

# Spinal Cord Stimulation for Heart Failure: Preclinical Studies to Determine Optimal Stimulation Parameters for Clinical Efficacy

John C. Lopshire · Douglas P. Zipes

Received: 30 October 2013 / Accepted: 3 February 2014 / Published online: 26 February 2014  
© Springer Science+Business Media New York 2014

**Abstract** Spinal cord stimulation with implantable devices has been used worldwide for decades to treat regional pain conditions and cardiac angina refractory to conventional therapies. Preclinical studies with spinal cord stimulation in experimental animal models of heart disease have described interesting effects on cardiac and autonomic nervous system physiology. In canine and porcine animals with failing hearts, spinal cord stimulation reverses left ventricular dilation and improves cardiac function, while suppressing the prevalence of cardiac arrhythmias. In this paper, we present further canine studies that determined the optimal site and intensity of spinal cord stimulation that produced the most robust and beneficial clinical response in heart failure animals. We then explore and discuss the clinically relevant aspects and potential impediments that may be encountered in translating spinal cord stimulation to human patients with advanced cardiac disease.

**Keywords** Autonomic nervous system · Heart failure · Animal models · Spinal cord stimulation · Ventricular arrhythmias

## Introduction

Heart failure (HF) is a major cause of morbidity and mortality in the industrialized world. Novel therapies are sorely needed to combat this malady, which often results in repeated hospital admissions, ventricular tachyarrhythmias (VT), and significant lifestyle encumbrances on the afflicted patients.

Excessive autonomic nervous system activation is thought to underlie many of the complications of HF, and current therapies directed at reversing autonomic activation often are ineffective.

Neuromodulation of the autonomic nervous system with spinal cord stimulation (SCS) has been shown to be effective in treating HF and cardiac disease in animal models. In canines, coronary artery occlusion was associated with increased intracardiac nerve firing, and SCS at spinal segment T1 suppressed that nerve firing [1]. Preemptive SCS resulted in reduction in infarct size in rabbits in an infarction model [2]. In normal canines, acute epidural spinal cord stimulation at segment T1 significantly increased spontaneous sinus cycle length and the AH interval, and vagal transection eliminated this effect [3]. In canines with HF, SCS reduced ischemic VTs [4]. Similar results at VT reduction were seen in porcine studies [5]. A small study in humans with ischemic HF demonstrated that SCS could decrease microvolt T wave alternans, a marker of abnormal ventricular substrate [6]. In an experimental model of atrial fibrillation in canines, SCS increased atrial refractory periods and decreased AF episodes [7]. In a canine HF model, our laboratory showed that SCS at spinal segment T4 could suppress VT and improve left ventricular function [8]. SCS has also been shown to have a beneficial therapeutic effect in HF models in other species. In a porcine ischemic HF model, SCS treatment improved echocardiographic regional myocardial strain and LV function and decreased myocardial oxygen consumption [9]. Another recent study in pigs with ischemic heart failure suggested that continuous spinal cord stimulation was more effective than intermittent stimulation [10]. Taken together, the above studies suggest that the mechanisms by which SCS exerts end-organ cardiac effects are indeed very complex and likely involve significant actions and feedback responses at multiple levels (directly on cardiac tissues, the intrinsic cardiac and intrathoracic nervous system, and the central nervous system).

---

Associate Editor Craig Stolen oversaw the review of this article

---

J. C. Lopshire (✉) · D. P. Zipes  
Krannert Institute of Cardiology, Indiana University School of  
Medicine, 1800 N. Capitol Avenue, Suite E310, Indianapolis,  
IN 46202, USA  
e-mail: lopshirejohn@gmail.com

The above studies provide compelling evidence for examining the effects of SCS in human populations. To support the translation of these studies to human populations, we conducted a study to determine the SCS output intensity and stimulus location that produced the most beneficial therapeutic effect in a canine heart failure model.

## Methods

A well-validated canine model of HF that has decreased left ventricular systolic function and increased the incidence of VT [4, 8] was utilized for these studies. Thirty-eight adult male mongrel dogs (weight 25–30 kg) were tranquilized with thiopental sodium (15–20 mg/kg IV) and ventilated with room air containing 1–2 % isoflurane. A 12-lead ECG, oxygen saturation, arterial blood pressure, body weight, serum sample, and a transthoracic echocardiogram (TTE) were obtained during all procedures. The experimental protocol consisted of two stages of procedures (animals were anesthetized during each surgical procedure only) with an intervening 5-week heart failure induction interval followed by a 5-week treatment interval and 5-week wash-out interval (Fig. 1). In the first stage, animals underwent implantation of an implantable cardiac defibrillator (ICD) followed by creation of myocardial infarction (MI) and subsequent high-rate ventricular pacing at 240 ppm for 3 weeks to induce heart failure. In the second stage, 32 surviving animals were randomized to the following groups: control ( $n=3$ , no SCS), SCS90T1 ( $n=6$ ), SCS90T4 ( $n=5$ ), SCS60T4 ( $n=6$ ), SCS30T4 ( $n=6$ ), and SCS90T8 ( $n=6$ ), where 90, 60, and 30 represented SCS stimulation strengths at 90, 60, and 30 % motor threshold, and T1, T4, and T8 represented thoracic levels 1, 4, and 8. Animals were followed for 5–10 weeks after randomization, with SCS ON for 5 weeks (all animals; treatment weeks 1–5) and SCS OFF (all animals except those randomized to SCS90T8; treatment

weeks 6–10) for 5 weeks. At the end of stage 2, animals underwent diagnostic testing and eventual euthanasia (all animals). All procedures adhered to NIH guidelines for animal testing and were approved by the Indiana University Institutional Animal Care and Use Committee.

