PŘÍLOHA 1

Effects of Spinal Cord Stimulation on Cardiac Sympathetic Nerve Activity in Patients with Heart Failure

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Background: *Spinal cord stimulation (SCS) reduces sympathetic activity in animal models of heart failure with reduced ejection fraction (HF) but limited data exist of SCS in patients with HF. The aim of the present study was to test the primary hypothesis that SCS reduces cardiac sympathetic nerve activity in HF patients. Secondary hypotheses were that SCS improves left ventricular function and dimension, exercise capacity, and clinical variables relevant to HF.*

Methods: *HF patients with a SCS device previously participating in the DEFEAT-HF trial were included in this crossover study with 6-week intervention periods (SCS-ON and SCS-OFF). SCS (50 Hz, 210-μs pulse duration, aiming at T2–T4 segments) was delivered for 12 hours daily. Indices of myocardial sympathetic neuronal function (heart-to-mediastinum ratio, HMR) and activity (washout rate, WR) were assessed using ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy. Echocardiography, exercise testing, and clinical data collection were also performed.*

Results: *We included 13 patients (65.3 ± 8.0 years, nine males) and MIBG scintigraphy data were available in 10. HMR was not different comparing SCS-ON (1.37 ± 0.16) and SCS-OFF (1.41 ± 0.21, P = 0.46). WR was also unchanged comparing SCS-ON (41.5 ± 5.3) and SCS-OFF (39.1 ± 5.8, P = 0.30). Similarly, average New York Heart Association class (2.4 ± 0.5 vs 2.3 ± 0.6, P = 0.34), quality of life score (24 ± 16 vs 24 ± 16, P = 0.94), and left ventricular dimension and function as well as exercise capacity were all unchanged comparing SCS-ON and SCS-OFF.*

Conclusion: *In patients with HF, SCS (12 hours daily, targeting the T2–T4 segments of the spinal cord) does not appear to influence cardiac sympathetic neuronal activity or function as assessed by MIBG scintigraphy. (PACE 2017; 40:504–513)*

heart failure, spinal cord stimulation, sympathetic nervous system, imaging

Introduction

Heart failure with reduced ejection fraction (HF) is characterized is characterized by chronic

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overactivation of the sympathetic nervous system and vagal withdrawal.[1] Mitigating the deleterious effects of sympathetic activity using β-blockers is fundamental in current HF treatment, but further reduction is likely an important therapy goal in HF.

In animal experiments, spinal cord stimulation (SCS) applied in the upper thoracic segments of the spinal cord can reduce cardiac sympathetic nerve activity directly.[2] This sympatholytic effect of SCS has been linked to reverse remodeling in animal models of HF.[3] However, data on SCS in human HF are limited and, in particular, the effect of SCS on cardiac sympathetic activity in human HF remains unknown.

Imaging of the norepinephrine analogue ^{123}I-*meta*iodobenzylguanidine (MIBG) can be used to evaluate cardiac sympathetic nervous system function and activity in humans.[4] It has previously been demonstrated that myocardial MIBG uptake (heart-to-mediastinum ratio, HMR) and retention (washout rate, WR) reflect myocardial sympathetic nerve function and activity, respectively.[4] Importantly, reduced HMR and increased WR are independent predictors of all-cause mortality and malignant arrhythmias in HF[5] and improve with clinically proven effective HF treatment.[6] The effect of SCS on MIBG-derived indices of cardiac sympathetic nerve activity and function in patients with HF remains largely unknown.

The main objective of the present study was to test the hypothesis that SCS improves cardiac sympathetic function and activity (increased HMR and reduced WR) in patients with HF. Secondary hypotheses were that SCS improves (1) left ventricular systolic function and dimensions, (2) exercise capacity, and (3) selected clinical variables relevant to HF.

Methods

Patient Selection

Patients were recruited from a pool of HF patients implanted with a SCS device as a part of the DEFEAT-HF clinical trial[7] at Karolinska University Hospital, Stockholm, Sweden and Na Homolce Hospital, Prague, Czech Republic.

Inclusion criteria were being enrolled as a study subject in the DEFEAT-HF trial for 12 months or longer, having an implanted SCS device with adequate battery life to complete the study, and willingness and ability to comply with the study procedures. Exclusion criteria were being prescribed tricyclic antidepressants that could not safely be withdrawn and current or planned pregnancy. Main original inclusion criteria in the DEFEAT-HF trial were New York Heart Association functional class (NYHA) III HF with left ventricular ejection fraction (EF) $\leq$ 35%, QRS duration $<$ 120 ms, and left ventricular end-diastolic diameter of 55–80 mm. Main original exclusion criteria were recent acute coronary syndrome, severe mitral regurgitation, and being implanted with a cardiac resynchronization therapy device.

Study Protocol

Figure 1 shows an outline of the study protocol, which was designed as a single blind (investigator), randomized, controlled, crossover study. Patients were included after completing the 12-month follow-up in the DEFEAT-HF trial. In the DEFEAT-HF trial, the outcome variables were evaluated at the 6-month visit when also all patients were programmed to SCS "ON" for an extended follow-up phase (even those originally randomized to "OFF"). Hence, all patients were on active SCS treatment when arriving at the baseline/randomization visit in the present substudy. At a baseline/randomization visit patients were subjected to a clinical, physical, and echocardiographic evaluation and were asked to self-rate their quality of life (QoL) by filing in the Minnesota Living with Heart Failure Questionnaire (MLHFQ). Moreover, dermatome mapping and determination of the SCS stimulation output resulting in minimal perceived paresthesia (MPP) and maximally tolerated paresthesia (MTP) were performed. Patients were subsequently randomized to either 6 weeks of SCS therapy on (SCS-ON) followed by 6 weeks with therapy off (SCS-OFF), or vice versa. At the 6- and 12-week study visits echocardiography, MLHFQ, and clinical and physical evaluations were performed again. Also, patients performed a symptom-limiting maximal exercise test for measurement of peak VO_2 and cardiac output (CO) reserve, and MIBG scintigraphy was performed.

Adverse events, any change in medication, and technical problems were continuously monitored and reported.

The study protocol was approved by the Institutional Review Board at both participating centers and complies with the principles outlined in the Declaration of Helsinki. All subjects provided oral and written informed consent to participate in the study.

SCS: Therapy Delivery

Patients had been implanted with a SCS device as follows: A single lead with eight electrodes (model 3777/3877, Medtronic, Plc, Minneapolis, MN, USA) was implanted in the epidural space targeting the midline of the T2–T4 segments of the spinal cord (Figs. 2A and B).

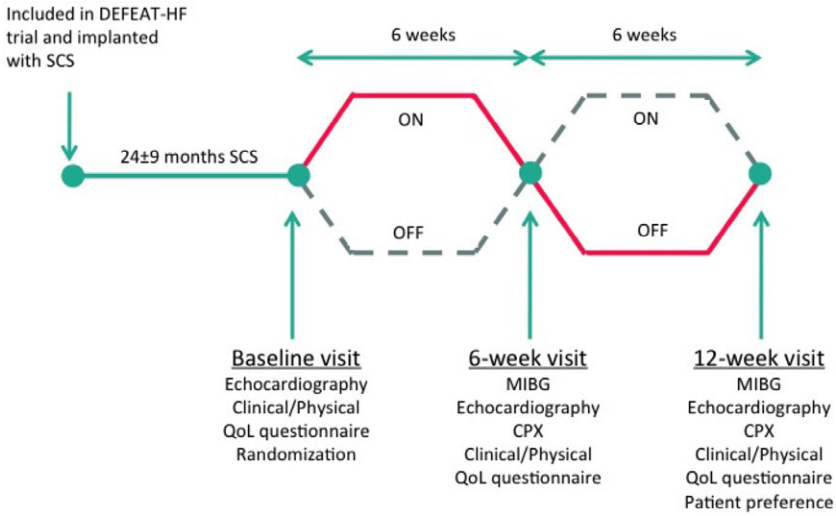

Figure 1. *Outline of the study protocol. CPX = cardiopulmonary exercise testing; MIBG = ^{123}I-metaiodobenzylguanidine scintigraphy; QoL = quality of life; SCS = spinal cord stimulation. [Color figure can be viewed at wileyonlinelibrary.com]*

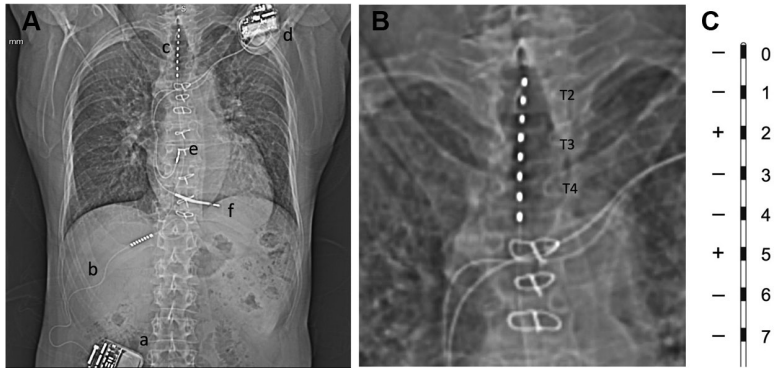

Figure 2. *(A) Thoracic CT scan image of a study patient with ICD and SCS implanted. The SCS (a) was inserted in the lateral abdominal region and attached to a lead (b) carrying the electrodes (c). The ICD (d) is seen below the left clavicle and is attached to the atrial (e) and ventricular (f) ICD leads. (B) Close-up of the SCS electrode implanted in the T2–T4 spinal cord region. (C) Schematic illustration of the distal part of the lead carrying the eight electrodes. All the eight electrodes were simultaneously active (either + or −). CT = computed tomography; ICD = implantable cardioverter defibrillator; SCS = spinal cord stimulation.*

The lead was connected to a PrimeADVANCED™ neurostimulator (Model 37702, Medtronic, Plc) that was placed subcutaneously on the lateral abdomen.

During SCS-ON stimulation was delivered at 90% of the MTP (frequency: 50 Hz; pulse duration: 210 μs). All eight electrodes were active (Fig. 2C) and therapy was delivered for 12 hours per day (daytime).

MIBG Scintigraphy: Procedure and Data Analysis

MIBG scintigraphy has been described in detail elsewhere.[4] Patients were asked to abstain from dietary products known to interfere with the investigation, including caffeine. Pharmacological blockage of thyroid gland uptake of free ^{123}I was advised but optional. After a 30-minute bed rest 160–300 MBq of MIBG was slowly injected

during 2–3 minutes. Anterior planar scans were performed 15 minutes (early) and 4 hours (late) after the isotope injection using a gamma camera with a matrix size of 256 × 256, a 1.5x zoom, and a time per frame of 10 minutes.

An experienced investigator blinded to the interventions analyzed all MIBG data offline. A region of interest (ROI) was manually drawn around the contour of the left ventricle, including the lumen. Next, a second ROI was manually placed in the mediastinum. HMR was then calculated as the ratio between counts per pixel in the heart ROI divided by the counts per pixel in the mediastinum ROI on both early (HMR-early) and late (HMR-late) planar images. WR was calculated without background or decay correction using a standard formula.[4]

Cardiopulmonary Exercise Testing and Echocardiography

A symptom-limiting cardiopulmonary exercise test was performed at the 6- and 12-week follow-up visits. Gas exchange was continuously measured breath-by-breath using either a Jaeger Oxycon Pro® (Erich Jaeger GmbH, Friedberg, Germany) or Innocor® (Innovision A/S, Glamsbjerg, Denmark). Peak VO_2 was defined as the maximum VO_2 value obtained during a 30-second average. In addition, a device based on inert gas rebreathing (Innocor®, Innovision A/S) was used to measure CO at rest and during peak exercise.

