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Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Systolic Heart Failure

The DEFEAT-HF Study

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ABSTRACT

OBJECTIVES The primary objective of the study was a change in left ventricular end-systolic volume index (LVESVi) from baseline to 6 months of spinal cord stimulation (SCS) therapy in the treatment arm compared to the control arm as measured by echocardiography. Secondary objectives were changes in peak oxygen uptake and N-terminal pro-B-type natriuretic peptide (NT-proBNP) between the treatment arm and control arm from baseline through 6 months.

BACKGROUND Abnormal neurohormonal activation is often responsible for progression of heart failure (HF). Treatment has often included drug therapy to modulate the neurohormonal axis. The purpose of the DEFEAT-HF (Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure) clinical study was to evaluate whether direct modulation of the nervous system through SCS improved HF metrics, including heart size, biomarkers, functional capacity, and symptoms.

METHODS The DEFEAT-HF study was a prospective, multicenter randomized (3:2), parallel, single-blind, controlled study to investigate whether SCS was a feasible therapy for the treatment of systolic HF for patients with New York Heart Association functional class III HF, left ventricular ejection fraction (LVEF) ≤35%, QRS duration <120 ms, and left ventricular end-diastolic dimension ≥55 mm. The primary objective of the DEFEAT-HF study was to evaluate the reduction in LVESVi after 6 months of SCS therapy in the treatment arm compared to the control arm.

RESULTS In total, 81 patients were enrolled, with 66 successfully randomized and implanted with the SCS device system. Seventy-six percent (50 of 66) had an implantable cardioverter-defibrillator at the baseline visit. Among randomized patients, the mean age was 61 years, 79% were male, mean LVEF was 27%, and mean QRS duration was 105 ms. The change in LVESVi over 6 months was not significantly different between randomization arms (SCS OFF: -2.2 [95% confidence interval: -9.1 to 4.6] vs. SCS ON: 2.1 [95% confidence interval: -2.7 to 6.9]; p = 0.30). Analyses of secondary endpoints for the study were also not significantly different.

CONCLUSIONS The present study does not provide evidence to support a meaningful change in clinical outcomes for HF patients receiving SCS. (Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure [DEFEAT-HF]; NCT01112579) (J Am Coll Cardiol HF 2016;4:129–36) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

HF = heart failure

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

LVESVi = left ventricular end-systolic volume index

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

SCS = spinal cord stimulation

VO_2 = oxygen consumption

Dysregulation of the autonomic nervous system in heart failure (HF) is due, in large part, to increased sympathetic activity and the elaboration of biologically active neurohormones (1). Treatment has resulted in the clinical use of neurohormonal antagonists such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, neprilysin inhibitors, aldosterone antagonists, and β-blockers to treat patients with a reduced left ventricular ejection fraction (LVEF) (2).

There is growing interest in using device-based therapies to reverse the sympathovagal imbalance that develops in HF. Spinal cord stimulation (SCS) has been used for many years to treat patients with intractable neuropathic pain syndromes, pain from extremity ischemia (3,4) and nonrevascularizable angina (5–9). The beneficial mechanisms of SCS may relate in part to modulation of the (alpha) sympathetic tone (10) and/or vagal stimulation (11). Other mechanisms may be, and probably are, operative (12–20). A recent single-arm nonrandomized pilot study in 15 patients with New York Heart Association (NYHA) functional class III HF (21) demonstrated that T1 to T3 SCS 24 h/day with 2 epidural electrodes improved a variety of HF endpoints. In addition, an earlier report in humans demonstrated less pronounced deterioration of LV function during adenosine provocation with SCS as compared to control (22).

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The purpose of the DEFEAT-HF (Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure) trial was to test the hypothesis that SCS is sufficient to reverse the adverse LV remodeling that occurs in patients with advanced HF and narrow QRS complex.

METHODS

STUDY DESIGN AND OVERSIGHT. The DEFEAT-HF study was a multicenter, prospective, randomized, controlled study. Upon enrollment, eligible patients underwent SCS implantation. After successful implantation, patients were then randomized in a 3:2 fashion to SCS stimulation on (SCS ON) versus stimulation off (SCS OFF). The study was single blinded. All patients were implanted with leads and stimulator, and patients were not told whether they were randomized to SCS ON or SCS OFF. Treating physicians were aware of randomization assignments. At 6 months, in all patients randomized to SCS OFF, stimulation was turned ON. Both groups were subsequently followed for an additional 6 months while receiving SCS therapy as outlined in **Figure 1**.