### Stage 1—Animal Model Preparation

#### ICD Implantation

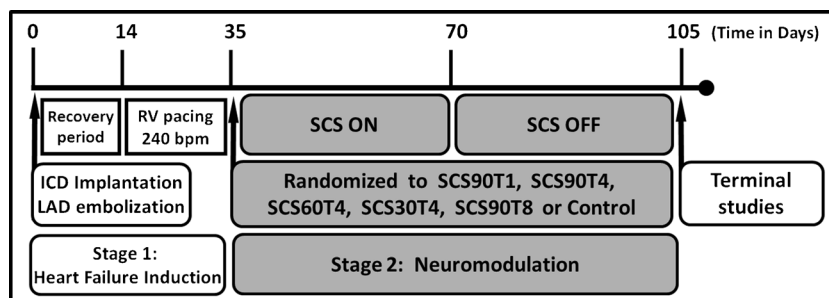
An ICD was implanted as previously described [8]. Arrhythmia detection zones were set at  $\geq 230$  bpm for ventricular tachycardia and  $\geq 250$  bpm for ventricular fibrillation at all times, except during high-rate pacing. The device therapies were enabled to deliver full device output (35 J) for VT detections during the infarction procedure and were disabled at other times.

#### Creation of Myocardial Infarction and Heart Failure Induction

An anterior infarction was created in the LAD via injection of an embolizing foam as previously described [8]. The appearance of acute ST segment and T wave changes on surface 12-lead ECG and new anterior wall motion abnormalities on TTE were used to confirm MI. The animal was subsequently monitored for 1–2 h for arrhythmias and hemodynamic instability. After a 2-week recovery period, continuous rapid right ventricular pacing at 240 bpm was initiated and maintained for 3 weeks to induce heart failure. Pacing was discontinued 1 h prior to randomization into stage 2.

### Stage 2—Neuromodulation

After a 30-min anesthesia equilibration period, all surviving animals received repeat vital sign determination and serum testing and underwent ECG and TTE studies. Animals



**Fig. 1** Stage 1, the heart failure induction stage, involved ICD implantation followed by left anterior artery embolization to create a myocardial infarction. After a 2-week recovery period, RV pacing at 240 bpm was started and maintained for 3 weeks. Surviving animals then entered Stage 2, the neuromodulation stage, and were equally randomized to the spinal cord stimulation at different sites and intensities for 5 weeks followed by a 5-week washout period. Treatment groups: control ( $n=3$ , no SCS),

SCS90T1 ( $n=6$ ), SCS90T4 ( $n=5$ ), SCS60T4 ( $n=6$ ), SCS30T4 ( $n=6$ ), and SCS90T8 ( $n=6$ ), where 90, 60, and 30 represented SCS stimulation strengths at 90, 60, and 30 % motor threshold, and T1, T4, and T8 represented thoracic levels 1, 4, and 8. Key: ICD implantable cardiac defibrillator, LAD left anterior descending artery, SCS spinal cord stimulation

randomized to receive SCS underwent SCS system and lead implantation at the randomized location using the same SCS system and methods previously described [8]. The lead electrode configuration was set to deliver SCS via the two most distal electrodes, with the most distal electrode negative and more proximal electrode in the positive configuration. The other electrodes were inactive. This resulted in a bipolar stimulus field of approximately 2 cm. Device outputs were then set at 90, 60, or 30 % of the motor threshold (per randomization sequence) at 50 Hz with 0.2 ms of pulse duration, and chronic SCS was delivered for 2-h intervals three times daily (onset at midnight, 8 AM, and 4 PM) for 5 weeks. At 2 and 5 weeks post-SCS implantation, repeat SCS threshold testing and fluoroscopic evaluation confirmed stable stimulation thresholds and epidural lead position. SCS was turned off in all animals after 5 weeks, and most animals were monitored for another 5 weeks. The SCS90T8 group was euthanized after SCS ON 5-week interval and was not followed through the washout period. At completion of stage 2, all animals were euthanized, and the heart was removed and preserved for later analysis.

#### Measurements

Heart rate, blood pressure, oxygen saturation, body weight, and ICD interrogation were obtained at time of entry into each stage, before initiation of high-rate pacing, and the 5- and 10-week intervals during stage 2. VTs (which included all ventricular tachyarrhythmias detected by the ICD) were evaluated and characterized by number, type, duration of episodes, and requirement of ICD therapy by an observer blinded to the randomization. Surface ECG, serum collection, and TTE were performed at time of entry into each stage and after 2 and 5 weeks of stage 2. All TTEs were interpreted in a blinded fashion for ejection fraction (EF), left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), and regional wall motion abnormalities. Standard echocardiographic methods and formulas were utilized for this analysis [11]. Serum samples were tested for norepinephrine (NE) with ELISA (Rocky Mountain Diagnostics, Boulder, CO, USA). SCS was discontinued for 30 min prior to any data collection noted above.

#### Statistical Analysis

Continuous variables were expressed as mean  $\pm$  SD and analyzed with a paired Student's *t* test, one-way ANOVA, or two-way repeated measures ANOVA with a Bonferroni post hoc test. A chi square test was used for qualitative or categorical variables. A *p* value of <0.05 was considered significant for all tests. The authors had full access to the data and take responsibility for their integrity.

#### Results

All randomized animals survived to study end without complications or evidence of SCS system malfunction. The SCS lead remained in stable position in all animals throughout the course of the study. SCS stimulation parameters, as assessed by motor threshold determination, ranged between 0.3 and 0.8 V for all animals and remained stable during the experimental timeline. This finding is compatible with that of our prior studies [8]. There was also no significant difference in SCS motor threshold between groups at any point during the study. Additionally, there was no evidence of significant SCS stimulation artifact in any ICD electrogram at any spinal level or stimulus intensity. There were no discernible effects of acute SCS (at any stimulus intensity below motor threshold) on heart rate or blood pressure during the study procedures—which we attributed to the presence of inhalational anesthesia, which can blunt nervous system responses.

