Pain Physician 2007; 10:677-685 • ISSN 1533-3159

Case Series

Acute Cardiovascular Effects of Epidural Spinal Cord Stimulation

David M. Schultz, MD[1], Shailesh Musley, PhD[2], Peggy Beltrand, RN[2], Jill Christensen, BS[2], Dave Euler, PhD[2], and Eddy Warman, PhD[2]

From: [1] Medical Advanced Pain Specialists (MAPS), Minneapolis, MN, [2]Monitoring and Diagnostics Research, Cardiac Rhythm Disease Management, Medtronic Inc.

[1]Dr. Schultz is Director, Medical Advanced Pain Specialists, Minneapolis MN.
[2]Dr. Musley is Principal Scientist, Monitoring and Diagnostics Research, Cardiac Rhythm Disease Management, Minneapolis, MN
[2]Beltrand is MAPS Implant Manager Minneapolis, MN.
[2]Christensen is Clinical Study Manager, Software and Database Department, Cardiac Rhythm Disease Management, Minneapolis, MN.
[2]Dr. Euler is Senior Principal Scientist, Heart Failure Research, Cardiac Rhythm Disease Management, Minneapolis, MN.
[2]Dr. Warman is Senior Principal Scientist, Monitoring and Diagnostics Research, Cardiac Rhythm Disease Management, Minneapolis, MN.

Address correspondence:
David Schultz, MD
MAPS Medical Pain Clinics
2104 Northdale Boulevard,
Minneapolis, Minnesota 55433
E-mail: dschultz@painphysicians.com

Disclaimer: There was no external funding in the preparation of this manuscript.
Conflict of interest: None

Manuscript received: 12/11/2006
Revisions received: 07/03/07
Accepted for publication: 07/31/2007

Free full manuscript:
www.painphysicianjournal.com

Background: Several animal studies support the contention that thoracic spinal cord stimulation (SCS) might decrease arterial blood pressure.

Objective: To determine if electrical stimulation of the dorsal spinal cord in humans will lower mean arterial pressure (MAP) and heart rate (HR).

Design: Case Series

Methods: Ten normotensive subjects that were clinically indicated for SCS testing were studied. Two of the 10 patients who underwent testing were excluded from the analysis because they did not respond to the Cold Pressor Test (CPT). Systolic blood pressure, diastolic blood pressure, and heart rate were measured continuously at the wrist (using the Vasotrac device). SCS was administered with quadripolar leads implanted into the epidural space under fluoroscopic guidance. SCS was randomly performed either in the T1-T2 or T5-T6 region of the spinal cord during normal conditions as well as during transient stress induced by CPT. The CPT was conducted by immersing the non-dominant hand in ice-cold water for 2 minutes.

Results: There were moderate decreases in MAP and HR during SCS at the T5-T6 region compared to baseline that did not reach statistical significance. However, SCS at the T1-T2 region tended to increase MAP and HR compared to baseline but the change did not reach statistical significance. Arterial blood pressure was transiently elevated by 9.4 ± 3.8 mmHg using CPT during the control period with SCS turned off and also during SCS at either the T1-T2 region or T5-T6 region of the spinal cord (by 9.2 ± 5 mmHg and 10.7 ± 8.4 mmHg, respectively). During SCS at T5-T6, the CPT significantly increased MAP by 5.9±7.1 mmHg compared to control CPT (SCS off).

Conclusion: This study demonstrated that SCS at either the T1-T2 or T5-T6 region did not significantly alter MAP or HR compared to baseline (no SCS). However, during transcient stress (elevated sympathetic tone) induced by CPT, there was a significant increase in MAP and moderate decrease in HR during SCS at T5-T6 region, which is not consistent with previous data in the literature. Acute SCS did not result in adverse cardiovascular responses and proved to be safe.

