacing-induced HF canine model, dogs were subjected to 8 weeks of high-rate ventricular pacing with concomitant VNS in the active group and no stimulation in the control group.[11] After 12 weeks, animals in the VNS group had significantly lower LV end-diastolic and end-systolic volumes and higher LVEF. This result was obtained in the absence of any HR effect since both groups were paced.[11] Finally, low-intensity VNS not decreasing HR, exerted positive effect on LV function and multiple biomarkers in the canine microembolization HF model.[19]

Chronic vagus nerve stimulation in human

In humans, electrical stimulation of the carotid sinus nerve was proposed in pioneering works by Schwartz *et al.*[20] and Braunwald *et al.*[21] for the management of hypertension and angina pectoris, respectively. However, the technique was soon abandoned, mainly for technical problems. More recently, VNS has been used as a therapy for refractory epilepsy.[12,13] More than 50 000 patients have been implanted worldwide with an acceptable side-effect profile.[12,13,22] Although VNS for epilepsy is performed on the left cervical vagus, we stimulated the right vagus, following the previous animal experience[3,9–11] and because the greater influence of the right-sided vagus nerve on HR[23] would facilitate correct surgical electrode positioning.

Side-effects and safety

Three patients (including one of the two class IV patients) died during the study. These mortality events, as well as the episodes of acute cardiac decompensation were considered predictable by the investigators considering the severity of HF, and not related to the investigational device. As happens when performing studies in chronic patients with advanced diseases, it is difficult to determine that a clinical condition is certainly not related to the investigational procedure. Despite this general consideration, the findings suggest that safety was good without major AEs clearly related to the device. Although the presence of local side-effects (e.g. dysphonia) often prevented the attainment of higher stimulation amplitudes, overall, these AEs were expected on the basis of the large experience gathered in patients with epilepsy.[12,13,22]

Chronic implantation with the CardioFit electrode does not appear to cause nerve damage. In chronic canine studies, histopathological analysis after 6–9 months showed no difference between right (implanted) and left (control) vagus nerve in myelinated axon density and nerve function studies showed no difference in nerve conduction velocity (ML Cohen, and H Sabbah, manuscript *in preparation*). Clinically, the HR variability increase observed in our patients strongly argues against vagus nerve damage.

Clinical effects

The NYHA class decreased significantly and both quality of life and exercise capacity improved markedly during the follow-up. The clinical effects could not be evaluated in the three patients who died, possibly contributing to the overall positive response of the remaining 29 subjects. Also, the absence of a control group in this phase II study, an important limitation shared by all first studies assessing the effects of medical devices, does not allow one to exclude the contribution of a placebo effect, a likely contributor to the favourable results observed. However, the changes observed in the present study were greater than those observed in the placebo group of studies enrolling similar patients.[24] In the

MIRACLE ICD trial,[24] quality of life improved in the control group (ICD implantation with resynchronisation therapy off) by 11 points, with 95% confidence intervals 6–16 points. Thus, the average effect observed in the present study (17 points) exceeds the 95th percentile of the control group distribution of the MIRACLE ICD trial and is actually identical to the effect observed in the active treatment group (17 points, significantly better than control). Also, we demonstrated persistence of the improvements after 12 months, whereas the placebo effect is known to progressively decrease over time. These considerations, together with the favourable effects on HR variability, suggest that a true biological effect played a major role.

The significant reduction in LV end-systolic volume (by an average of 17%) and the significant increase in LVEF derived from an off-line blinded analysis are in good agreement with the experimental findings[9–11] and also argue against a significant placebo effect. These changes may have clinical implications, since *post-hoc* analyses from the response to cardiac resynchronisation therapy indicate that a 10% reduction in LV end-systolic volume is associated with markedly lower long-term mortality and less HF events.[25]

Mechanisms of action

Vagal stimulation may potentially produce beneficial effects in patients with HF through several different mechanisms.[26,27] In the present study, the acute change in HR during stimulation was modest, and the average HR observed during 24-h Holter was actually unchanged, thus suggesting that HR was not the main mediator of the apparent favourable effects.

The concept that VNS may have positive direct effects at ventricular level, independently of its sinus node effects, is in agreement with our earlier findings[3] in conscious dogs that the vagally mediated protection from ventricular fibrillation was, in approximately half of the cases, completely independent from HR reduction.

Notably, the two most recent experimental studies[11,19] found a beneficial effect of vagal stimulation in the absence of any HR change. Heart rate-independent effects may include, among others[26,27] anti-adrenergic effects at ventricular level due to sympathetic–parasympathetic interaction, anti-apoptotic effects, increase in nitric oxide, reduction in the ischaemia/reperfusion damage, as well as the so-called anti-inflammatory reflex postulated by Tracey.[28]

Conclusions

With the caution necessary in assessing a small size non-controlled clinical trial, the present findings show that chronic VNS in symptomatic CHF patients and LV systolic dysfunction may be safe and tolerable. This novel therapeutic approach improved quality of life, decreased LV systolic volume, and increased LVEF at 1-year follow-up. Vagus nerve stimulation deserves to be tested in a controlled clinical trial to assess whether it can indeed represent a new non-pharmacological approach for the treatment of symptomatic HF.

Supplementary material

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

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