Table 1 shows the effect of myocardial infarction and RV high-rate pacing on standard clinical, electrocardiographic, and echocardiographic parameters in all animals prior to randomization. As can be seen, there were significant changes in these parameters commonly seen in clinical heart failure. Table 2 provides these same parameters across the experimental time course. As can be seen, the SCS90T1, SCS90T4, and SCS60T4 groups demonstrated significant changes in the parameters as compared to the untreated control group.

Figure 2 provides ambulatory heart rates across the experimental series. In general, heart rate increased after heart failure induction and remained elevated in the untreated control animals. It was significantly decreased in animals after treatment with SCS at T4 at 90 and 60 % of threshold (SCS90T4 and SCS60T4). There was no significant effect on heart rate in the SCS90T1, SCS30T4, and SCS90T8 groups. After the 5-week washout period, the significant decrease in heart rate was preserved in only the SCS90T4 group.

In all groups, left ventricular ejection fraction (LVEF) was significantly reduced from baseline levels after heart failure induction (Fig. 3). As shown, SCS treatment caused significant increases in LVEF in the SCS90T1, SCS90T4, and SCS60T4 groups. This effect was preserved after the 5-week washout period in these groups. The SCS30T4 and SCS90T8 groups had no change in LVEF compared to the untreated control untreated group (CTRL) group.

A high number of spontaneous VT were noted in all groups in the 2-week interval after myocardial infarction (Fig. 4). VTs were significantly decreased during the SCS treatment interval in the SCS90T1, SCS90T4, and SCS60T4 groups. Interestingly, this effect was not maintained during the washout period, as the number of spontaneous VTs was not significantly different in any of the treatment groups compared to CTRL during the washout period. This is in contrast to the

**Table 1** Parameters at study entry and after induction of heart failure for all randomized animals

| Parameter                         | Study entry | 2 weeks after embolism | After high-rate pacing | <i>p</i> value |
|-----------------------------------|-------------|------------------------|------------------------|----------------|
| Systolic blood pressure (mmHg)    | 124±13      | 109±13                 | 86±17                  | 0.001/0.001    |
| Diastolic blood pressure (mmHg)   | 76±10       | 68±18                  | 56±10                  | 0.024/0.001    |
| Heart rate (bpm, sternal)         | 113±12      | 128±13                 | 124±15                 | 0.001/0.005    |
| Weight (kg)                       | 28.6±2.7    | 30±3                   | 30.3±2.8               | 0.077/0.018    |
| Oxygen saturation (% on room air) | 98±1        | 93±1                   | 92±1                   | 0.001/0.001    |
| Heart rate (bpm, on anesthesia)   | 115±14      | –                      | 115±12                 | 0.809          |
| PR interval (ms)                  | 106±16      | –                      | 105±18                 | 0.811          |
| QRS frontal axis                  | 53±18       | –                      | 48±27                  | 0.386          |
| QRS interval (ms)                 | 63±8        | –                      | 70±8                   | 0.004          |
| QT interval (ms)                  | 251±22      | –                      | 264±26                 | 0.111          |
| QTc interval (ms)                 | 354±24      | –                      | 374±22                 | 0.001          |
| T wave peak-end (ms)              | 47±11       | –                      | 53±10                  | 0.045          |
| Ejection fraction (%)             | 60±4        | –                      | 20±3                   | 0.001          |
| Fractional shortening             | 0.42±0.1    | –                      | 0.16±0.04              | 0.001          |
| LV end diastolic diameter (cm)    | 4.0±0.3     | –                      | 5.6±0.5                | 0.001          |
| LV end systolic diameter (cm)     | 2.3±0.4     | –                      | 4.6±0.5                | 0.001          |
| Serum norepinephrine (pg/ml)      | 232±39      | –                      | 672±128                | 0.001          |

sustained beneficial effect of SCS on LVEF in these groups after the washout interval. The SCS30T4 and SCS90T8 groups had no change in spontaneous VTs compared to the untreated CTRL group during the treatment interval.

## Discussion

This study demonstrated that neuromodulation with SCS, in a site- and stimulus intensity-specific manner, can cause significant improvement in left ventricular function and significantly decrease ventricular tachyarrhythmias and heart rate in this canine model of heart failure. Differences in the response pattern by treatment group for the endpoints described in this study may yield some insights into potential mechanisms of action of SCS in this model.

### SCS Effects on Heart Rate

In our study, chronic spinal cord stimulation was only effective at reducing ambulatory heart rates when applied at spinal segment T4 (at both 90 and 60 % stimulus intensities), with SCS90T4 producing the most robust effect that persisted through the washout period. There was no discernible effect of the other treatment groups on heart rate compared to untreated controls, suggesting that the groups with significant reductions in heart rate were potentially acting via distinct or multiple mechanisms rather than simply activating ascending spinal cord pathways. However, earlier studies have shown that acute SCS at spinal segment T1 reduced heart rate in canines in the same model [4]. This may reflect a difference in

mechanisms of action between chronic versus acute SCS in this model.