Key words: Spinal cord stimulation, mean arterial pressure, heart rate, cold pressor test

Pain Physician 2007; 10: 677-685

The use of spinal cord stimulation (SCS) was first described in 1967 (1) and has since been used for the treatment of diverse conditions such as neuropathic pain and peripheral vascular disease. Recently, SCS has emerged as a treatment option for patients with refractory angina pectoris, despite maximally tolerated conventional medical treatment (2,3). Several animal studies support the contention that SCS might decrease blood pressure. Tanaka et al (4) examined the effects of SCS on blood flow at intensities below motor threshold in anesthetized rats with stimulus parameters used clinically, i.e. 50 Hz, 0.2 ms and stimulus intensities at 30%, 60% or 90% of motor threshold. They observed SCS-induced vasodilation that was mediated by peripheral release of Calcitonin Gene Related Peptide (CGRP) via antidromic activation of sensory fibers. Olgin et al (5) demonstrated that SCS at the T1-T2 spinal region in canines modulates autonomic activity by enhancing parasympathetic activity or sympathetic withdrawal. A recent study by Issa et al (6) showed that thoracic SCS at the T1-T2 spinal region in a canine model of heart failure resulted in a significant decrease in systolic blood pressure. These results suggested that autonomic modulation might reduce blood pressure. Additionally, animal studies conducted by Linderoth et al 1994 (7), Croom et al 1997 (8), and Tanaka et al 2004 (9) further demonstrated that SCS produces a sustained cutaneous vasodilatory effect. However, in the clinical setting multiple mechanisms may be involved in altering blood pressure during SCS and therefore, the relationship between these mechanisms needs to be understood. Since there is no previous human data regarding SCS and its effect on blood pressure, we conducted this study in subjects without any documented cardiac conditions such as hypertension, angina, myocardial infarction, or heart failure. The present study tested the hypothesis that SCS at the T5-T6 region will lower mean arterial pressure and heart rate during transient stress.

Methods

Subject Selection and Experimental Protocol

Ten patients were investigated and 8 patients, (5 female and 3 male), aged 21– 66 years, were ultimately chosen for data analysis (Table 1). All patients had been previously diagnosed as suffering from neuropathic back and/or limb pain. SCS testing has application where implantation of a permanent neurostimulation system is indicated, and is intended for patients with chronic neuropathic pain. Data collection in this study took place during SCS testing. All equipment used, including the temporary leads, the system delivering the electrical impulses, and the instruments used to collect data, are market released and were used in accordance with their labeling. Prior to initiation of this study, the Western IRB-approved informed consent form was signed by each patient. All patients were scheduled to receive SCS therapy for neuropathic pain and were screened to ensure they met all of the inclusion criteria and none of the exclusion criteria.

Patients met the following inclusion criteria for enrollment in this study:

1. Patients were at least 18 years of age.
2. Patients were selected to receive SCS therapy for neuropathic pain.
3. Patients were willing and able to give informed consent.

The exclusion criteria were:

1. Patients with stable or unstable angina.
2. Patients with a history of myocardial infarction.
3. Patients not willing or able to complete 3 CPTs.

On the study day, subjects were instrumented with a surface electrocardiogram (ECG) and a non-invasive continuous arterial blood pressure monitor (Vasotrac™, St. Paul, MN). The SCS lead implantation was performed under light sedation (2 mg Midazolam and 100µg Fentanyl, intravenously). A local anesthetic agent (1% buffered Lidocaine) was administered to numb the area where the leads were inserted. Two SCS leads (Pisces Quad Lead, model # 3487A-45, Medtronic Inc, MN) were implanted into the epidural space under fluoroscopic guidance.

Lead Implantation Procedure

Under fluoroscopic guidance and using the loss of resistance technique, the epidural space at the T12-L1 level was entered with Touhy needles. Two Medtronic model 3487A Pisces-Quad leads with inter-electrode spacing of 1 cm were used. Each lead was introduced through the Touhy needle slightly to the left and right region of the midline and advanced until the tips were at the level of spinal cord randomization (T1-T2 or T5-T6 region). Figure 1 illustrates the fluoroscopic view of typical electrode placements. The distal electrode was the cathode and the 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 was

Table 1. *Patient characteristics.*

Patient Id	First Randomization	Age	Gender	Weight (Lbs)	Indication For SCS
01-MVA	T5-T6	38	female	154	Neuropathic pain
02-TMS	T5-T6	21	male	130	Neuropathic pain
03-SRM	T1-T2	41	female	120	Neuropathic pain
04-JAU	T1-T2	46	female	260	Neuropathic pain
05-LAL	T1-T2	65	female	159	Neuropathic pain
06-JMW	T5-T6	48	male	240	Neuropathic pain
07-HWA	T1-T2	66	male	195	Neuropathic pain
08-JMJ	T5-T6	45	female	150	Neuropathic pain