Echocardiography was performed using a Vivid E9 (GE Vingmed Ultrasound, Horten, Norway) or a Philips iE33 (Philips Healthcare, Andover, MA, USA) at baseline and the 6- and 12-week follow-up visits. An experienced interpreter blind to the study protocol analyzed all echocardiographic images offline. Left ventricular end-diastolic and end-systolic volumes and EF were quantified using biplane disk summation from 2D images from the apical 2- and 4-chamber views. In case of poor image quality, left ventricular volumes were assessed using the Teicholz method. Volumes were then normalized to body surface area. E/e' was measured from the lateral and septal part of the mitral ring and subsequently averaged. Echocardiographic variables were measured over ≥3 consecutive beats and averaged.

Evaluation of Clinical Variables

Patients' NYHA class was assessed at each study visit. Furthermore, patients self-reported their QoL using the MLHFQ and a global assessment form. In the latter, subjects were asked to compare their present HF symptoms to those during the previous study visit on a 7-point scale ranging from markedly improved to markedly worse. The global assessment form was used as a part of the HF global composite score categorizing patients as either worsened, unchanged, or improved comparing SCS-ON to -OFF. Patients were considered worsened if any of the following occurred during the ON phase: death, hospitalization for worsening HF, worsening NYHA class, or self-reported markedly or moderately worse symptoms on patient global assessment form. Patients were considered improved if no worsening conditions were met and NYHA class improved and/or patients self-reported moderately or markedly improved symptoms on the patient global assessment form. Patients who were neither categorized as worsened nor improved were considered unchanged.

At the last study visit patients were also asked which study period they preferred (SCS-ON, SCS-OFF, or indifferent).

Statistical Analysis

Significance tests for treatment effects on continuous variables were performed using paired *t*-tests. Associations between selected patient- and therapy-related factors and treatment effect (ΔHMR-late and ΔWR) were assessed using linear regression analyses for continuous variables (HMR-late, WR, EF, N-terminal pro B-type natriuretic peptide (NT-proBNP), and stimulation amplitude). Categorical variables were dichotomized (etiology) or divided into three groups (daily dose β-blockers and electrode position) and compared using analysis of variance. All statistical analyses were performed using SAS (Ver.9.4, SAS Institute, Inc., Cary, NC, USA) and a P-value <0.05 was considered statistically significant.

Results

Baseline Characteristics and Therapy Delivery

Table I summarizes the baseline characteristics of the study subjects. Thirteen patients (age: 65 ± 8 years, four females) were recruited. Average EF and indexed left ventricular end-diastolic volume (LVEDVI) were 43 ± 14% and 78 ± 27 mL/m^2, respectively. Average NYHA class was 2.2 ± 0.4 while median (interquartile range) NT-proBNP was 431 (195–4340) ng/L. EF was significantly higher at inclusion in this substudy (43 ± 14%) compared to at inclusion in the DEFEAT-HF study on average 26 ± 8 months earlier (31 ± 5%, P = 0.007). For descriptive purposes, individual longitudinal changes in EF and left ventricular volumes comparing the baseline visit in the DEFEAT-HF study and the baseline/randomization, as well as the intervention phases, of this substudy is shown in supplementary Figure 2. NYHA

Table I.

Baseline Characteristics

Variable	
Age, years	65 ± 8
Female sex, n = (%)	4 (31%)
NYHA class	2.2 ± 0.4
LVEF, %	43 ± 14
LVESVI, mL/m^2	43 ± 26
LVEDVI, mL/m^2	78 ± 27
E/e', ratio	14 ± 6
NT-proBNP, ng/L (median [IQR])	431 [195–4,340]
Systolic blood pressure, mm Hg	125 ± 17
Diastolic blood pressure, mm Hg	77 ± 13
BMI, kg/m^2	29 ± 6
Heart failure duration, years	4.4 ± 2.6
Ischemic etiology, n = (%)	6 (46%)
Nonischemic etiology, n = (%)	7 (54%)
Previous MI, n = (%)	6 (46%)
Previous CABG/PCI, n = (%)	6 (46%)
History of hypertension, n = (%)	9 (69%)
COPD, n = (%)	1 (8%)
Glomerular filtration rate, mL/min	70 ± 23
Current or past smoker, n = (%)	8 (62%)
Diabetes mellitus, n = (%)	2 (15%)
ICD implanted, n = (%)	11 (85%)
% of patients on β-blocker/ACEI or ARB/MRA	100/92/77
% target daily dose of β-blocker, %	63 ± 33
% target daily dose of ACEI/ARB, %	60 ± 45
% target daily dose MRA, %	71 ± 71
Average daily dose loop diuretics, mg	46 ± 36
% of patients on amiodarone	8

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; E/e' = E-wave (mitral inflow)/e' (tissue Doppler imaging); ICD = implantable cardioverter defibrillator; IQR = interquartile range; LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA class = New York Heart Association functional class; PCI = percutaneous coronary intervention.

class was now significantly lower (2.2 ± 0.4) compared to at inclusion in the DEFEAT-HF trial (3.0 ± 0, P < 0.001). Background treatment of HF drugs was high and kept stable for >3 months before, and during, the study. Patients had been treated continuously with SCS for 24 ± 9 months (all patients ≥9 months) at the baseline/randomization visit in this substudy.

In this study, average duration of the SCS-ON intervention was 6.8 ± 1.7 weeks and average duration of the SCS-OFF period was 6.0 ± 1.3 weeks. Supplementary Figure S1 shows the distribution of segments where study subjects perceived paresthesia during dermatome mapping. The accumulation of patients with perceived paresthesia in the thoracic region suggests that thoracic neurons were indeed targeted. Average output that produced MPP and MTP was 3.2 ± 2.6 V and 4.0 ± 2.9 V, respectively. This resulted in an average programmed output of 3.6 ± 2.6 V (90% of MTP). Location of the cranial tip of the SCS electrode was T1 in five patients, T2 in two patients, and T4 in six patients.

Effect of SCS on Cardiac Sympathetic Function and Activity

Three patients withdrew consent to MIBG scintigraphy at one or both visits, resulting in paired data from 10 patients comparing SCS-OFF and SCS-ON. Figure 3 shows the main findings from the MIBG scintigraphy evaluations of cardiac sympathetic function (HMR) and activity (WR). Cardiac sympathetic function was not affected by SCS, as HMR-late was unchanged comparing SCS-ON (1.37 ± 0.16) and SCS-OFF (1.41 ± 0.21, P = 0.46). Similarly, cardiac sympathetic activity was unchanged by SCS, as WR was unchanged between therapy ON (41 ± 5%) and OFF (39 ± 6%, P = 0.30). In fact, although most changes were small, most patients showed a reduction in HMR-late (70%) and increase in WR (60%), reflecting worse myocardial global neuronal distribution and function and increased activity with SCS-ON.

Effect of SCS on Exercise Capacity and Left Ventricular Structure and Function

Supplementary Table S1 details the effect of SCS on cardiopulmonary exercise testing variables. All 13 patients completed both exercise tests and on average gave a close-to-maximum effort evident as a high respiratory exchange

Table II.

Effects of Spinal Cord Stimulation on Echocardiographic Variables

Variable	SCS-OFF	SCS-ON	P-Value
LVEF (%)	40 ± 11	42 ± 14	0.42
LVESVI (mL/m^2)	52 ± 30	53 ± 27	0.95
LVEDVI (mL/m^2)	85 ± 39	85 ± 34	0.89
E/e' (ratio)	15 ± 9	12 ± 7	0.38

E/e' = E-wave (mitral inflow)/e' (tissue Doppler imaging); LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; SCS = spinal cord stimulation.

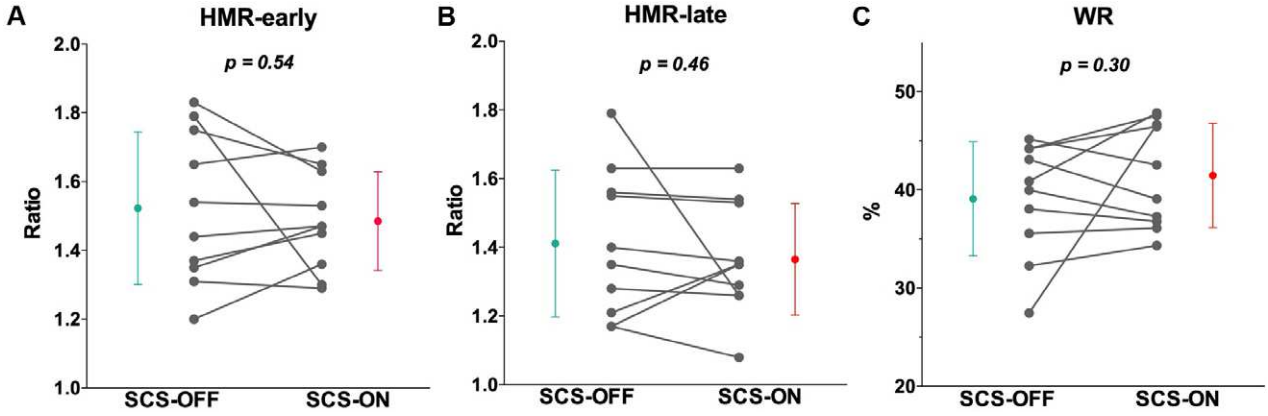

Figure 3. *Individual (and mean ± standard deviation) effects of spinal cord stimulation on myocardial sympathetic neuronal function (HMR) and activity (WR) assessed by MIBG scintigraphy. HMR = heart-to-mediastinum ratio; SCS = spinal cord stimulation; WR = washout rate. [Color figure can be viewed at wileyonlinelibrary.com]*

ratio (1.0 ± 0.1) and rate of perceived exertion at maximum work level (Borg scale: 17 ± 2). SCS-ON was not associated with improvement in exercise duration (555 ± 262 seconds) or maximum resistance level (107 ± 66 W) compared to SCS-OFF (541 ± 251 seconds and 104 ± 73 W, respectively, $P > 0.05$ for both). Furthermore, peak VO_2, CO at maximum exercise, and CO reserve were all largely unaffected by SCS-ON or -OFF (Supplementary Table S1).

Table II shows the effect of SCS on left ventricular structure and function. LVEDVI did not change significantly with SCS-ON (85 ± 34 mL/m^2) compared to SCS-OFF (85 ± 39 mL/m^2, $P = 0.89$). Similarly, EF and indices of LV filling pressure (E/e') were not affected by therapy ON or OFF.

Clinical Effects of SCS

Figure 4 shows the effect of SCS on clinical variables. Compared to SCS-OFF, SCS-ON had no significant effect on the HF clinical composite score, QoL assessed with MLHFQ, or average NYHA class.

There were two adverse events reported during the ON phase and four during the OFF phase. No hospitalizations occurred during the ON phase. This was not significantly different compared to the OFF phase (one hospitalization).