### SCS Effects on Left Ventricular Function

Spinal cord stimulation at thoracic segments T1 and T4 was effective in improving ventricular function at the 90 % and 90 or 60 % motor threshold, respectively. This beneficial clinical effect persisted in all these groups after SCS had been discontinued for 5 weeks during the washout period. This suggests that significant and persistent remodeling of the LV and/or effector pathways had occurred during the SCS treatment interval. Other studies in canines and pigs with HF have also found that SCS at T1 or T4 produced significant recovery of LV function [9, 10]. Earlier studies have shown that SCS can have direct effects on autonomic efferent pathways and cause significant and lasting changes on the intrinsic cardiac nervous system [1, 2]. It seems likely that the therapeutic response of SCS in experimental HF is working via similar mechanisms. Ongoing studies in our laboratory are evaluating these mechanisms in greater detail, with the goal that these findings may aid the design of human studies of SCS therapy in HF. In fact, several early human studies [12] are evaluating the effect of SCS in heart failure, and most of these studies are providing SCS stimulation between spinal segments T1 and T4. An important issue in translating the therapeutic SCS response from preclinical studies into human research settings will be patient selection (etiology, class, severity, and duration of HF, etc.). To more closely model the preclinical studies, translational and early human studies with SCS would focus on ischemic heart failure patients with shorter duration and

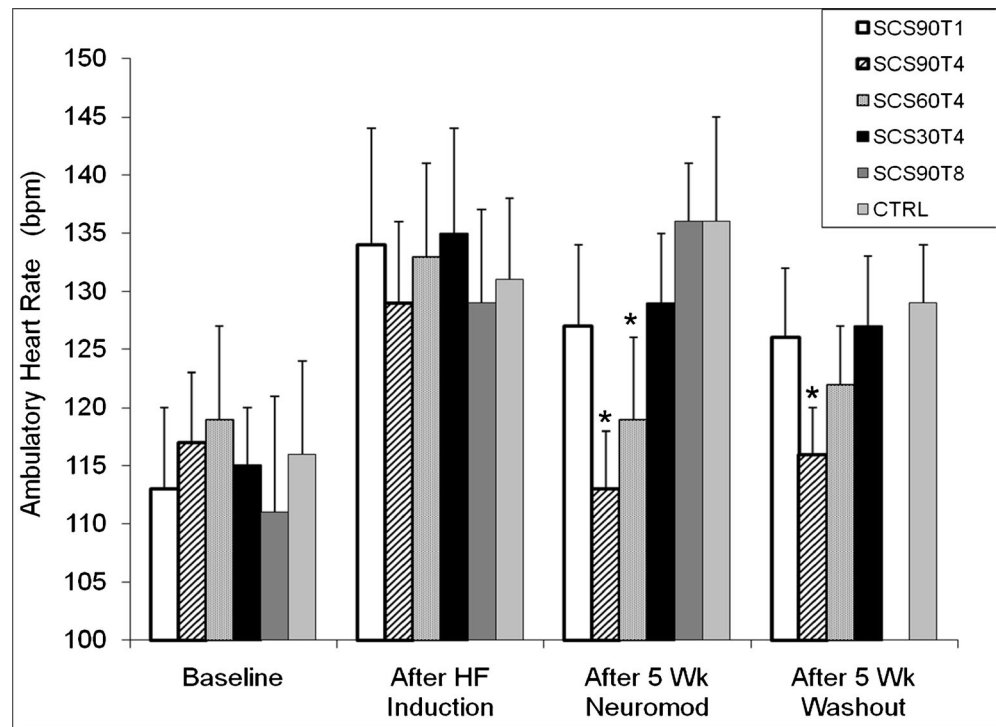
**Table 2** SCS effects on clinical parameters