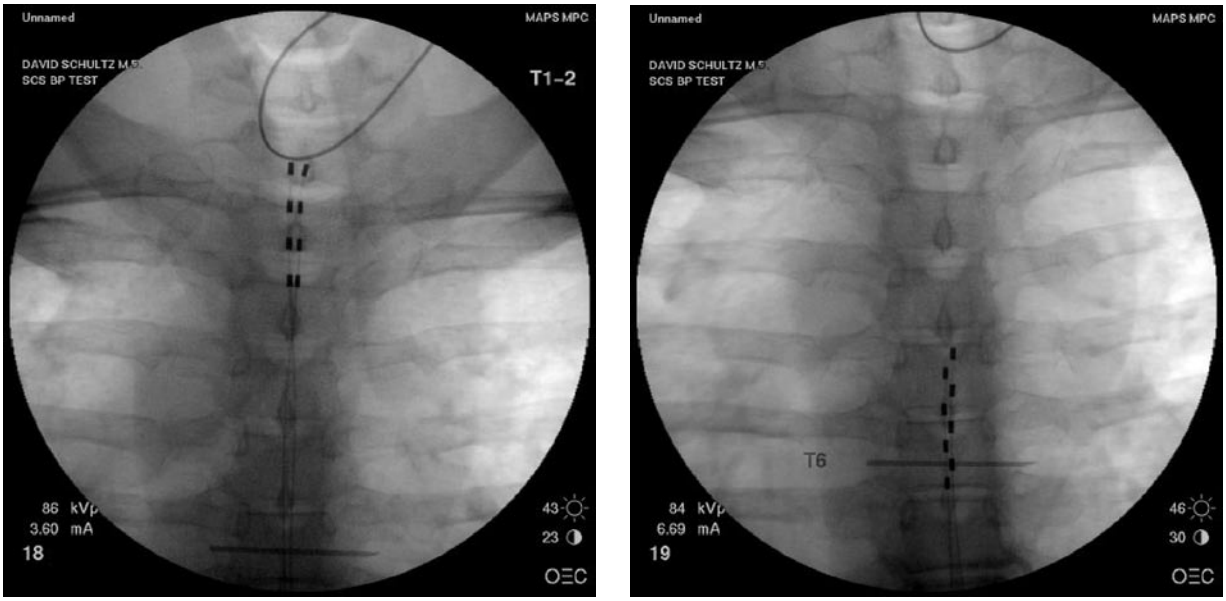

Fig.1. *Fluoroscopic images of lead placement in the T1-T2 region (left) and the T5-T6 region (right) of the spinal cord.*

adjusted by feedback from the patient to determine the intensity that would be used in each patient to investigate changes in MAP and HR. The SCS intensity (used in bipolar mode) was increased to the level tolerated by the patient. The threshold was chosen as the output required that was comfortable to the patient and was assessed by gradually increasing the stimulus voltage with pulse width (0.2 ms) and stimulus frequency (50 Hz) held constant. Transient paresthesia or a sensation of tingling occurred during SCS when the stimulation voltage was increased beyond a threshold value (usually 6–8 volts). This sensation disappeared after the SCS was turned off. The subjects perceived the tingling sensation during the SCS procedure. In one subject we were not able to position the SCS leads in the T1-T2 region. The same subject did not respond to the CPT and was excluded from the analysis.

The Cold Pressor Test (CPT)

The CPT is a cardiocirculatory challenge conventionally performed by immersing one hand in ice cold water for 2 minutes (or as tolerated) to acutely raise the blood pressure, thus imposing resistance to ejection of blood from the left ventricle into

the systemic arterial system and consequently acutely increasing afterload (afterload = increased left ventricular wall stress). Sympathetic activation increases immediately during the CPT. After 2 minutes, a very consistent elevation in blood pressure is achieved (10,11). The CPT has frequently been validated for activation of the sympathetic nervous system.