Association between Patient- and Therapy-Related Factors and Therapy Effect

Baseline HMR-late (SCS-OFF) correlated significantly and inversely with the SCS-associated *change* in HMR-late (Fig. 5A). Similarly, baseline WR (SCS-OFF) correlated significantly but positively with the treatment effect on HMR-late (Fig. 5B). We found no significant associations

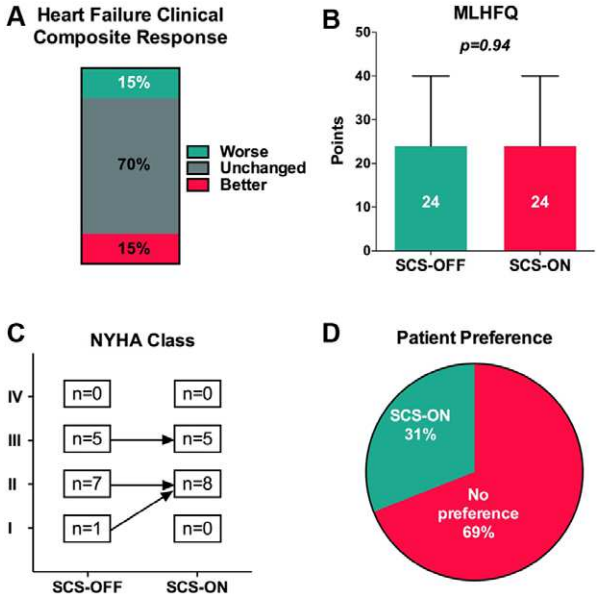

Figure 4. *Effect of spinal cord stimulation on clinical variables relevant to heart failure. MLHFQ = Minnesota Living with Heart Failure Questionnaire; NYHA class = New York Heart Association functional class; SCS = spinal cord stimulation. [Color figure can be viewed at wileyonlinelibrary.com]*

between baseline NYHA class, NT-proBNP, stimulation amplitude, or electrode position and the SCS effect on HMR-late (Supplementary Table S2). Similarly, patients with EF > 40% at baseline in this substudy (n = 5, indicating ≥10% improvement in EF compared to the baseline in the main DEFEAT-HF trial) displayed a similar SCS effect on HMR-late compared to patients with EF < 40%.

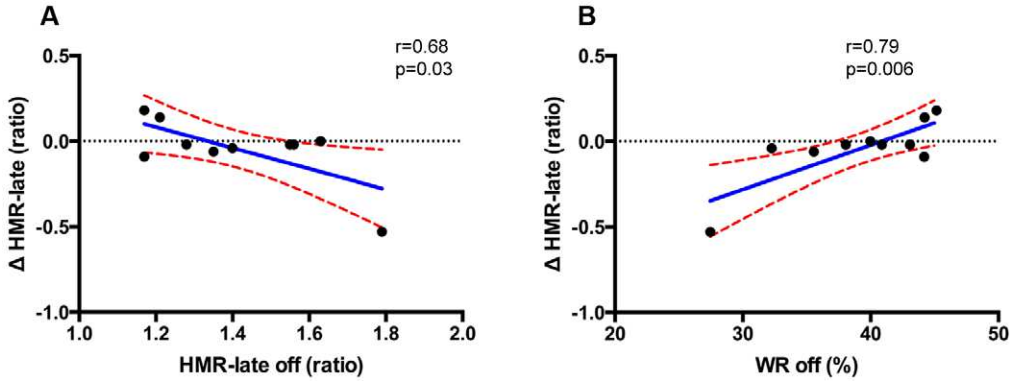

Figure 5. *(A) Correlation plot showing association between* baseline *heart-to-mediastinum ratio (HMR) and SCS-induced* change *in HMR. (B) Correlation plot depicting the association between baseline washout rate (WR) and SCS-induced change in HMR. Solid blue line is the best-fit regression line and the dotted red lines its 95% confidence band. SCS = spinal cord stimulation. [Color figure can be viewed at wileyonlinelibrary.com]*

Discussion

In the present study we show that SCS appears not to improve cardiac sympathetic neuronal function or activity, as assessed with MIBG scintigraphy, in patients with HF. Furthermore, we could not document any significant positive effects of SCS on exercise capacity, cardiac structure or function, or relevant clinical variables. However, we did find an association between the degree of sympathetic function and activity at baseline and the SCS effect on HMR.

While this is the first study to investigate the effect of SCS on cardiac sympathetic nerve activity in patients with HF, there are a few studies in patients without overt HF but treated with SCS for retractable angina pectoris. Although two smaller studies showed that heart rate variability (HRV) improved acutely with SCS,[8,9] another study directly measuring cardiac norepinephrine spillover could not document any beneficial effects of SCS on cardiac sympathetic activity[10] despite a reduction in total body norepinephrine spillover. In a fourth study in similar patients with longer-term follow-up, SCS failed to improve cardiac sympathetic nerve activity function or activity assessed with MIBG scintigraphy.[11] Considering the profound difference in sympathetic activity and signaling comparing patients with and without HF, these data cannot be generalized to a HF population. Nevertheless, the main finding from the present study is in agreement with most published data displaying a neutral effect of long-term SCS on cardiac sympathetic nerve activity in human subjects.

These neutral results from studies in humans with and without HF are contrasted by experimental studies in animal models where SCS consistently has demonstrated a cardiac sympatholytic effect.[2,12] This discrepancy may be attributed to several factors. First, therapy is usually delivered at higher output (90% of motor threshold) in animal studies. Second, a somewhat more cranial electrode placement, targeting the T1 and T2 segments, has usually been applied in animal experiments. Third, most animal studies of sympatholytic effect of SCS are acute investigations and data on longer-term stimulation and benefits on cardiac sympathetic nervous system exist but are few in numbers.[13] If and how the cardiac effects of SCS depend on stimulation amplitude, spinal cord segment stimulated, treatment time, and intermittent versus continuous stimulation remains poorly defined, especially in HF patients. There are a few studies comparing different stimulation modes on the cardiac effect of SCS. In one small study with HF induced in canines, the beneficial effects of SCS on LV remodeling and arrhythmia suppression was observed in a dose- and segment-dependent manner: Although stimulating with 60% or 90% of motor threshold conveyed similar results, a 30% amplitude was ineffective. Also, stimulation at T1 and T4 yielded similar results but T8 stimulation was ineffective.[14] Furthermore, Liao et al. demonstrated that both intermittent and chronic SCS was superior to no SCS in terms of reduction in cardiac sympathetic activity and reverse remodeling in a porcine model of HF, but intermittent stimulation was associated with a larger positive effect.[13]

In the present study we could not find any evidence of association between stimulation amplitude or lead placement and therapy effect, but this analysis was limited by the small

sample size. However, we did find an inverse correlation between baseline HMR-late and the SCS-associated change in HMR-late, and a positive correlation between WR and change in HMR-late. If confirmed in a larger study, these findings suggest that patients with worse cardiac sympathetic function and higher activity could derive a larger sympatholytic effect of SCS. Moreover, it implies that MIBG can be used to identify these patients.

In experimental animal studies of modeled HF, the decrease in sympathetic nerve activity observed with SCS is paralleled by improved cardiac pump function, reverse remodeling, and a reduced myocardial oxygen demand.[3,15] Although other documented SCS effects such as increased vagal tone and improved tissue perfusion by release of vasoactive substances[16] may be important mediators of these observed beneficial effects, the observed sympatholytic effect is an important rationale for pursuing SCS as a HF therapy in humans.

To date, two trials have investigated the effect of SCS on echocardiographic and clinical variables and exercise performance in patients with HF.[7,17] A third study has demonstrated safety and feasibility.[18] In the DEFEAT-HF clinical trial, from which the patients in this study were recruited, SCS had a neutral effect on reverse remodeling and exercise capacity.[7] On the contrary, the SCS HEART study reported improvements in cardiac dimensions and function, NYHA class, and peak VO_2 with SCS.[17] There are differences in study design and therapy delivery between these studies that may contribute to the difference in trial outcome. Contrary to the DEFEAT-HF trial, patients in the SCS HEART study were implanted with a dual electrode system and therapy was delivered continuously (24 hours/day). Also, there was no randomized control group in the SCS HEART study, which makes the results susceptible to a placebo effect. The main difference, however, between the two studies is likely the use of continuous SCS therapy in the SCS HEART study while we applied 12 hours of stimulation per day. It is possible that we "underdosed" SCS in the current study. However, this notion remains speculative since no studies of a dose-dependent effect of SCS in patients with HF have been conducted. In the present study the 12-hour/day stimulation protocol was used in order to match the therapy delivery in the main DEFEAT study. In the main DEFEAT study, a 12-hour daily stimulation strategy was chosen primarily due to concern that patients would not tolerate the stimulation-associated paresthesia during nighttime, which could necessitate reduction in stimulation amplitude (therapy delivery). Although applying a 24-hour per day stimulation protocol may have resulted in a larger SCS therapy effect in this study, it remains speculative. Importantly, when interpreting the data from this study the specific stimulation protocol used should be considered.

Based on the findings in the present study, it appears that longer-term SCS applied for 12 hours/day does not reduce cardiac sympathetic nerve activity in patients with HF. This may be one factor contributing to the neutral effect of SCS in the DEFEAT-HF trial. Further studies evaluating the effect of SCS, and how this is dependent on the stimulation mode, should be addressed in future experimental and clinical studies.

There are several methods to assess sympathetic nervous system activity in patients with HF, such as muscle sympathetic nerve activity (MSNA), catecholamine concentrations in peripheral blood, HRV, norepinephrine spillover, and MIBG scintigraphy. The main objective of the present study was to evaluate the effect of SCS on *cardiac* sympathetic nerve activity. Therefore, MSNA and catecholamine concentrations were considered nonideal as outcome variables. HRV reflects cardiac autonomic balance but is reliable only in patients with stable sinus rhythm. Since we included a large portion of HF patients with implantable cardioverter defibrillator, who are at risk of both atrial pacing and atrial fibrillation, we considered HRV to be a suboptimal method in the current study. Norepinephrine spillover is the gold standard method of assessing cardiac sympathetic activity in humans, but is invasive. We considered the risks associated with repeat catheterizations to outweigh the potential superior accuracy of this method. Instead, we chose MIBG since it is noninvasive and is known to reflect cardiac sympathetic function and activity.[4] Furthermore, it has been used previously to evaluate the effect of different HF treatments on cardiac sympathetic nerve activity[6] and provides independent prognostic information in patients with HF.[5]

Limitations

There are several limitations to this study.

First, the study population was small, resulting in limited statistical power when testing the study hypothesis. Although the SCS effect in terms of average values and statistical significance testing was neutral, we found that 70% of patients had a *reduced* HMR-late and 60% had an *increased* WR indicating *worsened* global myocardial sympathetic function and *higher* sympathetic tone with SCS. Furthermore, other effective therapies in HF have demonstrated beneficial effects of SCS with similarly small sample sizes.[19] Together this suggests that it is

unlikely that we would have demonstrated a substantial positive SCS effect in a larger sample size.

Second, patient inclusion in this study may be affected by selection bias since patients had survived the first 12 months after inclusion in the main DEFEAT-HF trial with improved EF and NYHA class. It is possible that the therapy effect is larger in patients with a more advanced disease state and that selection bias diminished our capacity for finding a positive SCS effect. Indeed patients in this trial showed some signs of mild HF at baseline, as average NHYA class and NT-proBNP were low and EF high. On the other hand, patients had other features of more severe disease such as a low average peak VO_2. Even more importantly, patients' average HMR-late was below the cut-off of 1.60 that previously has been shown to identify HF patients at high risk for adverse events.[5]

Third, the 6-week intervention duration may be too short to reflect effects of chronic therapy delivery and changes in autonomic nervous system function. However, previous studies have shown that changes in cardiac sympathetic function can be detected by MIBG scintigraphy as early as 2 weeks after cardiac resynchronization therapy initiation[19] and 11 days after symptom onset in Takotsubo cardiomyopathy.[20] Furthermore, in experimental animal studies the SCS effect on sympathetic activity occurs within minutes[2] and on cardiac structure and function within 5 weeks.[3]

Last, potential carry-over effects inherent to the crossover design chosen cannot be accounted for considering the small sample size.