The trial execution was supported by the sponsor, Medtronic (Minneapolis, Minnesota). Safety was assessed by collecting adverse events, including system and procedure related adverse events.

An independent Data Monitoring Committee regularly reviewed safety of study participants and trial conduct, and adverse events were classified by an independent Global Adverse Event Adjudication Committee. Primary and secondary study endpoint data, the change in left ventricular end-systolic volume index (LVESVi), and change in peak oxygen consumption (VO_2), were analyzed by blinded independent Core Laboratories (Online Appendix). Data were collected, managed, and analyzed according to a predefined statistical analysis plan. The authors prepared the manuscript. The protocol was registered at ClinicalTrials.gov (NCT01112579).

Twenty-four centers in the United States, Canada, Europe, and South Africa participated in the trial (Online Appendix). The ethics committee at each study center approved the trial. All enrolled patients provided written informed consent.

RECRUITMENT AND FOLLOW-UP. Patients selected for inclusion in the study had NYHA functional class III HF, EF ≤35%, QRS duration <120 ms, left ventricular end-diastolic dimension 55 to 80 mm, and stable evidence-based medical therapy for HF. Patients were excluded if they had a cardiac resynchronization therapy device implanted; coronary artery bypass surgery, percutaneous coronary intervention, or an acute coronary syndrome within the past 90 days; had a reversible cardiomyopathy, chemotherapy-induced HF; had a heart transplant; were unable to perform an exercise capacity test; or were pregnant or planning to become pregnant during this study. Patients were excluded if they had an implantable pulse generator or implantable cardioverter-defibrillator (ICD) from another brand than the SCS device.

and honoraria from Medtronic; has served as a consultant for and received honoraria from St. Jude Medical, Novartis, Cardio3, Vifor, and Medtronic. Dr. Linderoth has served as a consultant for Medtronic, St. Jude Medical, Boston Scientific, and ElektaAB. Mr. Kueffer and Mr. Sarazin are employees of Medtronic. Dr. DeJongste has received speakers fees from Medtronic and St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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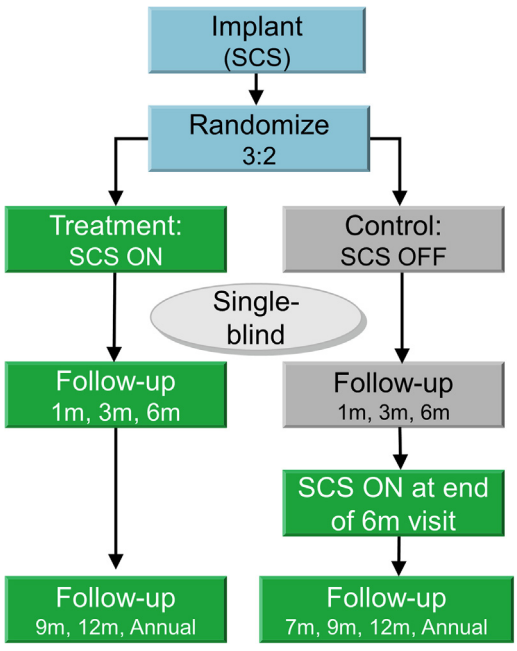
FIGURE 1 Clinical Trial Design



SCS = spinal cord stimulation.

Patients were seen in clinical follow-up at 1, 3, 6, and 12 months after randomization in both arms. Patients in the SCS OFF arm were also seen at 7 months after their device stimulation was turned ON. Clinical evaluation and device testing were carried out at each visit.

IMPLANT PROCEDURES. SCS delivery was accomplished by inserting a single lead with 8 electrodes (Medtronic Model 3777/3877) in the epidural space by a neurosurgeon or pain management specialist. Stimulation electrodes were placed to encompass the T2 to T4 level. Stimulation in the treatment group was programmed on for 12 h a day, on the basis of individual sleep/wake cycles, at a stimulation frequency of 50 Hz, 200 μs pulse duration, and output set at 90% maximum tolerated voltage determined while sitting. The electrode was connected to an SCS stimulator (Medtronic PrimeADVANCED Neurostimulator model 37702), which was placed subcutaneously in the lateral abdominal wall. If patients had a concomitant cardiovascular device implanted, the SCS was implanted on the opposite side of the body in order to minimize interference between both implanted devices. Studies performed before the beginning of the trial demonstrated no crosstalk interference between a Medtronic ICD and the neurostimulator.

