Observational Report

Cardiovascular Effects of Spinal Cord Stimulation in Hypertensive Patients

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Background: Several animal and clinical studies have shown that thoracic spinal cord stimulation (SCS) may decrease mean arterial pressure (MAP). A previous study in normotensive participants demonstrated a small reduction in MAP during SCS at the T5-T6 spinal level. It has also been demonstrated that chronic SCS at the subthreshold stimulation level significantly improved angina attacks and 6 minute hall walk distance in drug refractory angina patients.

Objectives: To determine if thoracic SCS at 2 different stimulation strengths would decrease blood pressure (BP) and heart rate (HR) during baseline conditions and during activation of the sympathetic system by the cold pressor test (CPT).

Methods: Six hypertensive participants and 9 normotensive participants were evaluated. The SCS leads were implanted under sedation (midazolam and fentanyl) 3 days prior to the study. The SCS device was not implanted at the time of lead implantation; the exteriorized leads were connected to an external programmer at the time of the study. MAP was measured at the finger using beat-to-beat photoplethysmographic recordings at rest and during CPT with a Finometer (Model 1, Finapress Medical Systems, Amsterdam, The Netherlands). SCS at threshold (100%, SCS100) and subthreshold (80%, SCS80) intensities were randomly performed in the T5-T6 region of the spinal cord during normal conditions as well as during CPT. Each participant had 3 CPTs with the placebo (control, no SCS) CPT always performed first. CPT was performed by immersing the right hand into ice water for 90 seconds. Thirty seconds of beat-to-beat data prior to starting each CPT (baseline) was analyzed. During the 90 second CPT, the median values of the last 30 seconds of data were used for analysis. Heart rate variability (HRV) during baseline and SCS was computed using Kubios HRV Version 2.0 software (University of Kuopio, Kuopio, Finland). Since the median values of HR, MAP and their changes did not follow a normal distribution, groups were compared with a non-parametric Friedman's or Wilcoxon's signed rank test. The HRV data were normally distributed and a repeated measures analysis of variance (ANOVA) was used.

Results: SCS did not significantly alter MAP or HR at baseline nor did it appear to blunt changes in MAP or HR in response to CPT. In the normotensive group, MAP was significantly elevated by a median value of 16 mmHg ($P<0.001$) during the placebo phase, and by 18 and 10.5 mmHg during the SCS80 and SCS100 phases, respectively. In the hypertensive group, an enhanced response to the CPT was observed. In these participants, the MAP was significantly elevated by a median value of 26.8 mmHg ($P<0.001$) during the placebo phase, and by 20 and 17 mmHg during the SCS80 and SCS100 phases, respectively. There was a non-significant trend for the CPT-induced increase in BP to be attenuated during SCS80. HRV tended to decrease in both the time and frequency domain in hypertensive participants, although this decrease was not statistically significant.

Limitations: This was a pilot study including a limited number of participants

Conclusions: Acute SCS at the T5-T6 region did not significantly alter MAP or HR compared to baseline (no SCS) in participants without sedation, supporting our previous findings in sedated patients. Hypertensive participants had a heightened response to transient cold stress, consistent with the literature. The observation of the tendency for a reduction in HRV in both the time and frequency domain in hypertensive participants is also consistent with the literature. In contrast to acute SCS, the hemodynamic effects of chronic SCS should be explored in the future.

Key words: Spinal cord stimulation, hemodynamics, cold pressor test, heart rate variability, hypertension

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Spinal cord stimulation (SCS), first described by Shealy and Mortimer (1), has since been used for the treatment of diverse conditions such as neuropathic pain, peripheral vascular disease, and refractory angina pectoris (2-10). Recently, several animal studies support the contention that SCS might decrease blood pressure (BP). Issa et al (11) showed that thoracic SCS in a model of heart failure in dogs resulted in a significant decrease in systolic BP. Olgin et al (12) demonstrated in canines that SCS modulates autonomic activity by enhancing parasympathetic activity or sympathetic withdrawal. These results suggest that autonomic modulation might reduce BP. Studies conducted by Linderoth et al (13), Croom et al (14), and Tanaka et al (15) in rats demonstrated that SCS produces a sustained cutaneous vasodilatory effect. Their combined results support the notion that SCS antidromically activates afferent fibers in the dorsal roots causing peripheral release of the vasodilator substance CGRP. However, in the clinical setting, multiple mechanisms might be involved in the cutaneous vasodilation during SCS and therefore the relationship between these mechanisms needs to be explored. Based on these studies, Schultz et al (16) studied electrical stimulation of the dorsal spinal cord in normotensive humans would lower arterial BP and found that the T5-T6 region, SCS reduced MAP to a moderate extent (3.1 mmHg), consistent with the previously known antisympathetic effect of SCS in animals, although this change was not statistically significant. Also, a recent study by Eddicks et al (17) demonstrated that SCS, even at 85% of therapeutic level, significantly improved angina attacks and 6-minute walk distance, suggesting that SCS strength that is lower than the conventional therapeutic level might modulate the severity of myocardial ischemia.

Hypertension is a major cardiovascular disorder that is estimated to affect over 74 million persons in the United States alone (18). Of those with hypertension, it is reported that fewer than 30% have their BP under control (19). Although BP can be managed with pharmaceutical agents in many patients, about 10-15% of them do not respond well or cannot be on chronic medication due to associated side effects (20). Finding an alternative therapy to control hypertension in patients for whom conventional methods are not appropriate might allow physicians to treat a subset of the currently untreatable refractory hypertensive patients. In addition, hypertension is a costly and burdensome disease. Health care and productivity costs are estimated to be $108 billion for hypertension related cardiovascular complications (21).

This was an acute, single center, randomized feasibility study, intended to determine if electrical stimulation of the dorsal spinal cord at different stimulation strengths (threshold and subthreshold stimulation strengths for paresthesia) will lower a transiently elevated BP and heart rate (HR) in participants with and without a history of hypertension. In this study, we examined the hemodynamic response to the cold pressor test (CPT) as an indicator of generalized sympathetic nervous system activation between the hypertensive and normotensive participants, during thoracic (T5-T6) spinal cord stimulation.