Conclusions

In patients with HF, SCS (12 hours daily, targeting the T2–T4 segments of the spinal cord) does not appear to influence cardiac sympathetic neuronal activity or function as assessed by MIBG scintigraphy.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Figure S1. Distribution of patients with perceived paresthesia in different dermatomes during dermatome mapping.
Figure S2. Longitudinal individual changes in left ventricular systolic function (A) and volume (B) comparing the baseline visit at the DEFEAT-HF trial, the baseline visit in the sub-study and the "OFF" and "ON" phases in the sub-study.
*=SCS therapy ON or OFF according to randomization in the DEFEAT-HF trial.
Table S1
Table S2

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Spinal cord stimulation in heart failure: effect on disease-associated biomarkers

Background and aims

Several preclinical studies have shown that spinal cord stimulation (SCS) reduces sympathetic activation, reverses adverse cardiac remodelling, improves pump function, and suppresses ventricular arrhythmias in animal models of heart failure (HF) with reduced ejection fraction and suppresses ventricular arrhythmias in animal models of HF with reduced ejection fraction.[1–4] However, the mechanism of SCS benefit in experimental HF remains poorly defined, and data on SCS in patients with HF is limited. Several biomarkers reflect pivotal aspects of HF pathophysiology and severity (e.g. neurohormonal activation, inflammation and cytokine triggering), and cardiac injury and stress. The effect of SCS on these biomarkers in patients with chronic HF remains largely unknown.

Therefore, the objective of the present study was to test the hypothesis that SCS improves levels of neurohormones, inflammatory markers and cytokines and that this is paralleled by a reduction in biomarkers reflecting cardiac stress and injury.

Methods

Patients were recruited from Na Homolce Hospital, Prague, Czech Republic, and Karolinska University Hospital, Stockholm, Sweden. The present study was a substudy to the DEFEAT-HF clinical trial.[5] Inclusion criteria were enrolment in the main trial for ≥12 months with adequate battery life remaining on the implanted neurostimulator and being willing and able to participate in the study. The main inclusion criteria in the original DEFEAT-HF trial were New York Heart Association (NYHA) functional class III HF, with left ventricular ejection fraction (LVEF) ≤35%, narrow QRS complex, echocardiographic evidence of left ventricular chamber dilatation, and on optimal medical therapy. Main exclusion criteria were cardiac resynchronization therapy treatment, recent acute coronary syndrome and uncorrected severe mitral regurgitation.

All patients included had completed the 12-month and final study visit in the DEFEAT-HF trial. Therefore, all study subjects had received at least 6–12 months of SCS before inclusion in the present study and were programmed to SCS-ON when arriving for the baseline visit. This study was a randomized, controlled, investigator-blind crossover study where SCS was either turned off (SCS-OFF) for 6 weeks followed by 6 weeks on (SCS-ON), or vice versa.

Patients had been implanted with a single lead with eight electrodes (Model 3777/3877, Medtronic Plc, Minneapolis, MN, USA) targeting the T2-T4 level of the spinal cord. The lead was tunnelled subcutaneously and connected to a PrimeADVANCED™ neurostimulator (Model 37002, Medtronic Plc) surgically implanted in the abdominal region. During the SCS-ON intervention, the stimulator was programmed to stimulate for 12 h/day at 50 Hz with a 0.21 ms pulse duration at an amplitude corresponding to 90% of the maximal voltage tolerated by the patient. This mode of SCS delivery was identical, as in the main DEFEAT-HF study.

The regional ethics review board at both participating institutions approved the protocol and all study subjects provided written informed consent to participate in the study. The investigation conformed with the principles outlined in the Declaration of Helsinki.

At baseline, and the 6- and 12-week visits, peripheral venous blood and saliva samples were collected from the study subjects after at least 15 min of supine rest. Patients were instructed to be fasting and abstain from caffeinated beverages for at least 12 h before each study visit. Blood and saliva samples were handled according to clinical routine and analysed at the Department of Clinical Chemistry at Karolinska University Hospital.

Comparisons of blood and saliva biomarker levels collected after SCS-ON and SCS-OFF were performed using a Wilcoxon signed-rank test. Pearson correlation coefficients were used to estimate any associations between SCS-associated change in high sensitivity troponin T (hs-TnT) and change in other biomarkers. All statistical analyses were performed using SAS (Ver 9.4; SAS Institute, Inc, Cary, NC, USA). A *P*-value <0.05 was considered statistically significant.

Results

The baseline characteristics and biomarker levels of the 13 study patients are presented in *Table 1*. Mean age was 65 ± 8 years and 69% of study subjects were male. Background treatment with evidence based drugs and devices was high. Average LVEF was 43 ± 14%, which was significantly ($P = 0.007$) higher compared with when patients were included in the main DEFEAT-HF trial 26 ± 8 months earlier (31 ± 5%). Ten patients were in NYHA functional class II and the remaining three were in NYHA class III. Hence, NYHA class had improved significantly ($P < 0.001$) compared with that at inclusion in the DEFEAT-HF trial, when all patients were in NYHA class III. There were nine patients from Na Homolce Hospital, Prague, Czech Republic, and four from Karolinska University Hospital, Stockholm, Sweden.

The level of hs-TnT was modestly but significantly higher during SCS-ON compared with SCS-OFF, which may reflect cardiac injury (*Figure 1a*). This sign of possible adverse effect of SCS was observed regardless of randomization arm (*Figure 1b*) and on a background of unchanged cystatin C comparing SCS-ON (1.2 ± 0.5 mg/L) and SCS-OFF (1.2 ± 0.4 mg/L) ($P = 0.24$) indicating unchanged renal function. A biomarker of cardiac stress, *N*-terminal pro-brain natriuretic peptide (NT-proBNP), was, however, not affected by SCS [SCS-ON 565 (273–3110 ng/L) vs. SCS-OFF 464 (146–3400 ng/L), $P = 1.00$].

Figure 1c–f shows the effect of SCS on biomarkers of inflammation and cytokine activation. The use of SCS was not associated with increase in high sensitivity C-reactive protein (SCS-ON 3.6 ± 4.5 mg/L vs. SCS-OFF 3.6 ± 4.9 mg/L, $P = 0.39$). There was a trend towards increased interleukin-1 (IL-1) and interleukin-6 (IL-6) with SCS although it did not reach statistical significance ($P = 0.08$ and $P = 0.09$, respectively) when comparing SCS-OFF and SCS-ON. There was no significant correlation between change in hs-TnT and change in either IL-1 ($r = 0.06$, $P = 0.83$) or IL-6 ($r = -0.42$, $P = 0.15$) with SCS applied compared with turned off. Tumour

Table 1 Baseline characteristics and biomarker levels

Variable	Value
Demographics	
Age, years	65 ± 8
Female sex, *n* (%)	4 (31)
Heart failure-associated characteristics	
NYHA class	2.2 ± 0.4
LVEF, %	43 ± 14
LVEDV, mL	155 ± 39
HF duration, years	4.4 ± 2.6
Ischaemic aetiology, *n* (%)	6 (46)
β-Blocker therapy, n (%)	13 (100)
ACEI/ARB therapy, *n* (%)	12 (92)
ICD therapy, *n* (%)	11 (85)
SCS therapy duration at baseline visit, months	23 ± 9
Biomarker levels at baseline (reference range within parenthesis)	
hsCRP, mg/L (<3)	5.3 ± 6.7
Cystatin C, mg/L (<1.25)	1.2 ± 0.4
NT-proBNP, ng/L (<194)	431 [195–4340]
Aldosterone, pmol/L (<650)	427 ± 348
Renin, mIE/L (≤40)	332 ± 512
Noradrenaline, nmol/L (≤2.3)	3.8 ± 1.6
hs-TnT, ng/L (<15)	21 ± 16
IL-1, pg/mL (<5)	58 ± 115
IL-6, pg/mL (<7)	21 ± 34
TNF-α, pg/mL (<12)	22 ± 21
Saliva-cortisol, µg/dL (≤1.6)	0.7 ± 0.5

All continuous variables are presented as mean ± standard deviation except NT-proBNP, which is presented as median [interquartile range].
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; hsCRP, high-sensitivity C-reactive protein; hs-TnT, high-sensitivity troponin T; ICD, implantable cardioverter defibrillator; IL-1, interleukin-1; IL-6, interleukin-6; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; TNF-α, tumour necrosis factor alpha.

necrosis factor (TNF)-α was unchanged comparing SCS-ON (27 ± 33 pg/mL) and SCS-OFF (22 ± 21 pg/mL, $P = 0.20$). Saliva levels of cortisol did not change significantly with SCS-ON.

It was found that SCS-ON did not have a significant impact on venous blood concentrations of noradrenaline, renin, and aldosterone (*Figure 1g–i*).

Discussion

In the present study we investigated the effect of SCS, delivered for 12 h/day, aimed at the T2–T4 segment of the spinal cord, on disease-associated biomarkers in patients with chronic moderately severe HF. We found a small but significant increase in hs-TnT, which may indicate cardiac injury, especially as renal function was unchanged. The modest increase in hs-TnT is not likely to be clinically relevant *per se* but may indicate a possible adverse cardiac effect of SCS in humans with HF that warrants further investigations as to its mechanism and significance. Notably, a recent study suggests that even minor changes in multiple individual biomarkers (including hs-TnT) may signal increased risk for adverse outcome in patients with HF.[6] The increase in hs-TnT was paralleled by a trend towards an increase in cytokine activation associated with SCS. In this small study, we could not find a strong association between the level of cytokine activation and cardiac injury measured with hs-TnT. Both IL-1 and IL-6 are pro-inflammatory cytokines produced by cells in the heart[7] in response to cardiac insult[8] and have been associated with reverse remodelling and HF development/worsening.[8] Use of SCS had a neutral effect on both sympathetic nervous system activation and the renin–angiotensin–aldosterone axis when assessed by levels of circulating hormones. Taken together, the data from this study suggest a potential deleterious effect of SCS in patients with HF that may be mediated through cytokine activation and result in myocyte injury.

Unlike in the main DEFEAT-HF trial, the present study did not evaluate clinical or echocardiographic variables of the patients but the absence of improvement, and any signalling of harm in the biomarker profile change associated with SCS in this study contrasts with previous experimental studies in animal models of HF and with the small clinical SCS HEART study that documented several beneficial effects of SCS.[2–4,9] In contrast, the main DEFEAT-HF trial was neutral in terms of the effect of SCS on reverse remodelling, quality of life, and exercise capacity.[5] The present study suggests that cytokine activation and myocyte injury may have contributed to the lack of benefit of SCS in the DEFEAT-HF trial.

Importantly, there are differences in therapy delivery between the present study and the DEFEAT-HF trial on one hand, and experimental animal studies and the SCS HEART study on the other. Differences include stimulation amplitude and hours/day with therapy delivery as well as spinal cord segment stimulated and lead/electrode number and stimulation mode. Whether therapy delivery can be modified and thereby improved compared with what was used in this study warrants further investigations.

Conclusion

In patients with HF, SCS delivered at the T2–T4 segment for 12 h/day was associated with a modest but significant increase in hs-TnT, which may reflect cardiac injury. This was paralleled by a trend towards elevated levels of circulating cytokines. The small magnitude of the hs-TnT increase is not likely to be clinically relevant but the findings from this study may imply a novel mechanism regarding SCS in HF: myocyte injury with associated cytokine release.