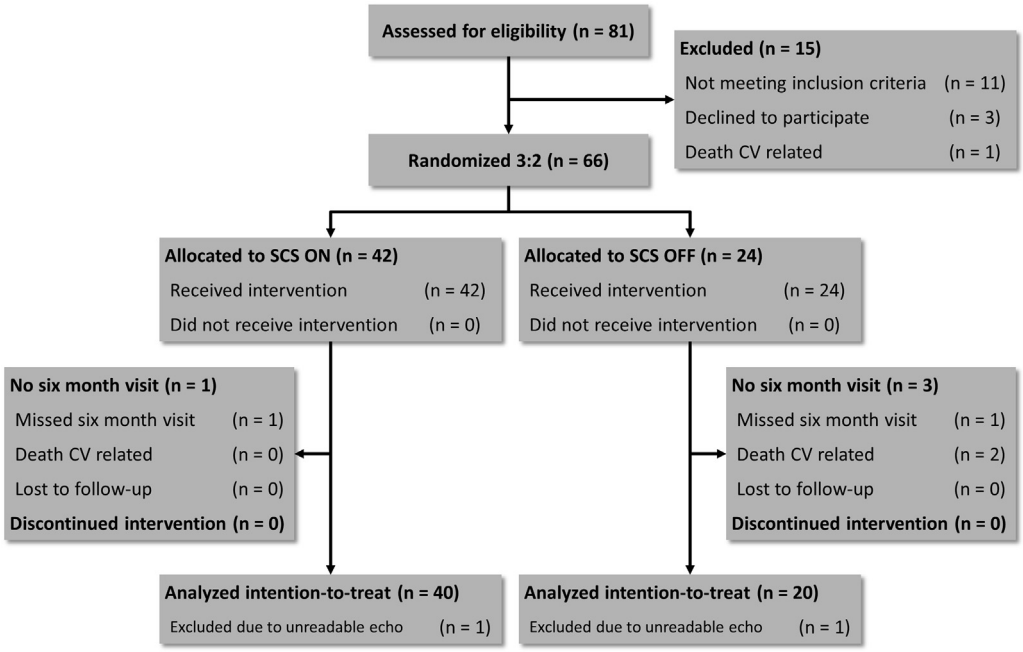
The Medtronic Model 3777/3877 lead and Medtronic PrimeADVANCED Neurostimulator Model 37702 are currently commercially released in the United States and Europe, and were used experimentally for the DEFEAT-HF study. The implant procedures utilized in DEFEAT-HF were performed in accordance with current labeling.

STUDY OBJECTIVES. The primary endpoint of the trial was the change in LVESVi from baseline to 6 months, as assessed by 2-D echocardiography. Secondary endpoints of the trial were change in peak VO_2 and change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) from baseline to 6 months.

STATISTICAL ANALYSIS. The primary endpoint of the trial was change in LVESVi from baseline to 6 months. The primary and secondary analyses were performed on all randomized patients according to the intention-to-treat principle. For the purpose of sample size calculation, the study assumed the SCS ON arm would have a 12.5% greater reduction in LVESVi at 6 months compared to the SCS OFF arm. Assuming a baseline mean LVESVi of 110 ml/m^2 in each randomized arm, it was calculated that 195 patients would be needed to test a 2-sided hypothesis for a difference of 12.5% greater reduction (13.75 ml/m^2 vs. 0 ml/m^2) in a change from baseline to 6 months between treatment arms with a power of 80% and α of 0.05, and a standard deviation of change in LVESVi equal to 29 ml/m^2. The sample size accounts for the loss of echocardiography data, patients exiting before 6 months and death by assuming that 20% of paired echo images would be missing. The primary objective was analyzed using an analysis of covariance model with change in LVESVi from baseline to 6 months as the response and randomization arm and baseline LVESVi as covariates. Because the randomized phase is through 6 months, but data collection on the study objectives continued through 12 months for all subjects, examination of the SCS therapy effect through 12 months was conducted via an additional analysis. A linear mixed effects model with indicators of treatment changes with time was fit with information included from baseline, 3, 6, 9, and 12 months for LVESVi and baseline, 6, and 12 months for NT-proBNP and peak VO_2 variables.