Methods

A total of 11 normotensive patients as well as 6 hypertensive patients who were clinically indicated for SCS testing for neuropathic pain were recruited for this study. The hypertensive participants were allowed to take their current medications prescribed for their BP control. The participants were instructed to avoid food, caffeine, exercise, and alcohol for at least 12 hours before arriving at the clinic. Prior to initiation of the study, the Western Institutional Review Board (WIRB)-approved informed consent form was signed and patient demographic and medical history information was collected. All anti-hypertensive medications prescribed to patients were documented. The patients who were hypertensive had been so for 6-8 years. We presumed that they were well managed prior to the study, though no chronic BP data were available to verify that. All the patients were allowed to take their medications.

The SCS leads were implanted under sedation (midazolam and fentanyl) 3 days prior to the study. The SCS device was not implanted at the time of lead implantation, and the exteriorized leads were connected to an external programmer, the N'Vision Clinician Programmer 8840 (Medtronic Inc., Minneapolis, MN) at the time of the study.

SCS was administered with participants in the reclining position with market-released octapolar leads Model 3778 (Medtronic Inc., Minneapolis, MN) implanted in the epidural space under fluoroscopic guidance. Figure 1 illustrates the fluoroscopic view of typical electrode placement. For each lead, the most distal electrode was the cathode and the most proximal electrode was the anode. Ideally, the 2 electrode arrays are located to the left and right of midline within the dorsal portion of the epidural space. The intensity of the stimulus (used in bi-

polar mode) was adjusted by feedback from the participant to determine the intensity tolerated. The threshold was chosen as the output that was comfortable to the patient and was assessed by gradually increasing the stimulus voltage (pulse width 210μs and stimulus frequency- 50Hz was maintained constant). Subthreshold output was defined as 80% of the maximum stimulation output (voltage) not causing paresthesia.

Arterial BP and electrocardiogram (ECG) data were collected continuously during the course of the study. Following baseline hemodynamic data collection for 5-10 minutes, each participant was moved into the placebo phase of the study. During the placebo phase, CPT was administered for 90 seconds while no SCS was delivered. Following the placebo CPT, hemodynamic and ECG data were collected for approximately 5 minutes or until measurements returned to baseline. A simple random sampling method was ensured so that each of the SCS treatment phases following the placebo CPT were selected equally. Randomization was performed by participant number when the SCS data form was generated. SCS crossover and a placebo phase were included in this study design so that participants would serve as their own control (Fig. 2). The location and programming of SCS was consistent for all participants so that data could be summarized to identify consistent responses among participants.

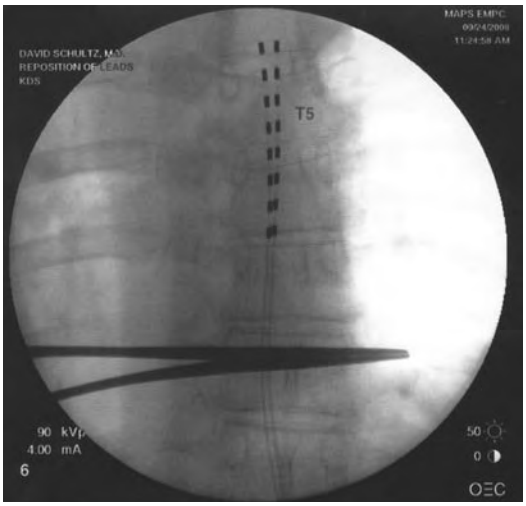

Fig. 1. *Fluoroscopic image of lead placement in the T5-T6 region of the spinal cord.*

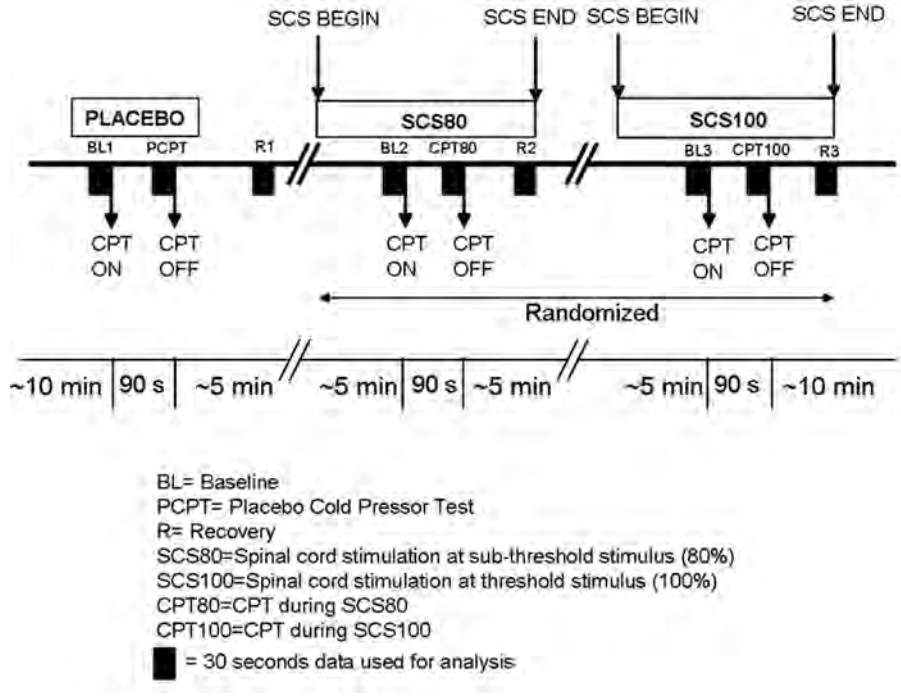

Fig 2. *Experimental protocol followed in this study.*

Instrumentation

Participants were first connected to a surface ECG, the DR180+ Holter monitor (NorthEast Monitoring, Inc., Maynard, MA). Continuous hemodynamic measurements were done using the Finometer (Model 1, Finapres Medical Systems, Amsterdam, The Netherlands) which measures beat-to-beat BP non-invasively. The Finometer has been shown to track acute changes in BP and is strongly correlated to intra-arterial radial pressure (22,23). After being connected, participants rested in the supine position for 15 min before data collection. The Finometer gives waveform measurements similar to intra-arterial recordings and computes beat-to-beat hemodynamic parameters including cardiac output (CO), stroke volume (SV), total peripheral resistance (TPR) and inter-beat-interval (IBI). The Finometer measures brachial pressure and corrects for finger pressure accordingly. The main component is the finger cuff, an inflatable air bladder, and a plethysmograph consisting of a light source (infrared light-emitting diode) and a light detector (infrared photodiode).