| Parameter                       | After high-rate pacing |           |           |           | After 5 weeks of SCS |           |           |            | After 5 weeks of washout |            |           |           |           |            |            |           |
|---------------------------------|------------------------|-----------|-----------|-----------|----------------------|-----------|-----------|------------|--------------------------|------------|-----------|-----------|-----------|------------|------------|-----------|
|                                 | CTRL                   | SCS90T1   | SCS90T4   | SCS60T4   | SCS30T4              | SCS90T8   | CTRL      | SCS90T1    | SCS90T4                  | SCS60T4    | SCS30T4   | CTRL      | SCS90T1   | SCS90T4    | SCS60T4    | SCS30T4   |
| Systolic blood pressure (mmHg)  | 86±4                   | 95±6      | 85±7      | 91±13     | 83±8                 | 89±12     | 95±8      | 115±8*     | 126±16*                  | 108±18     | 99±14     | 101±4     | 124±12*   | 122±9*     | 117±12     | 98±3      |
| Diastolic blood pressure (mmHg) | 52±14                  | 52±11     | 56±17     | 63±7      | 57±5                 | 52±6      | 55±10     | 67±7       | 80±7*                    | 75±11      | 63±11     | 74±6      | 75±6      | 77±8       | 79±8       | 66±6      |
| Weight (kg)                     | 31.7±0.6               | 28.8±2.7  | 31.4±0.9  | 31.9±2.1  | 29.4±2.1             | 29.7±3.1  | 31.4±1.7  | 28.5±3.8   | 29.3±0.7                 | 31.2±3.7   | 28.7±2.1  | 31.0±1.6  | 28.8±3.8  | 28.7±1.2   | 30.2±1.3   | 28.9±2.6  |
| Oxygen saturation (%)           | 94±1                   | 90±5      | 90±4      | 92±4      | 91±4                 | 91±2      | 92±1      | 97±1*      | 99±1*                    | 96±4       | 96±3      | 94±2      | 98±1*     | 99±1*      | 96±3       | 93±2      |
| QRS frontal axis                | 60±9                   | 44±38     | 53±8      | 49±32     | 58±18                | 28±30     | 63±7      | 54±8       | 42±27                    | 47±33      | 37±26     | 53±11     | 48±27     | 39±25      | 37±21      | 30±48     |
| PR interval (ms)                | 124±30                 | 101±18    | 101±18    | 108±26    | 107±10               | 107±9     | 133±18    | 110±15     | 111±17                   | 113±13     | 115±32    | 123±15    | 104±12    | 108±17     | 130±8      | 105±23    |
| QRS interval (ms)               | 75±10                  | 64±8      | 70±8      | 70±12     | 71±7                 | 74±3      | 65±1      | 69±9       | 68±5                     | 65±7       | 69±8      | 72±6      | 69±4      | 70±4       | 68±10      | 72±5      |
| QT interval (ms)                | 264±38                 | 254±32    | 268±13    | 276±32    | 261±30               | 263±18    | 257±12    | 238±30     | 235±20                   | 244±15     | 250±21    | 277±29    | 250±28    | 249±19     | 261±14     | 256±8     |
| QTc interval (ms)               | 391±46                 | 359±37    | 362±15    | 375±18    | 369±33               | 381±34    | 353±15    | 323±12*    | 330±33                   | 343±26     | 344±16    | 377±19    | 340±19    | 336±18*    | 344±23     | 366±16    |
| T wave peak-end (ms)            | 55±9                   | 48±9      | 54±17     | 59±9      | 52±9                 | 55±4      | 60±6      | 49±11      | 49±7                     | 57±5       | 55±7      | 61±11     | 52±12     | 46±8       | 60±11      | 64±22     |
| Fractional shortening           | 0.15±0.05              | 0.18±0.05 | 0.13±0.05 | 0.17±0.03 | 0.15±0.04            | 0.17±0.02 | 0.19±0.05 | 0.31±0.06* | 0.30±0.05*               | 0.34±0.06* | 0.23±0.09 | 0.21±0.05 | 0.23±0.04 | 0.36±0.05* | 0.32±0.04* | 0.21±0.02 |
| LV end diastolic diameter (cm)  | 5.4±0.2                | 5.4±0.6   | 5.8±0.4   | 5.7±0.3   | 5.5±0.5              | 5.5±0.5   | 5.1±0.3   | 4.3±0.4*   | 4.2±0.4*                 | 4.3±0.2*   | 5.1±0.7   | 5.0±0.3   | 4.1±0.4*  | 4.0±0.4*   | 4.2±0.4*   | 4.7±0.3   |
| LV end systolic diameter (cm)   | 4.6±0.1                | 4.4±0.6   | 5.0±0.5   | 4.7±0.6   | 4.7±0.6              | 4.5±0.4   | 3.9±0.2   | 2.9±0.6*   | 2.8±0.5*                 | 2.9±0.4*   | 3.9±0.8   | 3.7±0.03  | 2.8±0.6*  | 2.7±0.7*   | 2.7±0.3*   | 3.6±0.4   |
| LV end diastolic volume (ml)    | 112±20                 | 107±11    | 104±7     | 99±16     | 117±13               | 103±13    | 104±11    | 88±6*      | 82±3*                    | 81±11*     | 110±14    | 102±7     | 85±5*     | 77±12*     | 84±6*      | 102±14    |
| LV end systolic volume (ml)     | 92±7                   | 84±9      | 88±11     | 81±13     | 94±12                | 83±8      | 81±3      | 55±5*      | 51±7*                    | 53±4*      | 82±9      | 76±13     | 51±3*     | 46±7*      | 54±9*      | 76±13     |
| Serum norepinephrine (pg/ml)    | 766±233                | 841±227   | 613±192   | 817±181   | 595±169              | 577±102   | 707±123   | 313±74*    | 261±88*                  | 396±117*   | 519±133   | 570±194   | 529±159   | 193±76*    | 229±89*    | 613±244   |

\**p*<0.05 from control



**Fig. 2** SCS effects on ambulatory heart rates. *CTRL* control untreated group, *SCS* spinal cord stimulation, *HF* heart failure, *Neuromod* neuromodulation with SCS. \* $p < 0.05$  from CTRL



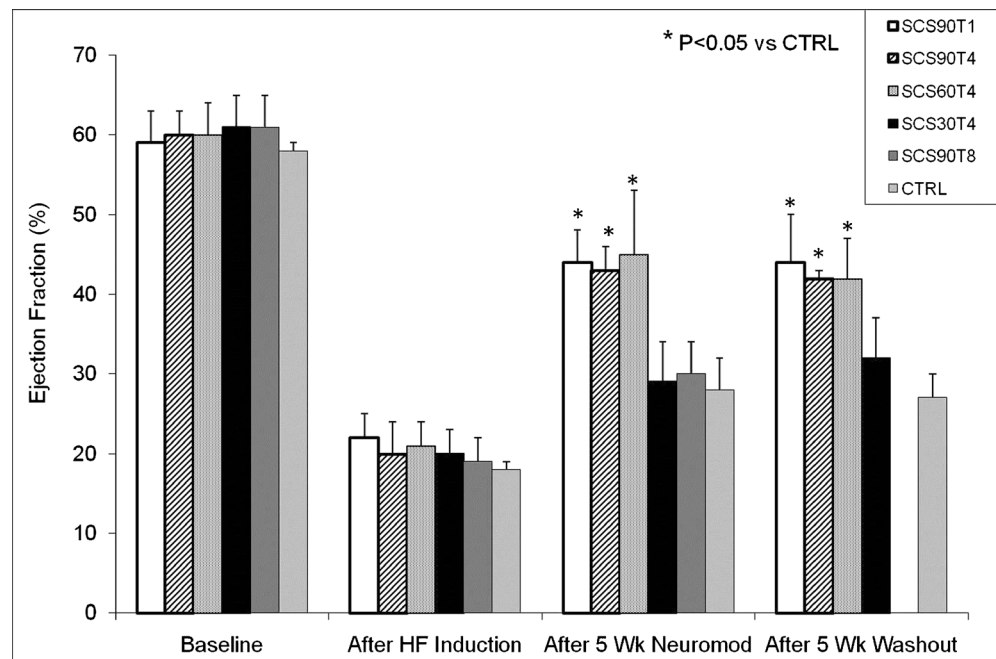
less severe heart failure—though this approach would likely not prove practical given the presence of fully approved competing therapies and the invasive nature of SCS. In fact, most early studies are targeting advanced heart failure patients with long-standing heart failure [12]. Earlier work from our laboratory on HF canines on standard medical therapies (beta blocker and ACE inhibitor) has shown that SCS can provide additive benefit on LV functional recovery [8], so SCS therapy

may yield additional benefit in chronic HF patients via a similar additive or novel mechanism.