At the end of 3 years of enrollment, 66 patients were randomized for a randomization rate of <0.1 patients per center per month. Due to enrollment futility, enrollment was closed after 3 years. All randomized patients continued with follow-up as defined in the protocol. Analyses have been conducted with the same methods as pre-defined in the study protocol and statistical analysis plan.

FIGURE 2 Consolidated Standards of Reporting Flow Diagram



CV = cardiovascular; SCS = spinal cord stimulation.

RESULTS

BASELINE CHARACTERISTICS. Between July 2010 and July 2013, a total of 81 patients were enrolled at 24 centers. As shown in the Consolidated Standards of Reporting diagram in Figure 2, 66 of the 81 enrolled patients underwent a successful SCS implant. Of the remaining 15 enrolled patients, 11 were excluded before implantation because they did not meet inclusion/exclusion criteria, 3 patients withdrew consent before implant, and 1 patient died before implant attempt.

Forty-two (42) patients were randomized to SCS ON and 24 patients to SCS OFF (Figure 2). Table 1 summarizes the demographics and background medical therapy of the enrolled patients who were randomized to SCS ON or SCS OFF. The mean age was 61 ± 12 years, 79% were male, and patients were receiving stable optimal medical therapy for HF, including β-blockers (95%) and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (91%), and diuretics (94%). Table 1 further shows that patients enrolled in the trial had advanced disease, as evidenced by the EF, left ventricular end-diastolic dimension, and Minnesota Living with Heart Failure Questionnaire scores. Approximately 45% of the patients had been admitted for an HF hospitalization within the 6 months before enrollment. There were no baseline differences between the 2 groups except for age, which was less for patients in the SCS ON group. Table 2 summarizes the general cardiovascular history of the enrolled patients who were randomized to SCS ON or SCS OFF.

TABLE 1 Patient Demographics

	Therapy (n = 42)	Control (n = 24)	Total	p Value
Male	32 (76.2)	20 (83.3)	52 (78.8)	0.55
Age, yrs	58 ± 11	66 ± 11	61 ± 12	0.01
Systolic blood pressure, mm Hg	114 ± 19	119 ± 16	116 ± 18	0.26
Diastolic blood pressure, mm Hg	70 ± 10	70 ± 11	70 ± 10	0.98
Body mass index, kg/m^2	31 ± 6	29 ± 6	30 ± 6	0.18
6-min walk test, m	309 ± 118	352 ± 118	324 ± 119	0.16
Baseline medications				
Beta-blocker	40 (95.2)	23 (95.8)	63 (95.5)	1.00
Diuretic	40 (95.2)	22 (91.7)	62 (93.9)	0.62
ACE-I or ARB	38 (90.5)	22 (91.7)	60 (90.9)	1.00
LVEF (Core Lab), %	29 ± 5	29 ± 5	29 ± 5	0.19
LVEDD (Core Lab), mm	60 ± 6	61 ± 8	61 ± 7	0.64
LVESVi (Core Lab), ml/m^2	55 ± 17	61 ± 16	57 ± 17	0.16
Minnesota Living with Heart Failure Questionnaire	51 ± 20	45 ± 18	49 ± 19	0.20
Heart failure hospitalization 6 months before enrollment	18 (42.9)	12 (50.0)	30 (45.5)	0.62

Values are n (%) or mean ± SD.

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; LVEDD = left ventricular end diastolic dimension; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end systolic volume index.