Physiological Measurements:

The systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, HR, IBI, CO, and TPR were recorded for every beat using the Finometer. The Finometer cuff was placed on the participant's right middle finger and the participant's hand was supported on the armrest of the recliner. The Finometer device, which uses the vascular unloading technique, has been demonstrated to provide reliable measures of BP (24).

Placebo

Following baseline data collection for approximately 10 minutes, the first CPT (placebo) was administered by immersing the non-dominant hand into ice water for 90 seconds while delivering no SCS. Following the CPT, BP data was collected for approximately 5 minutes, or until measurements returned to baseline. A continuous ECG recording was also collected during the placebo phase testing using a Holter Recorder (DR180+, Northeast Monitoring Inc., Maynard, MA).

SCS Treatment

Following the placebo phase, participants were randomized to receive SCS at 100% (SCS100) of the therapeutic threshold level (the amplitude was gradually increased until the participant felt the paresthesia and could tolerate the stimulation output) or SCS at 80% (SCS80) of the therapeutic level (subthreshold, no sensation of paresthesia) in the T5-T6 region of the spinal cord. During this phase, SCS was randomized to either 100% or 80% of the level required for paresthesia, and was turned on for about 5 minutes prior to CPT. A second CPT was then administered for 90 seconds. Approximately 5 minutes after completion of the second CPT, SCS was turned off and BP data collected for an additional 5 minutes or until measurements returned to baseline. The SCS was then programmed to the second level (80% or 100% depending on the randomization assignment), and SCS turned on for about 5 minutes prior to CPT. A third CPT was then administered for 90 seconds. Approximately 5 minutes after completion of the final CPT, SCS was turned off and BP data were collected for approximately 10 minutes or until measurements returned to baseline.

Cold Pressor Test

The CPT is a cardio circulatory challenge conventionally performed by immersing one hand in ice cold water for 2 minutes (or as tolerated) to acutely raise blood pressure, thus imposing resistance to ejection of blood from the left ventricle into the systemic arterial system and consequently acutely increasing afterload. The sensory afferents during CPT trigger a systemic sympathetic activation leading to marked vasoconstriction. The result is an elevated arterial pressure, and a reduced stroke volume due to an increase in afterload. The CPT has frequently been validated for activation of the sympathetic nervous system. Sympathetic activation increases immediately during the CPT and a consistent elevation in blood pressure is achieved (25,26).

Heart Rate Variability

Beatscope 1.1a software (Finapres Medical Systems, Amsterdam, The Netherlands) was used to download the data stored from the Finometer. The Finometer derived IBI data were used for calculations of heart rate variability (HRV). The IBI, which is a surrogate of R-R interval (time duration between 2 consecutive R waves of the ECG), was used for the HRV analysis. These intervals were processed in Kubios HRV Analysis 2.0 software (University of Kuopio, Kuopio, Finland). This software calculates time-domain metrics like the mean and standard deviation of the R-R intervals, and frequency-domain metrics. A power spectrum density (PSD) estimate was calculated for the R-R intervals (27). Since PSD estimators assume equidistant sampling, R-R interval series were interpolated using cubic spline interpolation. The HRV spectrum was calculated using the Welch's periodo-

gram FFT method, using a 256 second window and 50% overlap (27). The PSD gives us the low frequency (LF), high frequency (HF) band powers, and the LF/HF power ratio, as shown in the Kubios analysis output (Fig. 3).