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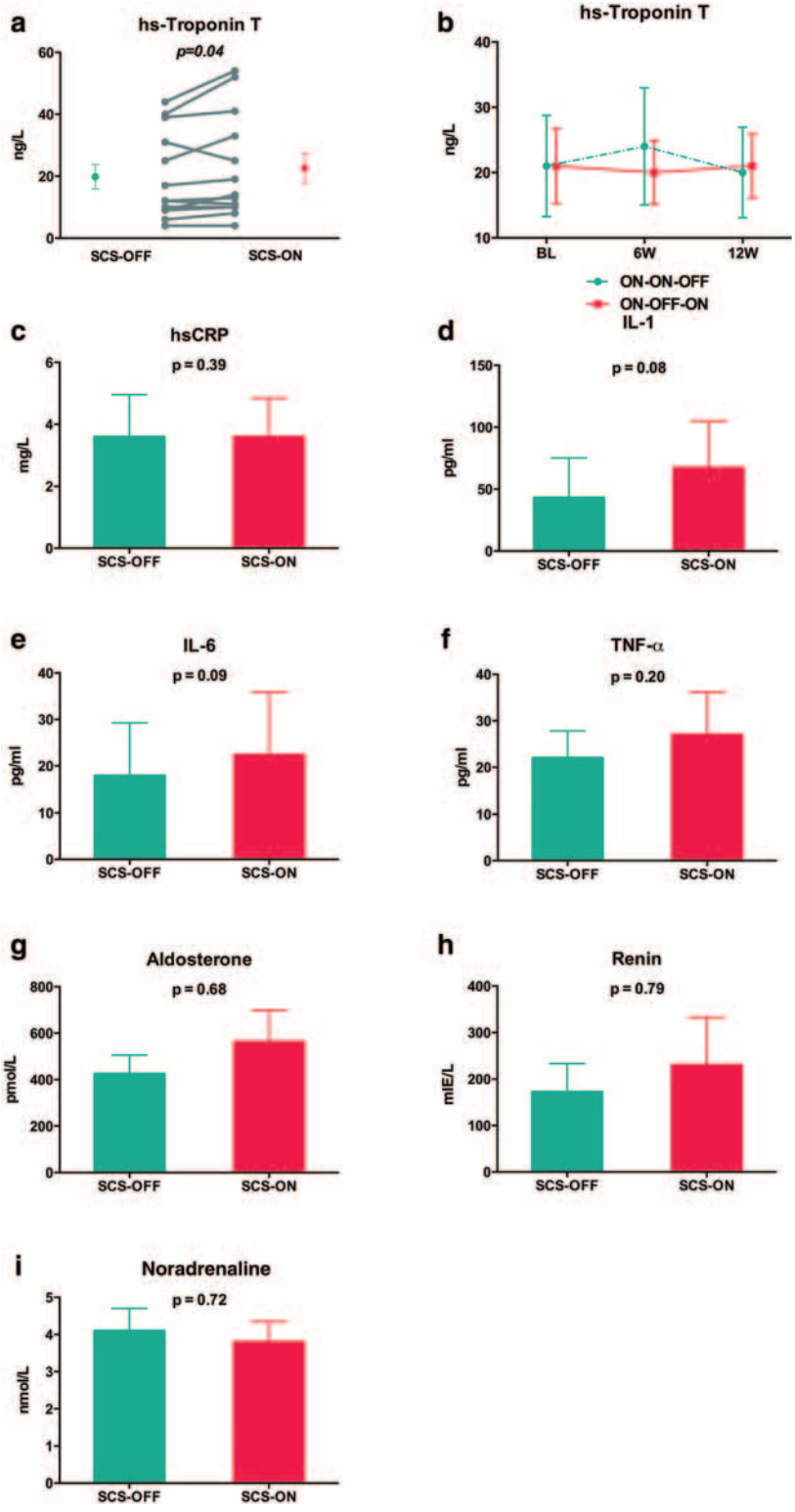

Figure 1 Effect of spinal cord stimulation (SCS) on heart failure associated biomarkers. (a) Individual (grey lines) and mean ± SEM change in high-sensitivity (hs)-Troponin T with SCS ON compared with SCS OFF. (b) Effect of SCS on hs-troponin T at 6 and 12 weeks as a function of randomization order. (c–f) Effect of SCS on inflammatory markers and interleukins. (g–i) Effect of SCS on neurohormonal activation. hsCRP, high sensitivity C-reactive protein; IL-1, interleukin-1; IL-6, interleukin-6; TNF-α, tumour necrosis factor-alpha.

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Conflict of interest: D.J. is an employee and owns stocks in Medtronic Plc. C.L., P.N., F.B., report a research grant, membership of the speakers' bureau, and consultant fees from Medtronic Plc. L.H.L. reports a research grant (Medtronic Plc). B.L. reports a research grant and consultant fees from Medtronic Plc, St Jude Medical, and Boston Scientific. F.K. and J.K. are employees of Medtronic Plc. M.S. reports membership of speakers' bureau and consultant fees from Medtronic Plc and St Jude Medical. J.N., P.D., L.M., F.M., M.B., G.L., and K.S. have nothing to declare.

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Original research article

Acute effect of spinal cord stimulation on autonomic nervous system function in patients with heart failure

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Abstract
Aims: To test the hypothesis that spinal cord stimulation (SCS) acutely improves heart rate variability (HRV) and baroreceptor sensitivity (BRS) in patients with heart failure (HF).
Methods: SCS (15 minutes) was delivered in four different settings: 90% of maximal tolerated stimulation amplitude (MTA) targeting the T1–T4 spinal cord segments (SCS90T1–4), 60% of MTA (SCS60T1–4), 90% of MTA with cranial (SCS90CR) and caudal (SCS90CA) electrode configuration. HRV and BRS were recorded continuously and stimulation was compared to device off.
Results: Fifteen HF patients were included. SCS90T1–4 did not change the standard deviation of intervals between normal beats (SDNN, $p = 0.90$), BRS ($p = 0.55$) or other HRV parameters. In patients with baseline SDNN <50 ms, SCS90T1–4 significantly increased SDNN ($p = 0.004$).
Conclusions: Acute SCS at 60–90% of MTA targeting upper thoracic spinal cord segments does not improve autonomic balance or baroreceptor sensitivity in unselected patients with heart failure but may improve HRV in patients with low SDNN.

Keywords: Baroreceptor sensitivity; Heart failure; Heart rate variability; Spinal cord stimulation

Highlights:
- SCS at T1–T4 segments did not acutely improve HRV in unselected patients with HF.
- SCS acutely improved HRV in HF patients with low baseline HRV.
- Baseline autonomic function may influence the response to SCS therapy in HF patients.
- This should be taken into account during recruitment for neuromodulation trials.

Introduction

Heart failure is characterized by sympathetic nervous system overactivity and vagal withdrawal (Azevedo and Parker, 1999; Parker, 1992). This autonomic imbalance has deleterious long-term effects and is accompanied by attenuated arterial baroreflex control, e.g. blunted baroreceptor sensitivity (BRS) (Wang et al., 1990). Increased sympathetic drive (Jacobson et al., 2010; Nakata et al., 2013) and blunted BRS (Mortara et al., 1997; Osterziel et al., 1995) are independent predictors of adverse outcome in heart failure.

Spinal cord stimulation (SCS) is a treatment option for adults with chronic intractable pain of neuropathic or ischemic origin, including refractory angina pectoris (Simpson et al., 2009). In canine models, SCS applied to the upper thoracic segments (T1–4) of the spinal cord elicits a direct sympatholytic effect on the heart by modulating efferent cardiac neuronal signalling (Foreman et al., 2000). In experimental heart failure models, the sympatholytic effect of SCS translates into improved left ventricular function and volumes and reduced propensity for ventricular arrhythmias (Lopshire et al., 2009). Importantly, stimulation amplitude and targeted thoracic spinal cord segments both modulated the sympatholytic effect of SCS (Lopshire and Zipes, 2014).

Heart rate variability (HRV) is thought to reflect autonomic function and its evaluation is usually automated using one of many commercial systems. This enables assessment of the key pathophysiological change in heart failure: impaired regulation of the cardiac autonomic nervous system. Likewise, BRS is an established tool for the assessment of autonomic control of the cardiovascular system and can also be quantified non-invasively. Thus, change in baroreflex function reveals alteration in autonomic control of the cardiovascular system (La Rovere et al., 2008). It has previously been shown that HRV improves with SCS in patients with refractory angina pectoris without

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heart failure (Anselmino et al., 2009; Moore et al., 2004). However, the acute effect of SCS on HRV and BRS in heart failure subjects remains largely unknown.

Therefore, the main aim of this study was to test the hypothesis that SCS acutely improves HRV and BRS in patients with heart failure. A secondary objective was to examine the impact of different stimulation amplitudes and targeted thoracic spinal cord segments on the effect of SCS.

Materials and methods

Patient selection

Patients participating in the DEFEAT-HF clinical trial were recruited from two study centers (Karolinska University Hospital, Stockholm, Sweden and Na Homolce Hospital, Prague, Czech Republic). The DEFEAT-HF trial was designed to evaluate the effect of SCS on left ventricular remodeling in patients with heart failure and reduced ejection fraction (Zipes et al., 2016). Main inclusion criteria in the DEFEAT-HF trial were age ≥18 years, New York Heart Association functional class (NYHA) III, left ventricular ejection fraction ≤35%, QRS duration <120 ms and left ventricular end-diastolic diameter of 55–80 mm. Main exclusion criteria in the DEFEAT-HF trial were coronary artery revascularization or acute coronary syndrome within 90 days of enrolment, a reversible type of left ventricular systolic dysfunction, cardiac resynchronization therapy and severe mitral regurgitation. In the present study, we included participants from the DEFEAT-HF study with ≥6 months SCS therapy and excluded patients that were unwilling or unable to comply with study procedures.

Spinal cord stimulation

The SCS device consists of a single octopolar lead (model 3777/3877, Medtronic, Plc) implanted in the epidural space, targeting the midline of the T1–T4 segments of the spinal cord. The lead is connected with a PrimeADVANCED™ pulse generator (Model 37702, Medtronic, Plc) that is placed subcutaneously in the region of the lateral abdomen. A stimulation frequency of 50 Hz and pulse duration of 210 μs were used.

Study protocol

Fig. 1A shows an outline of the study protocol. Data were collected during an outpatient visit 6 weeks after discontinuation of SCS therapy (wash-out). Study visits for all patients were conducted at approximately the same time of day and the patients were instructed to abstain from food and beverages containing caffeine or alcohol >12 hours before the investigation. None of the patients were on hormone replacement therapy.

First, sensitivity testing to determine maximal tolerated amplitude (MTA) and dermatome mapping were performed. Patients then rested comfortably in a supine position for >15 minutes before any measurements or interventions were started. Subsequently, four SCS settings were programmed for 15 minutes each in sequential order (Fig. 1B): 90% of MTA targeting the T1–T4 spinal cord segments (SCS90T1–4), 60% of MTA in the T1–T4 segments (SCS60T1-4) and 90% of MTA with cranial (SCS90CR) and caudal (SCS90CA) electrode configuration. We applied a 35-minute period of SCS off between each intervention to allow for wash-out of the previous stimulation. Throughout the protocol, continuous electrocardiogram (ECG) and beat-to-beat hemodynamic data using a non-invasive hemodynamic monitor Nexfin® (BMEYE, Amsterdam, Netherlands) were collected. Cardiac output assessed by a foreign gas rebreathing device (Innocor®, Innovision, Odense, Denmark) (Agostini and Cattadori, 2009) was used to calibrate Nexfin cardiac output measures. No change in medical therapy was allowed during the protocol.