TABLE 2 Patient General Cardiovascular History

	Therapy (n = 42)	Control (n = 24)	Total
Implanted implantable cardioverter-defibrillator at baseline	32 (76.2)	17 (70.8)	49 (74.2)
QRS width, ms	104 ± 14	105 ± 13	105 ± 14
Ischemic cardiomyopathy	25 (59.5)	12 (50.0)	37 (56.1)
Atrial arrhythmias	18 (42.9)	9 (37.5)	27 (40.9)
Atrial fibrillation	10 (23.8)	6 (25.0)	16 (24.2)
Sinus node dysfunction	3 (7.1)	0 (0.0)	3 (4.5)
Ventricular arrhythmias	16 (38.1)	16 (66.7)	32 (48.5)
Ventricular tachycardia	11 (26.2)	8 (33.3)	19 (28.8)

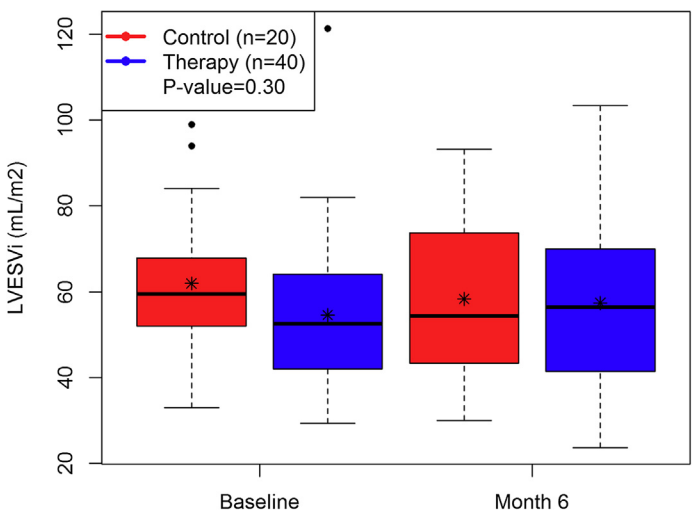
Values are n (%) or mean ± SD.

STUDY OBJECTIVES. The results of the primary objective of the trial (i.e., change in LVESVi) is presented in Figure 3. As shown, there was no significant difference in the change in LVESVi over 6 months between groups (p = 0.30). Patients in the SCS ON arm had a small increase in LVESVi from baseline to 6 months (54.6 ± 17.3 to 57.4 ± 19.6), whereas there was a small decrease in LVESVi in the SCS OFF arm (61.9 ± 16.3 to 58.3 ± 17.6). In the SCS OFF group, 70% of the patients showed some reduction in their LVESVi and in the SCS ON group, only 38% of the patients showed a reduction in their LVESVi over 6 months.

The secondary endpoints of the trial were change in peak VO_2 (Figure 4) and change in NT-proBNP (Figure 5) at 6 months. As shown in Figure 4, there was no significant difference (p = 0.93) in peak VO_2 between the SCS ON (0.6 ± 4.1 ml/kg/min) and the SCS OFF arms (-0.2 ± 3.3 ml/kg/min). Similar to the primary endpoint, patients in the SCS ON arm had a small increase in peak VO_2 from baseline to 6 months (14. 4 ± 5.3 ml/kg/min to 15.0 ± 4.9 ml/kg/min), whereas there was a decrease in peak VO_2 in the SCS OFF arm (16. 7 ± 3.0 ml/kg/min vs. 16.5 ± 3.1 ml/kg/min). Of the 62 patients completing a 6-month visit, 41 (28 SCS ON, 13 SCS OFF) completed maximal exercise testing at both baseline and 6 months. Reasons for missing data included patient refusal, orthopedic limitation such that patient did not complete the test, and uninterpretable data file for core lab analysis. Similarly, there was no significant (p = 0.79) difference with respect to change in NT pro-BNP level from baseline to 6 months in the SCS ON (-32 ± 994 pg/ml) and SCS OFF (74 ± 1,468 pg/ml) arms.