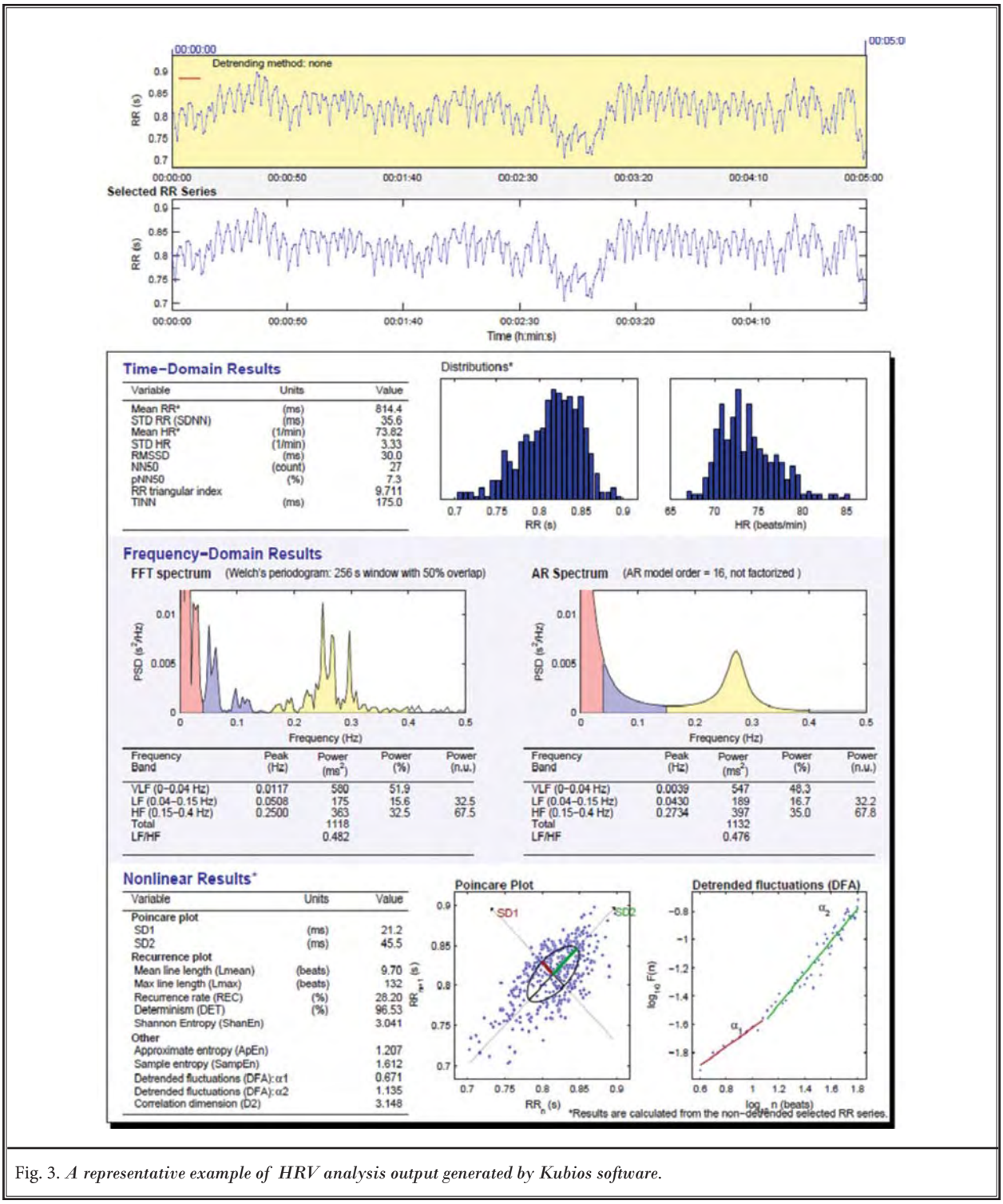

Fig. 3. *A representative example of HRV analysis output generated by Kubios software.*

Data analysis

Three baseline and 3 recovery values were obtained during the study protocol (Fig 2). The first baseline (BL1) was measured immediately prior to the initiation of the placebo CPT (SCS turned off). The recovery (R1) was measured approximately 5 minutes after the placebo CPT was completed. The second baseline (BL2) was measured immediately prior to the initiation of the second CPT during SCS of the first randomized threshold/subthreshold stimulus output. The associated recovery (R2) was measured approximately 5 minutes after the second CPT was completed. The third baseline (BL3) was measured immediately prior to the initiation of the third CPT during SCS followed by its associated recovery (R3) approximately 5 minutes after the third CPT was completed. For each participant, the median value of 30 seconds of raw beat-to-beat data were calculated, to prevent influence by an outlier (e.g., premature ventricular contractions). The median values were calculated prior to starting each CPT (baselines). Similarly, during each 90 second CPT, the median values of the last 30 seconds of data were used for analysis. For analysis of delta MAP and delta HR for each participant, the median of 30 seconds of MAP and HR values during CPT was subtracted from the median of 30 seconds MAP and HR data during baseline, just prior to the CPT to determine the changes in MAP and HR induced by CPT. Since the median values of MAP, HR and their changes did not follow a normal distribution, a non-parameteric Friedman's test was used for comparison of 3 groups, whereas a Wilcoxon's signed rank test was used for comparison of 2 groups. Furthermore, all results (except for the HRV data) are expressed as the median of each group and the interquartile (IQR) range (25% -75% percentile).

The HRV during baseline and SCS were computed using the Kubios HRV Analysis 2.0 software. Approximately 3-5 minutes of IBI data derived by the Finometer was used for the HRV analysis, which included measurements in time and frequency domains. The HRV data were normally distributed; a repeated measure ANOVA was used to compare the groups. These data are reported as mean ± SD. Statistical analyses were done using Minitab Statistical Software 15.1.10 (Minitab, Inc., State College, PA). A P value <0.05 was considered significant.

Results

Table 1 shows that the BPs of hypertensive participants were in the normal range before the SCS. Two normotensive patients were excluded from the analysis due to atrial bigeminy and BP variability in one patient

Table 1. *Note that the MAP and HR were similar in both groups, indicating that the hypertensive patients were well-managed at the time of the study. Values are medians and interquartile (IQR) range (25% -75% percentile).*

Clinical Characteristics	Normotensive Participants (n=9)	Hypertensive Participants (n=6)
Female/Male	5F/4M	2F/4M
Age, Years	46 (36-60)	59 (42-70)
Weight, lbs	170 (145-215)	185 (160-230)
Height, cm	162 (160-178)	175 (160-183)
MAP, mm Hg	106 (95-115)	105.7 (95-122)
HR, Beats per Min	76 (69-84)	75 (56-100)
Concurrent Medications, n (%)		
Beta Blockers	--	4 (67%)
ACE Inhibitors	--	1 (17%)
ARB's	--	1 (17%)
Statins	1 (11%)	2 (33%)
Diuretics	--	2 (33%)
Calcium Channel Blockers	--	1 (17%)
Opioids	9 (100%)	3 (50%)
NSAIDs	3 (33%)	--
Antidepressants	5 (55%)	3 (50%)
Oral Antidiabetic Agents	--	2 (33%)

and inability to complete the CPT in the second patient (Table 1). The participants had a number of medical problems in addition to neuropathic pain. Three of the 6 hypertensive participants were taking medications to treat depression in addition to taking an opioid derivative for pain (Table 1).

As seen in Fig. 4, continuous raw data obtained over an experimental session over time in a single participant shows the "signature" of a typical response to a cold pressor stimulus. Similar effects of CPT have been observed in the literature. The CPT induced a ramp like increase in BP followed by increase in HR. Two participants did not show a typical response suggesting autonomic dysfunction.

The stimulation threshold was determined by the response of the participant. An average amplitude of 4.3 volts (range: 2.4-8.4 volts) was delivered during the subthreshold stimulation (no paresthesia felt by the participant) and an average amplitude of 5.5 volts (range: 2.6-10.5 volts) was delivered during the threshold stimulation (tolerable paresthesia felt by the participant).

In the normotensive group, the median MAP was significantly elevated by 16 mmHg during the placebo phase and by 18 and 10.5 mmHg during the CPT80 and CPT100 phases, respectively (Fig. 5, top panel). The MAP increased from a baseline median value of 106 mmHg (IQR, 95-115) to 122 mmHg (IQR, 117.5-138; $P<0.001$) during the placebo cold pressor test (PCPT) phase. During the CPT80 phase, the MAP increased from a baseline value of 111 mmHg (IQR, 105-123) to 129 mmHg (IQR, 120.5-138.5; $P<0.001$). During the CPT100 phase, the MAP increased from a baseline value of 113 mmHg (IQR, 98-123) to 123.5 mm Hg (IQR, 118.5-135.2; $P<0.001$). However, the heart rate during the 3 CPTs did not change significantly (Fig. 5, lower panel).