Local authorities and Ethics Committees at both participating centers approved the study protocol and the study protocol was in compliance with the principles of the Declaration of Helsinki. All subjects provided written informed consent.

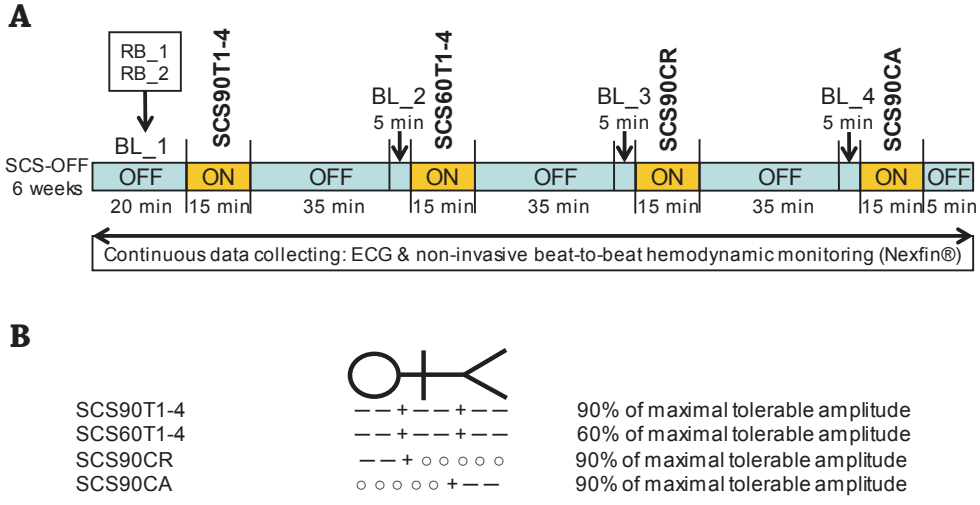

Fig. 1. Outline of the study protocol (**A**). Spinal cord electrode configurations and outputs used during intervention periods throughout the protocol (**B**). BL – baseline; ECG – electrocardiogram; OFF – spinal cord stimulation inactive; ON – spinal cord stimulation active; RB – inert gas rebreathing test; SCS – spinal cord stimulation; SCS60T1–4 – spinal cord stimulation with the amplitude of 60% of maximal tolerated amplitude targeting T1–T4 spinal cord segments; SCS90T1–4 – spinal cord stimulation with the amplitude of 90% of maximal tolerated amplitude targeting T1–T4 spinal cord segments; SCS90CA – spinal cord stimulation with the amplitude of 90% of maximal tolerated amplitude and an electrode configuration targeting caudal segments; SCS90CR – spinal cord stimulation with the amplitude of 90% of maximal tolerated amplitude and an electrode configuration targeting cranial segments.

Assessment of heart rate variability

Analysis was performed using PowerLab and LabChart software (ADInstruments, Dunedin, New Zealand). ECG recordings of the last five minutes of each intervention and the last five minutes of each preceding SCS-OFF period were used to analyze HRV according to recommendations from the European Society of Cardiology Task Force (Heart rate variability..., 1996). In the present study, we used three time-domain measures: standard deviation of intervals between normal beats (SDNN), square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals (pNN50), and several frequency-domain methods: high frequency (HF: 0.15–0.40 Hz) reflecting vagal activity, low frequency (LF: 0.04–0.15 Hz) reflecting baroreflex modulation of autonomic function (Goldstein et al., 2011; Rahman et al., 2011), very low frequency (VLF: <0.04 Hz) representing the strongest prognostic marker from all frequency bands (Hadase et al., 2004) and LF to HF ratio (LF/HF). Frequency-domain measures are expressed as power in each frequency range (ms^2). Previous studies have shown that SDNN <50 ms confers a particularly poor prognosis and this cut-off is recommended by the European Society of Cardiology Task Force for prognostication (Heart rate variability..., 1996). Therefore, we also tested the effect of SCS separately in patients with baseline SDNN >50 ms versus <50 ms.

Assessment of baroreceptor sensitivity

Spontaneous BRS was estimated by the sequence method as described previously (Parlow et al., 1995; Wang et al., 2004). Beat-to-beat systolic blood pressure (sBP) and RR intervals were analyzed using a custom MATLAB algorithm selecting all sequences of three or more successive beats where there were concomitant increases or decreases in sBP and RR interval. The average regression slope was calculated in different 5-minute segments for each stimulation setting (0–5 minute, 5–10 minute, last 5 minutes if total stimulation period was ≥12.5 minutes) and compared with baseline (5-minute segment preceding the stimulation period). The regression slope (expressed as ms/mmHg) is a representative of spontaneous BRS.

Assessment of hemodynamic data

Heart rate, sBP, diastolic blood pressure (dBP), mean arterial pressure (MAP), stroke volume (SV) and cardiac output were measured. An estimate of total peripheral resistance (eTPR) was calculated as: MAP/CO × 79.9 ($dyn/s/cm^{-5}$). A five-minute segment during SCS-OFF preceding each stimulation setting and 15-minute stimulation periods were used for hemodynamic analyses.

Statistical analysis

Normal distribution of HRV, BRS and hemodynamic data was controlled with the Shapiro–Wilk normality test, and parametric (paired two-tailed *t*-test) and non-parametric (Wilcoxon two-tailed matched pairs test) testing was used as appropriate. Data are presented as mean with 95% confidence interval (CI) for normally distributed data and median with 95% CI for skewed data. Differences between low and high baseline SDNN subgroups were compared using an unpaired two-tailed *t*-test. All statistical analyses were performed using GraphPad Prism version 8.3.0 (GraphPad Software, La Jolla California, USA). *P*-values <0.05 were considered statistically significant.

Results

Baseline characteristics and therapy delivery

Table 1 shows the baseline characteristics of the study population. Fifteen subjects (4 female, age 67 ± 8 years, 53% ischemic heart failure etiology) were enrolled. Average left ventricular ejection fraction and indexed end-diastolic volume (LVEDV) were 41 ± 14% and 162 ± 48 ml/m^2, respectively. Average NYHA class was 2.6 ± 0.6.

Table 1. Baseline characteristics

Age (years)	67 ± 8
Female sex (*n*; %)	4 (26)
NYHA class	2.6 ± 0.6
LVEF (%)	41 ± 14
LVEDV (ml)	162 ± 48
Systolic blood pressure (mmHg)	124 ± 18
Diastolic blood pressure (mmHg)	74 ± 9
BMI (kg/m^2)	28 ± 6
Heart failure duration (years)	4.3 ± 2.3
Ischemic etiology (*n*; %)	8 (53)
Previous CABG/PCI (*n*; %)	6 (40)
History of hypertension (*n*; %)	10 (67)
COPD (*n*; %)	2 (13)
Current or past smoker (*n*; %)	9 (60)
Diabetes mellitus (*n*; %)	2 (13)
ICD implanted (*n*; %)	13 (87)
% of patients on β-blocker/ACEI or ARB/MRA	100/93/87
% of target daily dose of β-blocker	66
% of target daily dose of ACEI/ARB	64

ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin II receptor blocker; BMI – body mass index; CABG – coronary artery bypass grafting; COPD – chronic obstructive pulmonary disease; ICD – implantable cardioverter defibrillator; LVEF – left ventricular ejection fraction; LVEDV – left ventricular end-diastolic volume; MRA – mineralocorticoid receptor antagonist; NYHA class – New York Heart Association functional class; PCI – percutaneous coronary intervention.

MTA was 3.3 ± 2.9 V, 3.5 ± 2.9 V and 4.2 ± 2.7 V respectively in SCS90T1–4, SCS90CR and SCS90CA. Distribution of perceived paresthesia during dermatome mapping in the three SCS lead configurations is displayed in Suppl. Figs. S1–S3.

Acute effect of SCS on heart rate variability

As shown in Fig. 2, heart rate was unchanged when comparing SCS90T1–4 (63.2 [49.4–76.8] bpm) to SCS-OFF (65.6 [53.5–75.3] bpm, $p = 0.29$), and SDNN did not change significantly with SCS90T1–4 compared to SCS-OFF (53.0 [27.3–78.1] ms versus 55.7 [22.8–105.3] ms, $p = 0.90$). No statistically significant differences in heart rate or SDNN were observed with SCS60T1-4, SCS90CR or SCS90CA. Similarly, we did not prove any change in RMSSD or pNN50 with SCS compared to SCS-OFF (Suppl. Fig. S4). As shown in Fig. 3, there was no significant change in any frequency-domain HRV parameter with SCS compared to SCS-OFF regardless of stimulation amplitude or lead configuration.

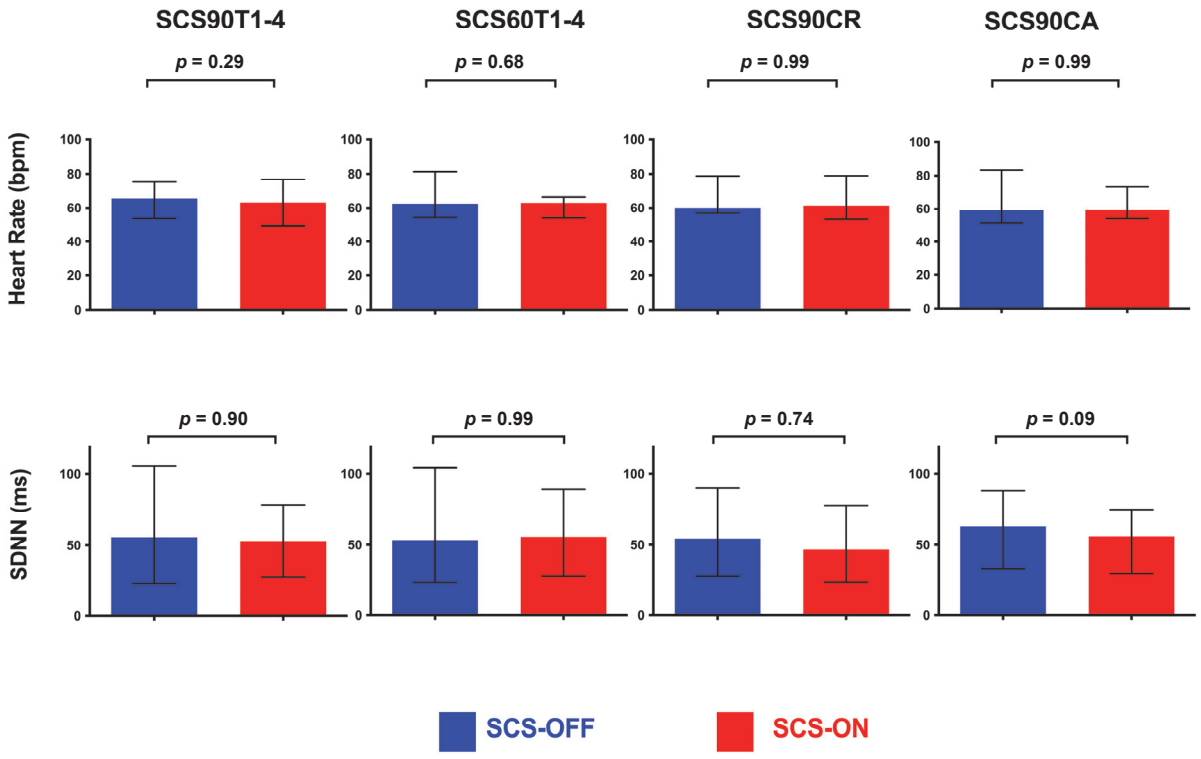

Fig. 2. Acute effect of SCS with different stimulation amplitudes and electrode configurations on heart rate and SDNN. Data are expressed as median with 95% confidence interval. Bpm – beats per minute; SDNN – standard deviation of intervals between normal beats.