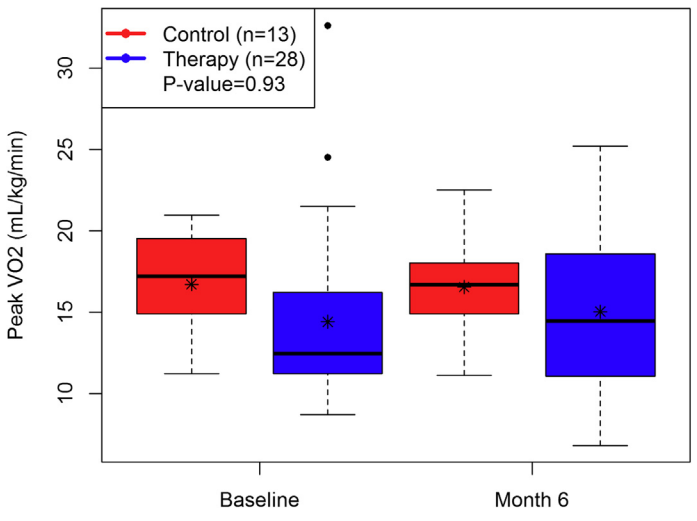
At the completion of the 6-month randomization period, all devices in the SCS OFF arm were switched to SCS ON and 12-month data were collected in both randomization arms. At 12 months, echocardiograms were performed on 54 patients (19 in SCS OFF and 35 in SCS ON). A linear mixed effects model was fit to

FIGURE 3 Change in LVESVi at 6 Months



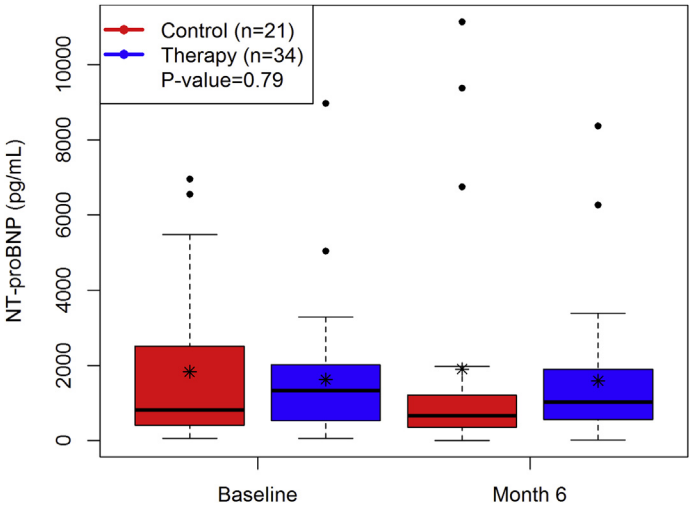
The **bottom line of the box** equals the 25th percentile, the **top line** equals the 75th percentile, the **line within the box** equals the median, and the **asterisk** equals the mean. Sixty-two patients completed a 6-month visit, but 2 echoes were unreadable and excluded, leaving 40 spinal cord stimulation (SCS) ON patients and 20 SCS OFF patients contributing to the primary endpoint. LVESVi = left ventricular end-systolic volume index.

FIGURE 4 Change in Peak VO_2 Uptake at 6 Months



The **bottom line of the box** equals the 25th percentile, the **top line** equals the 75th percentile, the **line within the box** equals the median, and the **asterisk** equals the mean. Sixty-two patients completed a 6-month visit, but only 41 completed a maximal exercise test at both baseline and 6-months; 28 spinal cord stimulation (SCS) ON, 13 SCS OFF. VO_2 = oxygen consumption.

FIGURE 5 Change in NT-proBNP at 6 Months



The **bottom line of the box** equals the 25th percentile, the **top line** equals the 75th percentile, the **line within the box** equals the median, and the **asterisk** equals the mean. Sixty-two patients completed a 6-month visit, but only 55 had an N-terminal pro-B-type natriuretic peptide (NT-proBNP) biomarker test at both baseline and 6-months; 34 spinal cord stimulation (SCS) ON, 21 SCS OFF.

examine the effect of SCS therapy from baseline to 12 months. No significant treatment effect was detected using this extended longitudinal analysis ($p = 0.36$). Online Figure 1 shows the longitudinal data used in the analysis. Similar linear mixed effects models were fit for peak VO_2 ($p = 0.49$) (Online Figure 2) and NT-proBNP ($p = 0.93$) (Online Figure 3) without any detected differences between randomization arms.

Additional endpoints, including freedom from first hospitalization with HF or death at 6 months, change in Minnesota Living with Heart Failure Questionnaire quality of life, change in NYHA functional class, and change in 6-min hall walk all showed no differences between groups (Table 3). No statistically significant differences in heart rates were observed between control and therapy arms. No statistically significant differences were observed between the control and therapy arms in treated ventricular tachycardia/ventricular fibrillation (VT/VF) episodes, or rate of nonsustained ventricular tachycardia (NSVT) and premature ventricular complexes (PVCs) among 19 control and 33 therapy patients that had concomitant ICDs and had reported device data available for analysis. There did not appear to be a subset within the SCS therapy group that benefitted. A total of 25% of therapy subjects had a history of atrial fibrillation, and 20% in the control group and did not impact outcome.