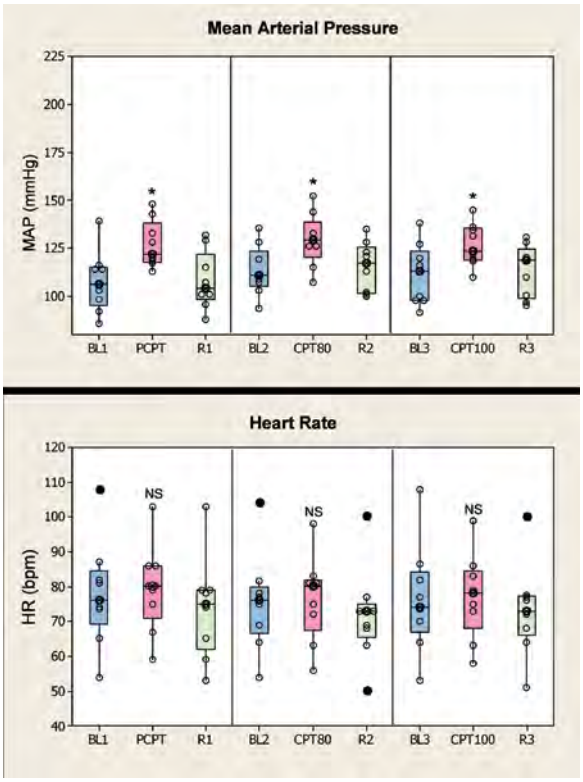

Fig. 5. *Changes in MAP and HR in normotensive participants (n=9). The top panel shows the effect of CPT on changes in MAP during SCS and the lower panel shows the effect of CPT on changes in HR during SCS. PCPT=placebo cold pressor test; CPT80=cold pressor test during subthreshold SCS at 80%; CPT100=cold pressor test during threshold SCS at 100%. The box-and-whisker plots show the median (50th percentile) and the interquartile range (25th and 75th percentiles). The upper whisker extends to the maximum data point and the lower whisker extends to the minimum data point. All values above the 95th percentile and below the 5th percentile are plotted as outliers [•]; [*] = P<0.001 versus baseline and recovery; NS =not significant.*

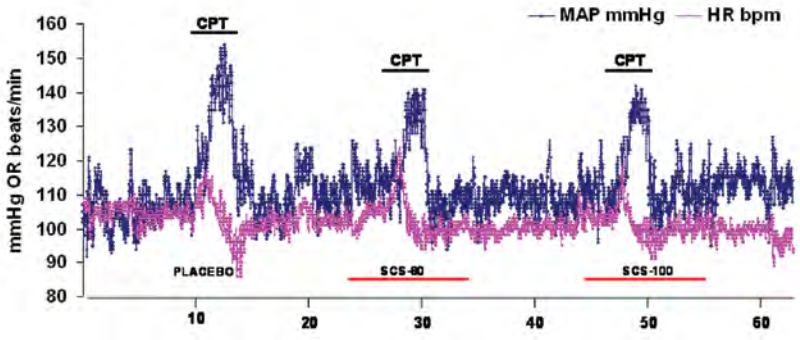

Fig. 4. *A representative example of the recordings of MAP and HR in a single participant during the 3 CPTs.*

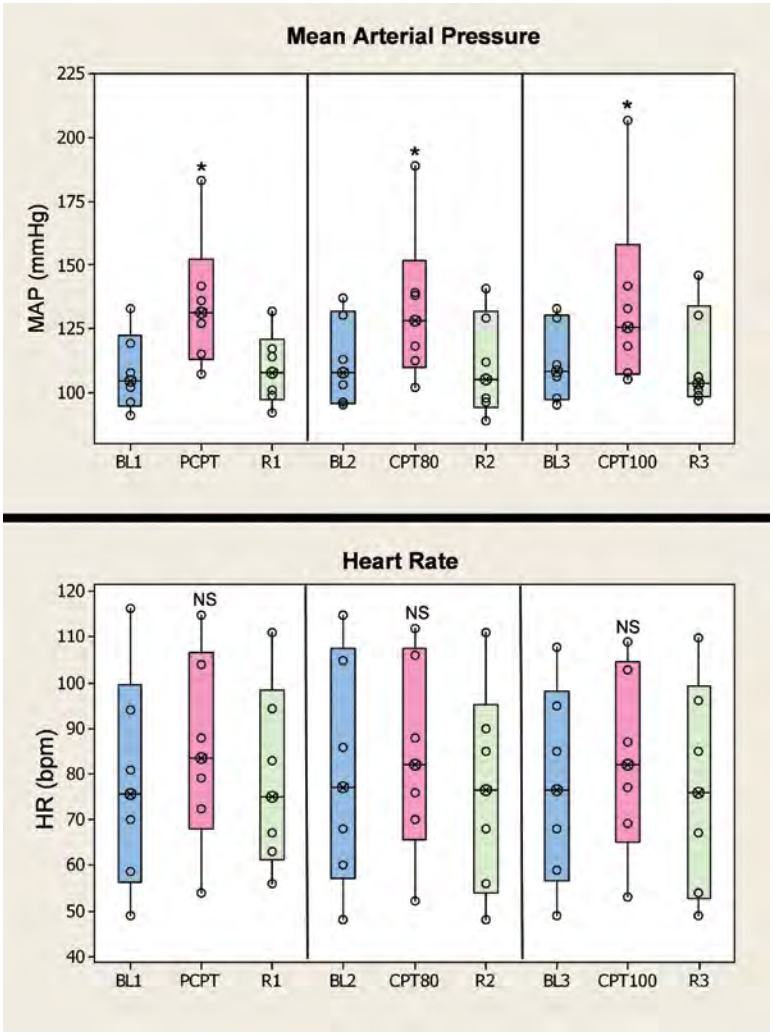

Fig. 6. *Changes in MAP and HR in hypertensive participants (n=6). The top panel shows the effect of CPT on changes in MAP during SCS and the lower panel shows the effect of CPT on changes in HR during SCS. The box-and-whisker plots show the median (50th percentile) and the interquartile range (25th and 75th percentiles). The upper whisker extends to the maximum data point and the lower whisker extends to the minimum data point. All values above the 95th percentile and below the 5th percentile are plotted as outliers [•]. PCPT=placebo cold pressor test; CPT80= cold pressor test during subthreshold SCS at 80%; CPT100= cold pressor test during threshold SCS at 100%. NS=not significant.*

The increase in median HR during placebo CPT was 4 bpm (not significant [NS]) and during both CPT80 and CPT100, the HR increased by 4 bpm and 4 bpm respectively (NS).