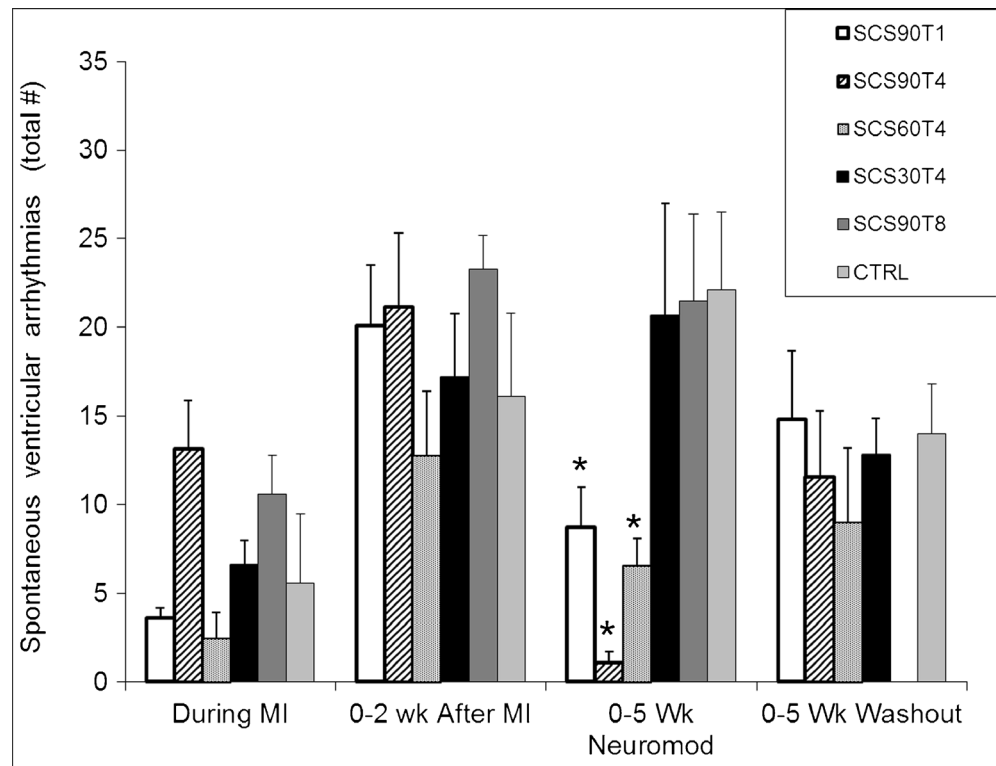
#### SCS Effects on Ventricular Tachyarrhythmias

SCS90T4 was particularly effective at reducing spontaneous VT incidence. The SCS60T4 and SCS90T1 groups also demonstrated significant decreases in VTs as well. Unfortunately,

**Fig. 3** SCS effects on left ventricular ejection fraction. *CTRL* control untreated group, *SCS* spinal cord stimulation, *HF* heart failure, *Neuromod* neuromodulation with SCS. \* $p < 0.05$  from CTRL



**Fig. 4** SCS effects on spontaneous ventricular arrhythmias. *CTRL* control untreated group, *SCS* spinal cord stimulation, *MI* myocardial infarction, *Neuromod* neuromodulation with SCS. \* $p < 0.05$  from CTRL



this effect did not persist after SCS was discontinued during the washout period in any of these groups. It is not clear why LV remodeling and recovery of function after SCS was persistent and the effect on VT incidence was lost during the washout period. One possibility is that SCS causes direct effects on cardiac sympathetic and/or parasympathetic efferents to suppress VT, and this effect was rapidly lost with cessation of active SCS during the washout period. VT was also suppressed in a porcine ischemic model by SCS [5], though persistence of this effect was not studied in that particular model. This could suggest a role for SCS (either acute or chronic) to suppress VTs refractory to conventional therapies in human populations. In fact, a small study has shown that SCS can suppress refractory VTs in two patients [13].

#### Effect of SCS by Site of Stimulation

SCS produced beneficial clinical effects when applied at spinal segment T1 or T4 in our model. There was no discernible effect of SCS when applied at spinal segment T8. This would again provide basis for the notion that the mechanism of action of SCS is more complex than simple activation of ascending spinal pathways, which would be expected at any of these thoracic sites. It is reasonable to conclude that SCS at T1 and T4 can potentially directly act on sympathetic efferents to the heart in causing some of these effects. Given the nature of SCS effects (heart rate slowing, increased conduction times, VT reduction), this SCS action would be expected to have a net suppressive action on sympathetic efferent output.