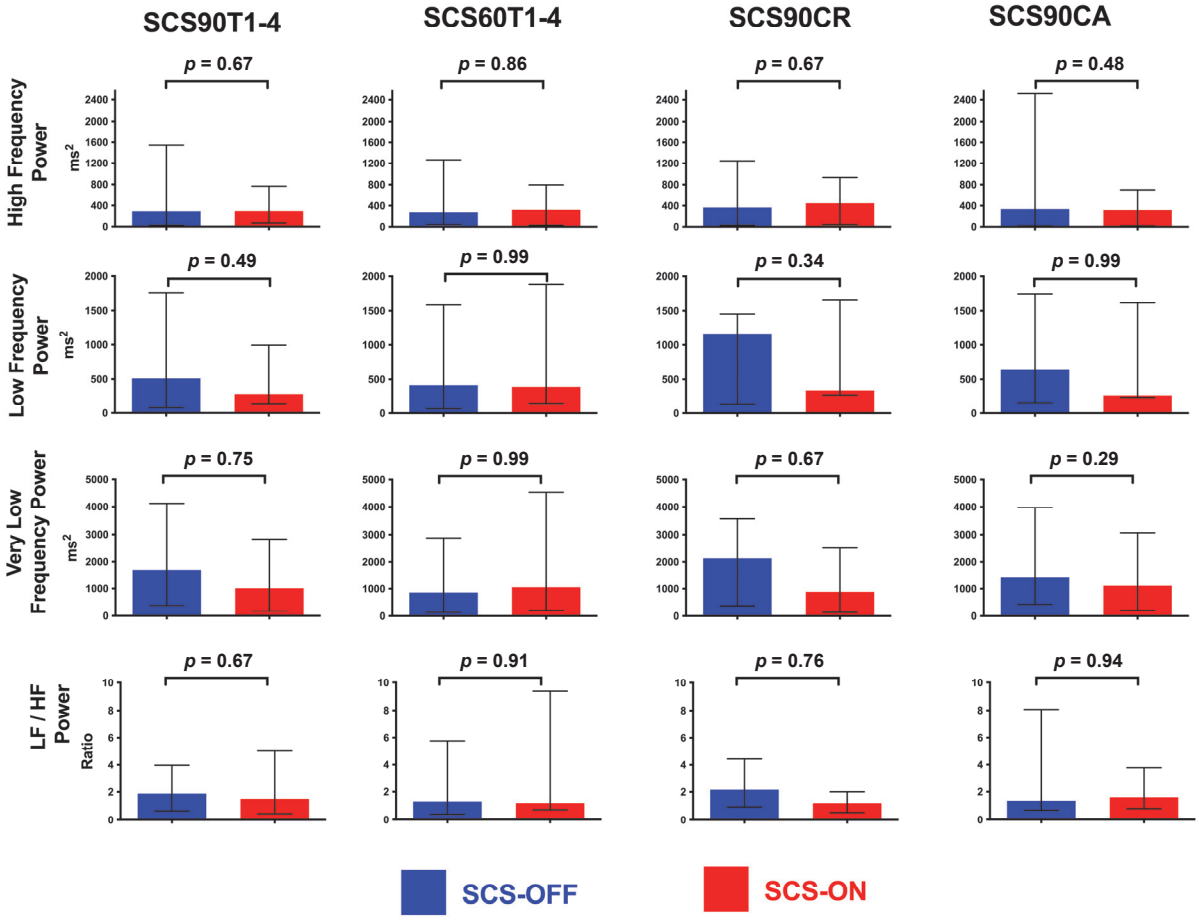

Fig. 3. Acute effect of SCS with different stimulation amplitudes and lead configurations on frequency-domain heart rate variability parameters. Data are expressed as median with 95% confidence interval.

Effect of baseline SDNN on SCS therapy

In the subgroup analysis, patients with low baseline SDNN (<50 ms, n = 4) displayed significantly increased SDNN with SCS90T1–4 compared to SCS-OFF, whereas SDNN in patients with high baseline SDNN (>50 ms, n = 7) did not change significantly with SCS (Fig. 4). This pattern was not observed with lower stimulation amplitude or other electrode configurations, where SDNN did not change with SCS (Suppl. Fig. S5). Table 2 shows the baseline characteristics of low and high baseline SDNN subgroups. Although the patients with baseline SDNN <50 ms tended to be more symptomatic and have lower ejection fraction, more pronounced left ventricular dilation and less titrated pharmacotherapy of heart failure, the low number of participants in subgroups does not permit correct statistical analysis.

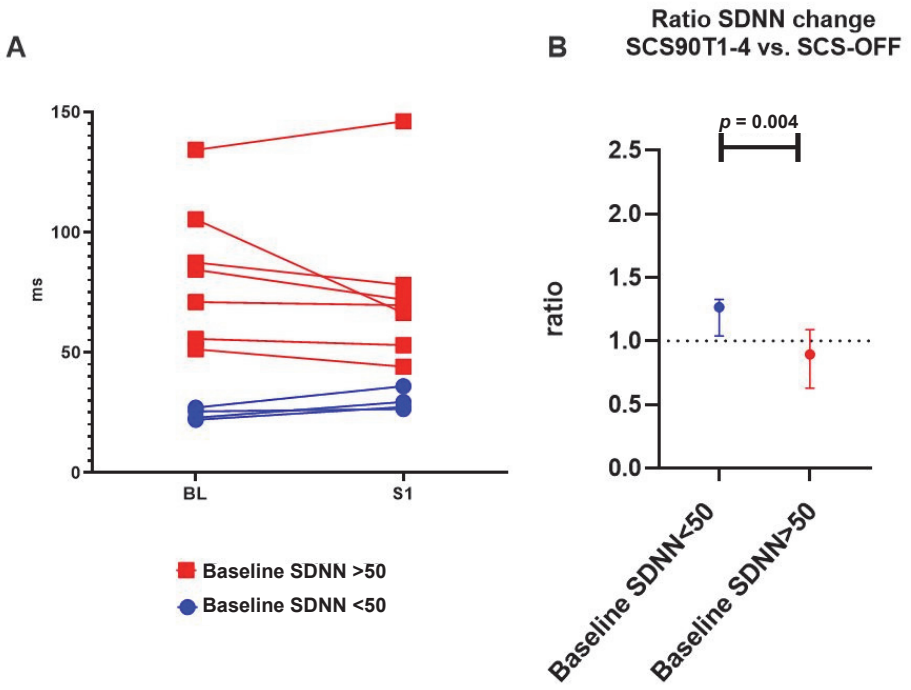

Fig. 4. Acute effect of SCS with 90% of maximal tolerated amplitude on SDNN in patients with low (<50 ms) versus high (>50 ms) baseline SDNN. Data are expressed as individual (**A**) and median with 95% confidence interval of delta ratios (**B**). SDNN – standard deviation of intervals between normal beats.

Table 2. Baseline characteristics of low and high SDNN subgroups

	SDNN <50 ms (n = 4)	SDNN >50 ms (n = 7)	p-value
Age (years)	64 ± 10	68 ± 9	0.5
BMI (kg/m^2)	29.6 ± 7	27.2 ± 7	0.6
Systolic blood pressure, mmHg	130 ± 21	122 ± 20	0.53
Diastolic blood pressure, mmHg	78 ± 9	70 ± 9	0.24
NYHA class	2.8 ± 0.5	2.3 ± 0.5	0.17
LVEF (%)	34 ± 11	44 ± 15	0.27
LVEDV (ml)	170 ± 62	139 ± 15	0.26
Time since heart failure diagnosis (years)	3.3 ± 1	4 ± 2	0.55
Ischemic etiology (n; %)	1 (25%)	5 (71%)	
% of target daily dose of β-blocker	47 ± 39	82 ± 43	0.21
% of target daily dose of ACEI/ARB	32 ± 21	80 ± 35	0.04

ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin II receptor blocker; BMI – body mass index; LVEF – left ventricular ejection fraction; LVEDV – left ventricular end-diastolic volume; NYHA class – New York Heart Association functional class; SDNN – standard deviation of intervals between normal beats.

Acute effect of SCS on baroreceptor sensitivity

We did not observe any significant acute effect of SCS on BRS regardless of amplitude and lead configuration tested (Fig. 5).

Acute effect of SCS on hemodynamic parameters

As detailed in Fig. 6, we did not observe any significant change in hemodynamic parameters with other SCS configurations except for a significant increase in sBP and dBP with SCS60T1–4 (118 ± 15 versus 115 ± 16 mmHg, $p = 0.03$ and 65 ± 6 versus 63 ± 7 mmHg, $p = 0.04$).

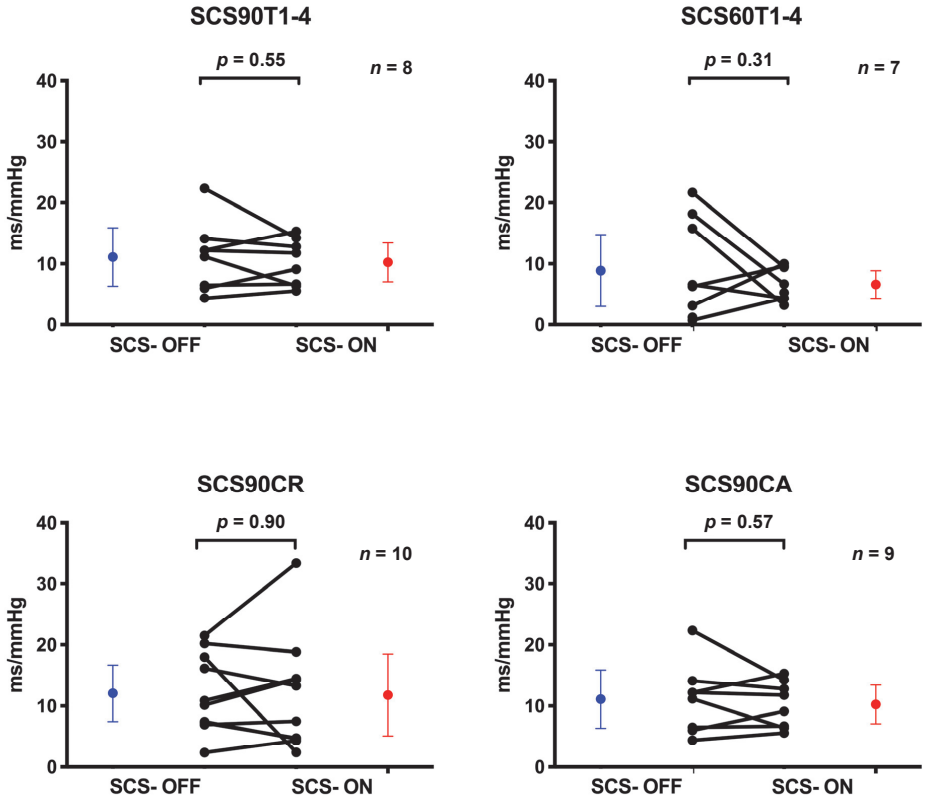

Fig. 5. Acute effect of SCS with different amplitudes and lead configurations on baroreceptor sensitivity. Results are displayed as individual, as well as median with 95% confidence interval.