Figure 6 shows the results obtained in hypertensive participants. In them, an enhanced response to the CPT was observed. The median MAP was significantly elevated by 26.8 mmHg during the placebo phase and by 20 and 17 mmHg during the CPT80 and CPT100 phases, respectively (Fig. 6, top panel). The MAP increased from a baseline median value of 104.7 mmHg (IQR, 95-122) to 131.5 mmHg (IQR, 113-152; $P<0.001$) during the PCPT phase. During the CPT80 phase, the MAP increased from a baseline value of 108 mmHg (IQR, 96-132) to 128 mmHg (IQR, 110-151; $P<0.001$). During the CPT100 phase, the MAP increased from a baseline value of 108 mmHg (IQR, 97-130) to 125 mm Hg (IQR, 107-151; $P<0.001$). However, HR during the 3 CPTs did not

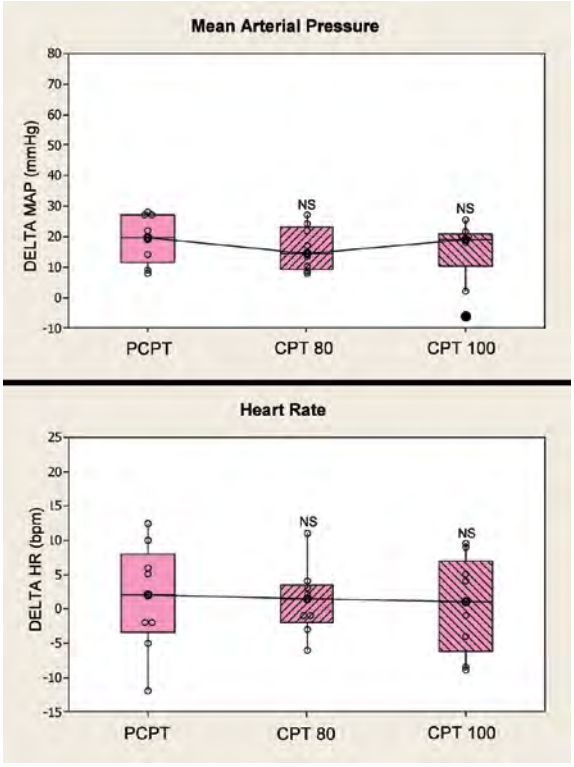

Fig. 7. *Box-and-whisker plots showing the distribution of delta MAP (top panel) and HR (lower panel) in normotensive patients. (Median, 25th and 75th percentile, and individual values). The upper whisker extends to the maximum data point and the lower whisker extends to the minimum data point. All values above the 95th percentile and below the 5th percentile are plotted as outliers [•]. NS = Not significant versus PCPT.*

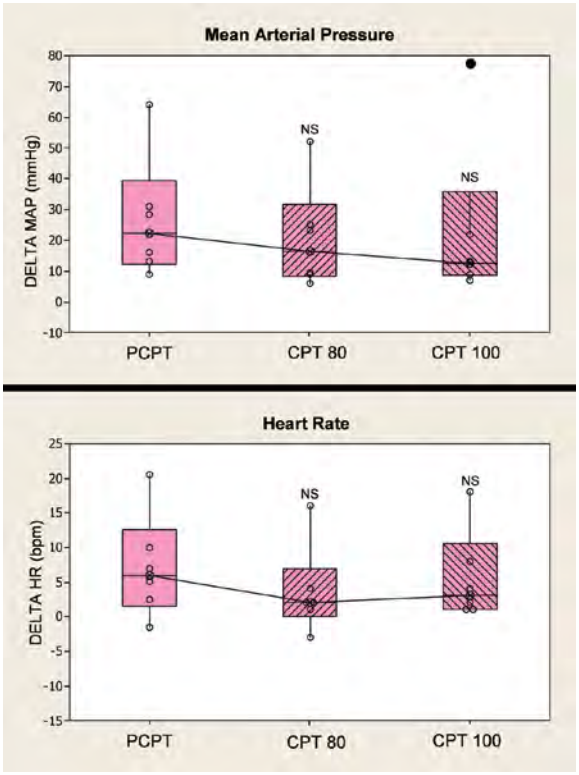

Fig. 8. *Box-and-whisker plots showing the distribution of delta MAP (top panel) and HR (lower panel) in hypertensive participants. (Median, 25th and 75th percentile, and individual values). The upper whisker extends to the maximum data point and the lower whisker extends to the minimum data point. All values above the 95th percentile and below the 5th percentile are plotted as outliers [•]. NS = Not significant versus PCPT.*

change significantly (Fig. 6, lower panel). The increase in median HR during placebo CPT was 8 bpm (NS) and during both CPT80 and CPT100, the median HR increased by 5 bpm and 5.5 bpm respectively (NS).

Figure 7 shows the distribution of delta MAP and delta HR changes during the 3 CPTs in normotensive participants. For each one, the median of 30 seconds of MAP and HR values during CPT was subtracted from the median of 30 seconds MAP and HR data during baseline, just prior to the CPT. Although SCS did not significantly alter the changes in HR and BP induced by CPT, there was a trend for lower mean delta MAP values with both CPT80 and CPT100 phases.

Figure 8 shows the distribution of delta MAP and delta HR changes during the 3 CPTs in hypertensive participants. Although SCS did not significantly alter the changes in HR and BP induced by CPT in hypertensive participants, there was a trend for lower mean delta values of MAP and HR with both CPT80 and CPT100.

Compared to normotensive participants, HRV was decreased in both the time and frequency domain in hypertensive participants. As shown in Fig. 9, there were trends towards decreases in SDNN, LF and HF components in the hypertensive group (lower panel, B, D and F). The LF/HF ratio also decreased in the hypertensive group from an average value of 1.47 to 1.43. However, none of these changes reached statistical significance in this small group of participants. Furthermore, subthreshold or threshold SCS did not appear to significantly alter any of the HRV parameters compared to baseline in either normotensive or hypertensive participants.