The mechanisms of this suppressive action could be very complex and involve preganglionic and/or postganglionic effects causing direct decreases in sympathetic neurotransmitter release or net sympathetic inhibition via modulation of the intracardiac nervous system. In fact, one study found that SCS applied at segments T1–T3 can decrease intrathoracic extracardiac nervous system activity (middle cervical ganglia) in response to myocardial ischemia [14]. Alternatively, the mechanism of SCS action could be by decreasing net sympathetic response via increased vagal efferent activities, thus shifting autonomic tone. The finding that SCS90T4 caused the most profound effect on heart rate, LV remodeling, and VT suppression, as compared to SCS90T1, would support this notion. In this scenario, an increase in vagal tone, either via activation of ascending spinal pathways or modulated at the level of the intracardiac nervous system, would be the key driver of SCS effects in this model—since a greater direct activation of sympathetic efferents by SCS would be expected at higher spinal stimulation levels. As mentioned above, most ongoing early human trials of SCS in heart failure patients are employing stimulation between thoracic sites T1 and T4, so it is reasonable to expect that SCS may work in a similar complex manner in human populations.

#### SCS Effects by Intensity of Stimulation

In this canine study, the minimal SCS stimulus intensity that caused a significant effect at spinal segment T4 was 60 % of the motor threshold, and 30 % motor threshold stimulation

had no discernible effect. Though extrapolation to humans should be viewed with some trepidation, this stimulus intensity (SCS60T4) may well be above the paresthesia or even painful level in humans. Thus, lower relative stimulus intensities may be needed for human studies—which may not be of sufficient intensity to produce clinically significant responses. However, when SCS is used to treat cardiac angina and is generally titrated to an output level that produces pain relief, this is often very near the level that produces a paresthesia over the precordial area. In practice, paresthesias are produced with SCS from 30 to 70 % of the motor threshold in the cervical area. Allowing for patient self-titration of stimulus intensity may confound clinical studies—but would potentially allow for a patient to quickly reduce SCS outputs in the instance of stimulation lead movement or dislodgement that might change patient sensation of paresthesias or pain. A key feature of any successful study of SCS in human HF will be to ensure the lead location and stimulus intensity are optimized for clinical response. Early studies examine whether acute autonomic responses to SCS at time of implant can be used to guide and/or predict future cardiac response to chronic therapy. Unfortunately, our preclinical studies were performed in anesthetized animals that exhibited little to no acute changes in these parameters. Human studies will be able to be performed in awake and nonsedated patients, so acute measures of SCS effect may be obtainable and useful in guiding selection of SCS stimulation characteristics. Finally, our preclinical studies found no interaction between SCS stimulation and ICD arrhythmia detection algorithms on the intracardiac electrograms recorded by the ICD. This lack of interaction will need to be carefully examined and verified in human studies.

#### Limitations of the Study

This study was conducted in a small number of canines, and any extrapolation of these results to humans should be done with this consideration. The limited number of animals followed in this study could conceivably lower our ability to detect significant changes in the study endpoints. The experimental model to replicate ischemic cardiomyopathy used a combination of ischemia and high-rate ventricular pacing and was generated over 5 weeks; the human processes it was intended to mimic often develop over decades. In experimental models utilizing high-rate pacing alone to generate HF, there is often significant recovery of cardiac function with termination of pacing in the absence of any beneficial therapy. The clear differences noted with SCS over untreated control HF animals over the experimental period may not be maintained over longer durations of time. Also, SCS was applied at a frequency of 50 Hz in this study. Though this is likely not at the physiological firing rates of most neural structures, we used this frequency in our earlier studies—and wanted to be

able to compare results across these studies. Future studies may need to examine whether other stimulus frequencies alter the response to SCS in HF. Finally, intermittent SCS therapy was employed in this study (2 h on, 6 h off). A porcine study has found that continuous SCS therapy may yield a more significant effect on positive cardiac remodeling in heart failure. Thus, additional studies may be needed to examine the optimum duty cycle to deliver SCS that elicits the most favorable response. These limitations, however, can be controlled for in well-designed and well-conducted human studies.

#### Conclusions

SCS, when provided in experimental heart failure, is a safe and effective therapy. The arrhythmia suppression and remodeling response of canine heart failure to SCS are dependent on location and intensity of stimulation. These findings should guide the design of further human trials of this novel therapy in heart failure and arrhythmia patients. Specifically, early studies should evaluate the safety, tolerability, and efficacy of SCS in heart failure patients. Preclinical studies would suggest that initial studies should provide SCS stimulation centered on the T1–T4 spinal regions at the maximally tolerated stimulus outputs, at a stimulation frequency sufficient to avoid direct muscle stimulation (50 Hz was used in most preclinical studies), and for a duration sufficient to elicit clinical responses without inducing possible nerve tachyphylaxis. Based on the subacute or short-term nature of preclinical studies, patient selection for optimal clinical response may need to focus on earlier-stage HF patients or patients with refractory ventricular tachyarrhythmias—though clinical practice may dictate these studies are performed in patients with chronic and more advanced heart failure.

#### Studies Evaluating Effects of SCS in Human Heart Failure

The preclinical studies examining SCS in HF provide compelling support for trials of SCS in the human HF population. In fact, ongoing trials are now evaluating the safety and efficacy of SCS in the human heart failure population. The largest study is Defeat-HF (Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure). This is a phase II clinical trial to determine the safety and efficacy of SCS in advanced heart failure patients [15, 16]. Inclusion criteria are HF patients with NYHA class III–IV symptoms, an LVEF  $\leq 35$  % and LV end diastolic diameter between 55 and 80 mm, no implanted cardiac resynchronization device, and stable medical HF therapy. An implanted SCS device will be placed in all enrolled patients, with 2:1 randomization to active treatment for 6 months with SCS or no therapy groups, respectively. The No therapy group will cross over to active SCS treatment at 6 months. Change in



left ventricular volumes as measured by cardiac echo at 6 and 12 months will be the primary endpoint, with secondary outcomes of changes in exercise capacity (peak oxygen uptake) and blood chemistry (pro-BNP). There will be 85 actively enrolled patients in the USA and Europe, with a targeted completion date in 2014 [15]. Additionally, two smaller human trials are also investigating the utility of SCS in HF patients. SCS-Heart [17] will enroll 20 NYHA class III HF patients in Hong Kong and Australia, and a phase I safety trial in advanced HF patients is also underway in Texas [18]. Results are expected sometime in 2014 for these smaller studies.