TABLE 3 Results of Study Ancillary Objectives

Outcome	Therapy (n = 42)	Control (n = 24)	p Value
Free from hospitalization with heart failure or death at 6 months	76%	88%	0.28
Change in Minnesota Living with Heart Failure Score (mean difference)	-12	-9	0.90
Change in New York Heart Association functional class			
Improved	58%	63%	0.70
Unchanged	42%	37%	
Worsened	0%	0%	
Change in 6-min hall walk (mean difference)	16	-24	0.47

The adverse events are shown in Table 4, and included lead dislodgement, lead fracture, implant site hematoma, and decompensated HF post-procedure. No complication type occurred in more than 5% of patients. The Data Monitoring Committee observed no safety concerns during the trial, and there were no observed differences between randomized arms. Additionally, at no point in the trial were any artifact interactions noted between the implanted SCS and an implanted Medtronic cardiac device (implantable pulse generator or ICD), indicating that patients can safely have dual Medtronic devices implanted and operational.

DISCUSSION

The results of the DEFEAT-HF trial show that, compared to guideline directed medical therapy alone, thoracic (T2 to T4) SCS in patients with NYHA functional class III HF and a reduced LVEF, did not lead to changes in LV structural remodeling (LVESVi) at 6 months. Moreover, thoracic SCS resulted in neither significant improvements in peak VO_2 nor circulating levels of NT-proBNP at 6 months, despite anecdotal stories of patient improvement. SCS stimulation appeared to be safe and well tolerated in patients with NYHA functional class III HF, consistent with the observation in patients without HF.

The rationale for the DEFEAT-HF trial was on the basis of several promising preclinical studies, which showed that thoracic SCS can improve LV function and structural remodeling in animal models of HF. Moreover, there have been 2 previous small trials in humans that suggested the potential benefit of SCS in patients with advanced HF (20,23). The results of DEFEAT-HF study differ from the first-in-human SCS HEART (Spinal Cord Stimulation for Heart Failure) study by Tse et al. (21), who showed that SCS-treated patients had significant improvement in NYHA functional class, LVEF, and LV end-systolic volume

during follow-up when compared to the patient's baseline measures. Although the reasons for the discrepant results between these studies are not known, several potential explanations merit discussion. First, Tse et al. (21) used thoracic SCS at the T1 to T3 level with a continuous duty cycle of 24 h/day, compared with the T2 to T4 stimulation for 12 h a day. Further, Tse et al. (21) used 2 stimulation leads in the epidural space, 1 positioned midline and the other to the left of the midline. Thus, there were major differences in stimulation "dose" and application between the SCS HEART and DEFEAT-HF studies. In addition, the DEFEAT-HF study did not enroll patients with a wide QRS complex. Last, it is important to recognize that the SCS HEART study was a single-arm study without an actual control group and effects observed could be due to a placebo or trial effect.

STUDY LIMITATIONS. First, although the DEFEAT-HF study was originally powered on the basis of a planned enrollment of 195 patients implanted, the trial was closed after 81 patients had been enrolled with 66 implanted. Thus, the study was not sufficiently powered to see a significant difference between the treatment and control arms. The observed baseline value of LVESVi was 56.8 ml/m^2 and the standard deviation for the change in LVESVi was 15.8 leading to a statistical power of 0.36 to detect a 12.5% change in LVESVi in 60 randomized patients with paired data. Nonetheless, the lack of efficacy of SCS on both the primary and secondary endpoints suggests that DEFEAT-HF was unlikely to have been positive if the trial had enrolled the pre-specified number of patients. Secondly, there are limitations in the ability to blind participants to their randomization arm due to the dermatome mapping and determination of minimally perceived and maximally tolerated paresthesia thresholds performed at baseline and follow-up visits. Of note, after the 6-month follow-up visit patients were asked if they knew which randomized arm they had been assigned to. All of those in the SCS ON arm who responded to the question correctly identified that they had been receiving SCS therapy for the first 6 months; however, 6 of 15 (40%) patients in the SCS OFF arm who responded to the question said they were in the treatment arm receiving SCS therapy in the first 6 months. Third, the SCS stimulation parameters were arbitrarily chosen, on the basis of those used for patients with intractable angina and from the animal studies. No physiologic surrogates were used to assess the effects of SCS stimulation and stimulation parameters were not individualized for each patient.