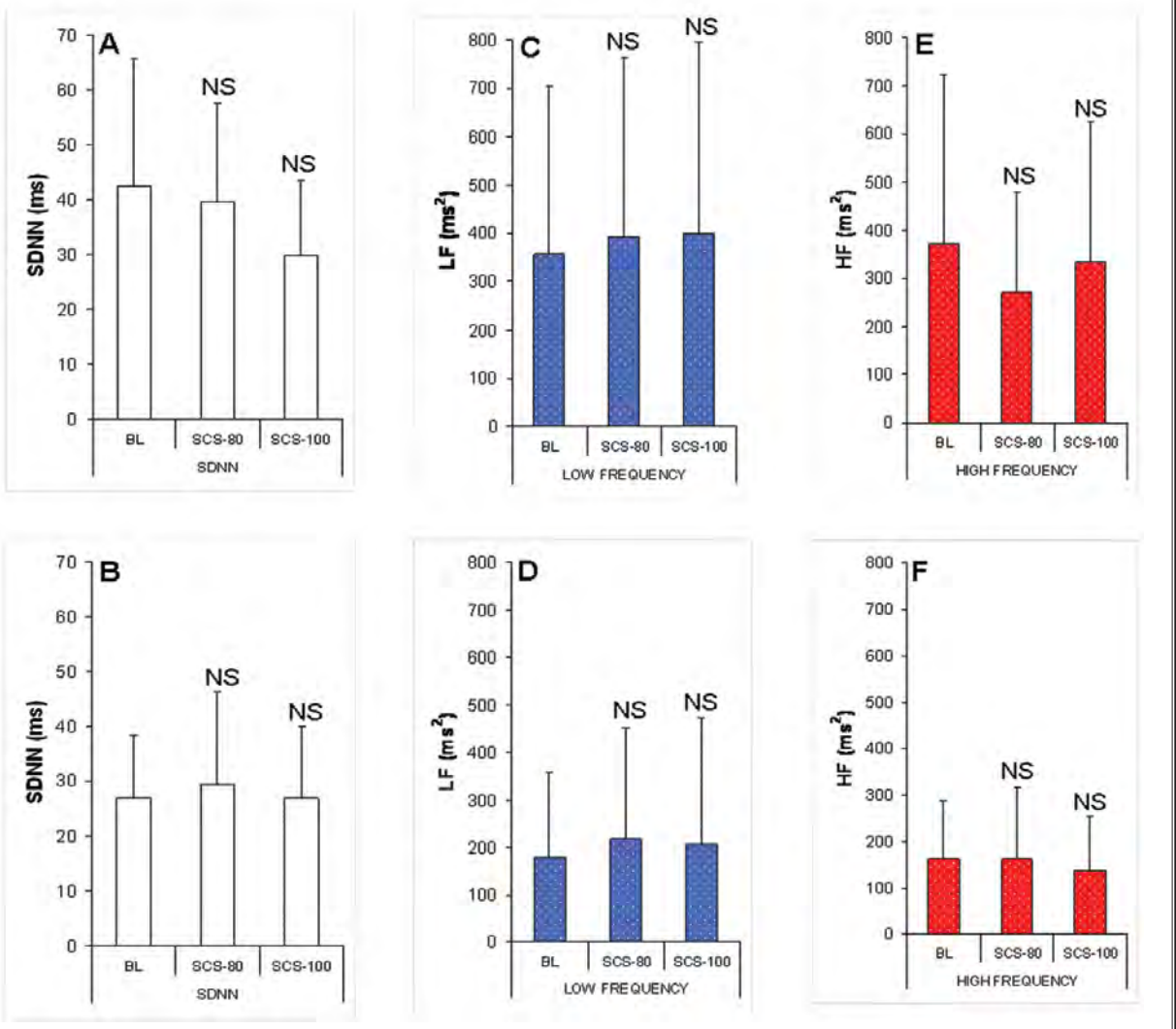

Fig. 9. *The upper panel (A, C and E) shows HRV measurements in both the time i.e., Standard Deviation of Normal-to-Normal Intervals (SDNN) and frequency i.e., low frequency (LF), and high frequency (HF) domain during baseline and SCS in normotensive participants. The lower panel (B, D and F) shows HRV measurements in hypertensive participants. Values are mean ± SD. NS = not significant compared to baseline (BL).*

Discussion

This study showed that acute SCS at T5-T6 region did not significantly alter MAP or HR compared to baseline (no SCS) in participants without sedation, supporting our previous findings in sedated participants (16). No difference in BP and HR was seen during CPT80 or CPT100 phases compared to respective baselines. The response of normotensive or hypertensive participants to cold stress was not significantly attenuated by SCS. However, there was a trend for the CPT induced increase in BP to be attenuated during SCS80. The non-significant trend towards a reduction in this range for the SCS group might have clinical relevance. It is likely

that the small sample size and large variation among participants reduced the power of the study to detect a significant difference caused by SCS. An additional study is needed to evaluate this effect in a larger number of participants.

Compared to normotensive participants, hypertensive participants had a heightened response to transient cold stress, which is consistent with previous reports in the literature (28). The tendency for a reduction in HRV in both the time and frequency domain in hypertension is also consistent with the literature. In a previous study that used a similar experimental protocol (16), normotensive participants that were mildly sedated were evaluated. In the current study, unsedated hypertensive participants were included. Also, the effects of SCS at 2 levels of stimulation were compared. Schultz et al (16) used the Vasotrac device (Medwave, Inc., Arden Hills, MN) to measure BP, which is a less sensitive instrument compared with the Finometer, which computes beat-to-beat data from a finger cuff. The Vasotrac device measures BP from a wrist cuff every 12-15 seconds. The data obtained in the current study therefore should be more accurate.