## Summary

Despite great advances in pharmacological and device-based treatments in cardiac patients, arrhythmias and heart failure remain prevalent and difficult-to-treat conditions, with high levels of morbidity and mortality. Many heart failure patients suffer from sudden cardiac arrest due to ventricular tachyarrhythmias, and there is a critical need for new lines of therapy for this condition. It is clear from the preclinical and clinical studies highlighted above that chronic neuromodulation with SCS may be a potential new treatment for heart failure and ventricular tachyarrhythmias. The active human trials examining SCS in the HF population should yield results soon and possibly usher in a new age of neuromodulatory therapy for heart failure.

**Acknowledgments** The authors would like to acknowledge Xiaohong Zhou MD for his contribution to this work.

**Conflict of interest** This study was funded in part by a grant from Medtronic CDRM. Dr Lopshire was supported by grants from the IU-CTSI Strategic Research Initiative and the Indiana Institute for Medical Research.

**Statement of Ethical Standards** The research reported in this work fully complies with the laws of the USA.

## References

- Foreman, R., Linderth, B., Ardelt, J., et al. (2000). Modulation of intrinsic cardiac neurons by spinal cord stimulation: implications for its therapeutic use in angina pectoris. *Cardiovascular Research*, *47*(2), 367–375.
- Southerland, E. M., Milhorn, D. M., Foreman, R. D., et al. (2007). Preemptive, but not reactive, spinal cord stimulation mitigates transient ischemia-induced myocardial infarction via cardiac adrenergic neurons. *American Journal of Physiology: Heart and Circulatory Physiology*, *292*, H311–H317.
- Olgin, J. E., Takahashi, T., Wilson, E., et al. (2002). Effects of thoracic spinal cord stimulation on cardiac autonomic regulation of the sinus and atrioventricular nodes. *Journal of Cardiovascular Electrophysiology*, *13*(5), 475–481.
- Issa, Z. F., Zhou, X., Ujhelyi, M. R., et al. (2005). Thoracic spinal cord stimulation reduces the risk of ischemic ventricular arrhythmias in a post-infarction heart failure canine model. *Circulation*, *111*(24), 3217–3220.
- Odenstedt, J., Linderth, B., Bergfeldt, L., et al. (2011). Spinal cord stimulation effects on myocardial ischemia, infarct size, ventricular arrhythmia, and noninvasive electrophysiology in a porcine ischemia–reperfusion model. *Heart Rhythm*, *8*(6), 892–898.
- Ferraro, P., Castagno, D., Massa, R., et al. (2008). Spinal cord stimulation affects T-wave alternans in patients with ischaemic cardiomyopathy: a pilot study. *Europace*, *10*, 506–508.
- Bernstein, S. A., Wong, B., Vasquez, C., et al. (2012). Spinal cord stimulation protects against atrial fibrillation induced by tachypacing. *Heart Rhythm*, *9*(9), 1426–1433.
- Lopshire, J. C., Zhou, X., Dusa, C., et al. (2009). Spinal cord stimulation improves ventricular function and reduces ventricular arrhythmias in a canine postinfarction heart failure model. *Circulation*, *120*, 286–294.
- Liu, Y., Yue, W. S., Liao, S. Y., et al. (2012). Thoracic spinal cord stimulation improves cardiac contractile function and myocardial oxygen consumption in a porcine model of ischemic heart failure. *Journal of Cardiovascular Electrophysiology*, *23*(5), 534–540.
- Tse, H.-F., Lie, Y., Zuo, M., et al. (2012). Intermittent versus continuous spinal cord stimulation for treatment of ischemic heart failure. *European Heart Journal*, *33*, 963–964.
- Feigenbaum, H. (2004). *Echocardiography* (6th ed., pp. 201–263). Baltimore: Williams and Wilkins.
- Lopshire, J. C., & Zipes, D. P. (2012). Device therapy to modulate the autonomic nervous system to treat heart failure. *Current Cardiology Reports*, *14*(5), 593–600.
- Grimaldi, R., de Luca, A., Komet, L., et al. (2012). Can spinal cord stimulation reduce ventricular arrhythmias? *Heart Rhythm*, *9*(11), 1884–1887. doi:10.1016/j.hrthm.2012.08.007.
- Ardell, J. L., Cardinal, R., Vermeulen, M., et al. (2009). Dorsal spinal cord stimulation obtunds the capacity of intrathoracic extracardiac neurons to transduce myocardial ischemia. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*, *297*(2), R470–R477.
- Determining the feasibility of spinal cord neuromodulation for the treatment of chronic heart failure (DEFEAT-HF). Available at: <http://clinicaltrials.gov/ct2/show/NCT01112579>. Accessed 14 Feb 2014.
- Cornelussen, R. N., Splett, V., Klepfer, R. N., et al. (2011). Electrical modalities beyond pacing for the treatment of heart failure. *Heart Failure Reviews*, *16*, 315–325.
- Spinal Cord Stimulation for Heart Failure (SCS-HEART). Available at: <http://clinicaltrials.gov/ct2/show/NCT01362725>. Accessed 14 Feb 2014.
- Neurostimulation of spinal nerves that affect the heart. Available at: <http://clinicaltrials.gov/ct2/show/NCT01124136>. Accessed 14 Feb 2014.