Discussion

This is the first clinical study investigating the acute effect of SCS on HRV and baroreceptor reflex control in patients with heart failure. We did not detect any acute salutary effects in the unselected sample of patients. However, we observed an association between the HRV at baseline and a significant increase in SDNN with SCS, indicating a favourable effect of SCS on the autonomic function in patients with an initially low HRV.

Effect of SCS on the autonomic nervous system in subjects without heart failure

There is preclinical and clinical trial evidence that SCS improves autonomic nervous system balance in subjects *without* heart failure. Foreman et al. (2000) showed that SCS suppresses cardiac sympathetic nerve activity evaluated by direct microneurography in anesthetized dogs with and without myocardial ischemia. SCS has also been shown to reduce susceptibility to atrial fibrillation in non-failing canine models (Bernstein et al., 2012). Furthermore, two clinical studies have documented an acute effect of SCS on HRV in patients with refractory angina but without heart failure. Moore et al. (2004) observed significant reductions in LF/HF and LF in a study with sixteen subjects suffering from refractory angina pectoris, and Anselmino et al. (2009) documented a significant reduction of LF/HF in eight patients with refractory angina.

However, it is not trivial to extrapolate these data to a heart failure population due to intrinsic differences in autonomic balance and reflex regulation between patients with and without heart failure.

Effect of SCS on the autonomic nervous system in subjects with heart failure

Several preclinical studies on ischemia/reperfusion and myocardial infarction (but not heart failure *per se*) models have shown that SCS reduces infarct size, prevents ventricular arrhythmias and improves stressor tolerance (Cardinal et al., 2004; Issa et al., 2005; Odenstedt et al., 2014). Preclinical data of SCS efficacy in heart failure are scarce, however two studies (canine and porcine) have shown that SCS improves myocardial contractility, induces reverse remodeling and protects from ventricular arrhythmias in ischemic heart failure (Liu et al., 2012; Lopshire et al., 2009). Hence, preclinical studies on mainly ischemic heart disease models suggest a direct sym-

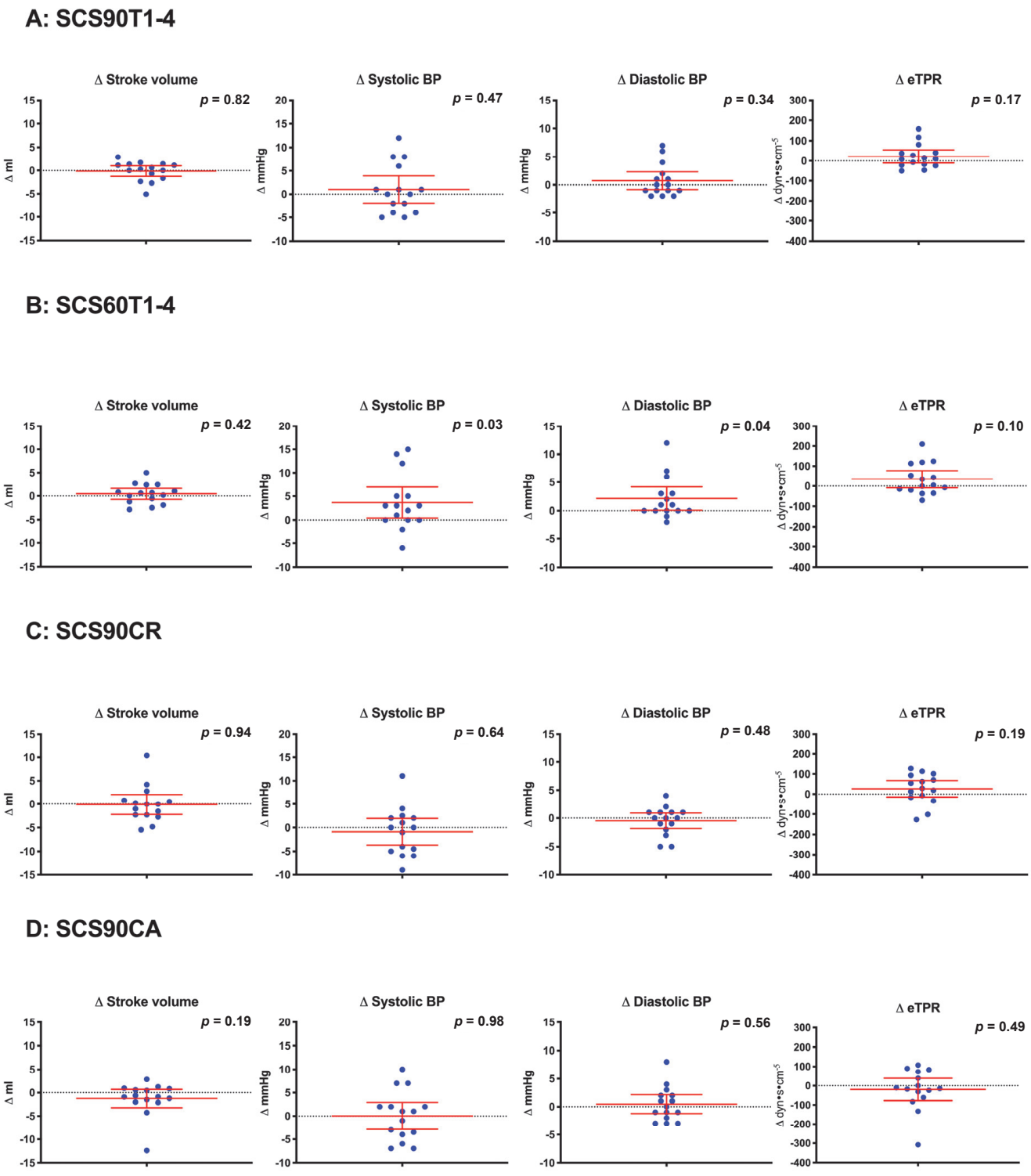

Fig. 6. Individual and mean changes of hemodynamic parameters in four spinal cord stimulation settings. Data are shown as change of mean with 95% confidence interval. BP – blood pressure; eTPR – estimated total peripheral resistance.

patholytic effect of SCS that translates into salutary hemodynamic, structural and electrophysiological effects. Although these preclinical studies are suggestive of a salutary SCS effect in heart failure, data from clinical studies are scarce and inconsistent. The only randomized and controlled trial in patients with heart failure (DEFEAT-HF) failed to show any effect of SCS on left ventricular reverse remodeling or patient functional capacity (Zipes et al., 2016). Furthermore, in a subset of patients from the DEFEAT-HF study, we were unable to detect any mid-term effect of SCS on cardiac sympathetic nerve activity assessed by ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy (Naar et al., 2017a). Furthermore, we did not see any beneficial effect of SCS on heart failure-associated biomarkers, i.e. renin-angiotensin-aldosterone hormonal axis activation, levels of circulating inflammation markers or norepinephrine level (Naar et al., 2017b). The main finding of the present study supports the neutral results from the DEFEAT-HF trial and previously published data on sub-groups from the main trial, as decreased sympathetic nerve activity is a fundamental presumption regarding the mechanism of action of SCS in heart failure (Linderoth and Foreman, 1999). These neutral data from the DEFEAT-HF study are in contrast to an uncontrolled observational study of SCS on patients with heart failure that demonstrated improved NYHA class, exercise capacity and left ventricular function associated with SCS (Tse et al., 2015). The reason for this is not clear but may be due to differences in patient selection, study design and therapy delivery aimed at a higher transfer of electric charge per unit time by using double leads and 24-hour SCS.

Role of the baseline autonomic nervous system function on the effect of SCS in heart failure

Clearly, most clinical data on SCS in heart failure are neutral. However, the subgroup analysis in the present study based on baseline SDNN suggests that patients with low baseline HRV may profit from SCS therapy in terms of HRV improvement. This finding is in agreement with a previous study from our group, where baseline cardiac sympathetic nerve activity assessed by ^{123}I-MIBG scintigraphy significantly and inversely correlated with an SCS-associated change in cardiac sympathetic activity (Naar et al., 2017a). Hence, these studies imply that SCS elicits a sympatholytic or HRV-improving effect in heart failure only in patients with more pronounced sympathetic overactivity or lower baseline HRV, respectively. Therefore, our data suggest that baseline sympathetic nerve activity or autonomic balance may play a key role when examining the effect of SCS in heart failure, and suggest that the amendable substrate (level of sympathetic activity) may be important in patient selection for SCS.

SCS therapy delivery

Most preclinical and clinical studies of SCS in cardiac disease have applied near motor threshold amplitudes (animal studies) or maximal tolerated stimulation amplitude (humans) in the T1–T5 spinal cord segments, corresponding to 90% of the maximal tolerated amplitude in the T1–T4 setting used in this study. However, one experimental study in a canine ischemic heart failure model suggested that targeted spinal cord segments and stimulation amplitude may affect SCS outcome (Lopshire et al., 2009). Particularly relevant to the present study, it was demonstrated that targeting the T4 segment with 90% and 60% of motor threshold significantly reduced the heart rate, while targeting the T1 or T8 spinal cord segments did not. In the present study on heart failure patients, targeting the T4 spinal cord segment using 90% of maximal tolerated stimulation amplitude did not confer an acute effect on heart rate or HRV and neither did targeting more caudal or cranial spinal cord segments. The failure to translate the efficacy of SCS therapy from an animal heart failure model to heart failure patients could be explained by the relatively higher stimulation output used in animals: 90% of motor threshold in canines versus 90% of maximal tolerable output in humans. Preclinical studies have also only used ischemic models of heart failure with a shorter duration than clinical cases. Furthermore, differences in stimulation parameters, stimulation duration, number of leads and lead position are present among studies.

Study limitations

We acknowledge that the sample size of the present study is small and no a priori formal power calculation was performed. Nevertheless, clinical studies with similar sample sizes have been able to prove significant amelioration of HRV with SCS in patients with refractory angina pectoris (Anselmino et al., 2009; Moore et al., 2004). This is also the first report on the acute effects of SCS on HRV in patients with heart failure. The exact washout period of the effect of SCS on the autonomic nervous system is unknown and we arbitrarily chose a 35-minute period. Therefore, carry-over effects may have influenced the results in this study. Additionally, the interpretation of HRV analyses is difficult. Recent evidence implies that the nature of frequency bands from HRV spectral analysis is complex and associating a particular frequency component with divisions of the autonomic nervous system (sympathetic or parasympathetic) is too simplistic (Hayano and Yuda, 2019). Thus the interpretation of LF and LF/HF is especially challenging. Taking these limitations into account, further studies evaluating directly the sympathetic nervous system in heart failure patients treated with neuromodulation therapy would be worthwhile, for example by assessment of muscle sympathetic nerve activity (MSNA) using microneurography of the common peroneal nerve, which is standard for the direct evaluation of sympathetic nerve activity in humans, although this method does not selectively assess *cardiac* sympathetic nerve activity.

Conclusions

Spinal cord stimulation delivered at 60–90% of maximal tolerated output targeting the T1–T4 segments of the spinal cord does not acutely improve heart rate variability or baroreceptor sensitivity in unselected patients with heart failure, but it may improve HRV in patients with low SDNN. This finding suggests that baseline autonomic function may influence SCS response in this patient population.

Acknowledgements

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Conflict of interests

The authors Jan Naar, Petr Neužil, Petr Doškář, Filip Málek, Bengt Linderoth and Göran Lind declare that they have no conflict of interests. Deborah Jaye is an employee of Medtronic, Plc. Marcus Ståhlberg has received speakers' honorarium from Medtronic, Plc.

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