Since consistent increases in MAP were obtained during the CPT, this pressor test was conducted appropriately. The CPT has been used to assess the function of the sympathetic nervous system and has been validated for activation of a sympathetic response (29). Sympathetic activation increases immediately during CPT resulting in a consistent elevation of BP. CPT is known to cause a global sympathetic activation in participants with different levels of baseline sympathetic tone, such as a group of normal subjects and patients with borderline hypertension (30). CPT results in a significant arteriolar vasoconstriction, with a subsequent increase in blood pressure and a slight increase in plasma catecholamines but with either no change or minor increases in heart rate (31-33). Since HR does not decrease with the rise in arterial BP during the CPT, it would appear that this reflex-mediated vasoconstriction might alter the sensitivity of the arterial baroreflex. In the present study, hypertensive participants had a heightened response to transient cold stress compared to normotensive participants, which is consistent with previous reports in the literature (34,35). Although SCS did not significantly alter the changes in MAP or HR induced by CPT, there was a trend towards lower delta MAP when CPT was performed during both threshold and subthreshold SCS. There was also a trend toward a lower delta HR with SCS in hypertensive participants. These trends could represent a possible therapeutic effect of SCS, or it could be due to an adaptation of the subject to repeated CPTs. Since CPT without SCS (placebo CPT) was always performed first, the participants could have adapted to the cold stress resulting in slightly smaller increases in MAP and/or HR during subsequent CPTs. We performed the placebo CPT first in all participants based on the results of studies by Foreman et al (36) and Jessuran et al (37). Results obtained from the experiments conducted showed that spinal cord neurons can modulate the intrinsic cardiac nervous system during thoracic SCS. They demonstrated that such modulation persists and that the spinal cord neurons continue to exert their suppressor effects on the intrinsic cardiac nervous system long after their activation terminates. Also, Jessuran et al (37) noted that the therapeutic effects of SCS are known to persist for hours after its termination in patients. An additional study with randomization of the placebo CPT and more time separating the 2 periods of SCS is needed to address this issue.

Studies by Linderoth et al (13), and Tanaka et al (15) have shown that the peripheral resistance of the vasculature decreases with SCS, in turn decreasing the afterload the ventricles must pump against. Issa et al (11) demonstrated in canines that 15 minutes of thoracic SCS significantly reduced systolic blood pressure by 9.8 mmHg. The authors suggest that these findings could be due to autonomic modulation. Thoracic SCS has also been shown to cause peripheral vascular vasodilation mediated by nitric oxide and release of the vasodilator calcitonin gene-related peptide-CGRP (14, 38). Although the exact mechanism by which thoracic SCS exerts its effects are not known, preliminary evidence suggests that SCS results in a decreased sympathetic tone. However, the results we obtained during stimulation of the T5-T6 spinal cord region do not support this contention. The baseline MAP was not significantly altered by either substhreshold or threshold SCS in either normotensive (Fig. 5) or hypertensive (Fig. 6) participants. Inspection of all the fluoroscopic images from each participant showed that the leads were indeed in the T5-T6 region. However, lead location, and in particular the programmed parameters, might play an important role in the study outcome. In our previous study (16), where SCS and CPT were performed under sedation just after lead insertion, threshold SCS at either T5-T6 or T1-T2 did not significantly alter baseline HR or MAP in response to CPT.

Eddicks et al (17) examined the therapeutic effects of subthreshold SCS in patients with refractory angina

and showed improvement in functional status and symptoms when subthreshold stimulation was compared to a control group that had SCS at an output of 0.1 Volts. SCS is generally performed with a stimulation intensity that causes a tingling sensation in the corresponding dermatome and therefore it has been difficult to conduct controlled clinical trials with a placebo-controlled design. Since neither subthreshold SCS (85% of the paresthesia threshold) or control SCS (0.1 volt output) resulted in any perceptible sensation in the study by Eddicks et al (17), the authors concluded that a placebo effect could not account for the anti-anginal effects of subthreshold SCS. Furthermore, animal studies showed that SCS at intensities below motor threshold produced cutaneous vasodilatation through antidromic activation of sensory fibers (15). Gherardini and co-workers (39) tested the effect of low-intensity stimulation (70% of motor threshold) in comparison with high-intensity stimulation (90% of motor threshold) in a rat model. Long-term survival of a groin flap was improved in the low-intensity (60% survival) and in the high intensity (90% survival) groups, compared with the control group (0% survival). In addition, low voltage cervical stimulation improved cardiac work efficiency in a pig model (40). In contrast to the results of these previous studies, neither subthreshold or threshold SCS had a significant hemodynamic effect in the present study.

In addition to measuring the effect of SCS on HR and BP in the present study, we also measured HR variability to further evaluate changes in cardiac autonomic tone. Our results showed that all HRV parameters tended to decrease in participants with hypertension, but the differences did not reach statistical significance. Furthermore, there was no significant effect of subthreshold or threshold SCS on any of the HRV parameters in either normotensive or hypertensive patients. Although we did not find any significant differences in the HRV parameters, studying a larger sample size might reveal differences.

Low HRV is an important risk factor for sudden cardiac death, and is also known to increase the risk of cardiovascular morbidity and mortality. The HF power is considered an indicator of cardiac parasympathetic activity. The LF component of HRV is mediated by both sympathetic and parasympathetic activities (41,42). The LF/HF ratio of HRV has been proposed to play a role in cardiac sympathovagal activity balance. The LF/HF ratio was slightly decreased in hypertensive participants in this study. The time domain measure of HRV (SDNN) is known to be a marker of parasympathetic activity. The tendency for a reduction in HRV in both the time and frequency domain in hypertension in the present study is also consistent with the literature (43).

Limitations: This was a pilot study including a limited number of participants. The 3 CPT interventions were not randomized. The placebo CPT was always performed first; only the 2 CPTs performed during SCS were randomized. The 2 periods of SCS were separated by about 10 minutes, and there might have been a carry-over effect from the first to the second period. The number of participants was small and the variability in the data might have been too large to establish statistical significance. SCS was applied for only a short duration of about 8-10 minutes, while in most clinical studies it is maintained for much longer time periods. All participants were having neuropathic pain at the time of the study and were on several concomitant medications, which could have influenced the results.

Conclusion

In summary, SCS does not seem to have a major effect on baseline MAP or HR, or the changes in these parameters induced by CPT, at least acutely. The lack of significant effect of SCS on hemodynamics was observed in both normotensive and hypertensive participants. In addition, there was no significant effect of SCS on HRV. In contrast to acute SCS, chronic SCS might have a different effect on BP and HRV and should be explored in the future.

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