TABLE 4 System- or Procedure-Related Complications

	SCS ON (N = 42)	SCS OFF (N = 24)	Total (n = 66)
System related			
Device dislocation	3 (3, 7.1%)	0 (0, 0.0%)	3 (3, 4.5%)
Device lead damage	1 (1, 2.4%)	1 (1, 4.2%)	2 (2, 3.0%)
Device extrusion	0 (0, 0%)	1 (1, 4.2%)	1 (1, 1.5%)
Implant site infection	1 (1, 2.4%)	0 (0, 0.0%)	1 (1, 1.5%)
System modification related unknown			
Device dislocation	1 (1, 2.4%)	0 (0, 0.0%)	0 (0, 0.0%)
Implant procedure related			
Decompensated heart failure	2 (2, 4.8%)	1 (1, 4.2%)	3 (3, 4.5%)
Device dislocation	2 (2, 4.8%)	0 (0, 0.0%)	2 (2, 3.0%)
Implant site hematoma	1 (1, 2.4%)	1 (1, 4.2%)	2 (2, 3.0%)
Apnea	0 (0, 0.0%)	1 (1, 4.2%)	1 (1, 1.5%)
Device lead damage	1 (1, 2.4%)	0 (0, 0.0%)	1 (1, 1.5%)
Implant site infection	1 (1, 2.4%)	0 (0, 0.0%)	1 (1, 1.5%)
Total adverse events	8 (7, 16.7%)	5 (4, 16.7%)	13 (11, 16.7%)

Values are the number of events (number of subjects with event, percent of subjects with event).
SCS = spinal cord stimulation.

CONCLUSIONS

In contrast to the promising results of multiple preclinical studies with SCS in animal models, and 2 small provisional studies with SCS in patients with HF, the results of the DEFEAT-HF trial did not show a benefit of SCS on LV structural remodeling, patient functional capacity, nor circulating levels of BNP. Thomas Huxley once said "the great tragedy of science is the slaying of a beautiful hypothesis by an ugly fact." (24). Although the results of the DEFEAT-HF study are disappointing, given the lack of information with respect to what constitutes an appropriate dose (i.e., duty cycle) (25) level of stimulation, and patient selection, it may be premature to conclude that neuromodulation using SCS will not have a role in treating patients with HF with a reduced EF in the future. Future studies should address the limitations noted, in particular monitoring physiologic responses to SCS so that appropriate stimulation parameters can be selected. Duty cycle, frequency, intensity of stimulation, electrode shape, and position can all affect outcomes as seen in the recent cervical vagal stimulation studies that showed no effect in the NECTAR-HF (NEural Cardiac TherApy foR Heart Failure) study (26) but an improvement in 6-month LVEF and LV end-systolic volume in the ANTHEM-HF (Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure) trial (27).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Despite promising results of multiple pre-clinical studies with SCS in animal models, and 2 small provisional studies in patients with heart failure, the results of the DEFEAT-HF trial did not show a benefit of SCS on LV structural remodeling, patient functional capacity, or circulating levels of BNP with the stimulation parameters used in this study. Although manipulations by drugs and sympathectomy have been used for years, vagal nerve stimulation, carotid sinus modulation, renal artery denervation, and SCS are recent additions.

TRANSLATIONAL OUTLOOK: Given the lack of information with respect to what constitutes an appropriate dose (i.e., duty cycle) of stimulation, and patient selection, it may be premature to conclude that neuromodulation using SCS will not have a role in treating patients with HF with a reduced EF. Future studies should address the limitations noted, in particular monitoring physiologic responses to SCS, so that appropriate stimulation parameters can be selected. Duty cycle, frequency, intensity of stimulation, electrode shape, and position can all affect outcomes.

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APPENDIX For an expanded Methods section as well as supplemental figures, please see the online version of this article.