Arterial Blood Pressure Measurement

The Vasotrac non-invasive blood pressure measuring system was used that provided continual blood pressure measurement with accuracy comparable to an indwelling radial artery catheter (12). The BP measurement and waveforms are displayed in approximately 15 seconds, with continual updates 4 to 6 times a minute. Several clinical studies comparing the accuracy of the Vasotrac system to arterial lines have been conducted. The data shows that there is a 0.97 correlation coefficient compared to measurements taken by a well managed indwelling radial artery catheter. The Vasotrac system uses a wrist module and a monitor/display that are connected by a cable. The wrist sensor is placed where the radial artery passes over the flat portion of the radius bone (the distal edge of the radius). This position allows the sensor to measure the amplitude of the radial pulse as pressure is increased against the artery. Analysis of the wave shape, form, and other characteristics are used to calculate the patient's systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure, and heart rate.

Experimental Protocol

Following placement of both the leads and baseline recording, each subject was moved into the control arm of the study (Fig. 2). During the control arm, the Cold Pressor Test (CPT) was administered for 2 minutes in the absence of SCS. Following the CPT, blood pressure data was collected during a recovery period of approximately 5 minutes. Following the control arm, subjects were randomized to receive SCS in the T1-T2 or T5-T6 segment of the spinal cord. SCS was turned on in the region of the spinal cord that was randomly selected for initial treatment. A second CPT was administered for 2 minutes starting approximately 3 minutes after the onset of SCS. SCS was turned off 3 minutes after CPT completion and blood pressure data monitored for a recovery period of approximately 5 minutes. The SCS lead was then moved to the second region and stimulation turned on. A third CPT was administered for 2 minutes starting approximately 3 minutes after the onset of SCS. SCS was turned off 3 minutes after CPT completion and blood pressure monitored for an additional 5 minutes. SCS crossover and a control arm were included in this study design so that subjects served as their own control. SCS locations were consistent across subjects and the data was summarized to identify consistent responses across subjects. The subjects were asked to rate their pain levels using a numeric pain rating, the Visual Analogue Score (VAS; a scale of 1 = no pain to scale 10 = excruciating pain). Pain levels were rated during baseline (shortly after the 2 leads were implanted) and also during SCS at the T1-T2 and T5-T6 regions (Fig. 2).

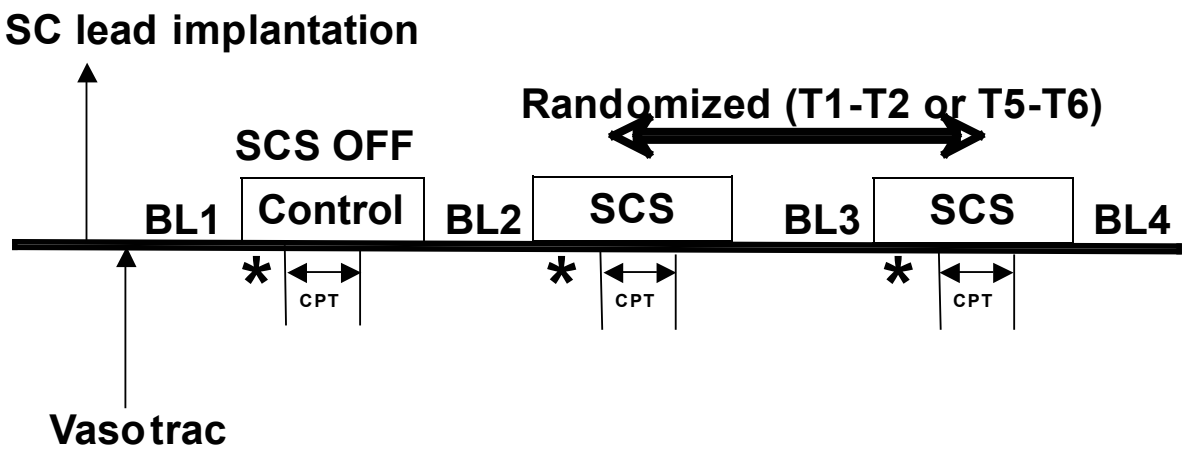

Fig. 2. *Experimental Protocol: BL=Baseline recording (5 min); CPT=Cold Pressor Test (2 min); *=Visual Analogue Pain Score.*

Data Analysis

Two patients did not appropriately respond to the CPT and were excluded from the data analysis because they were not able to continuously immerse their hand in ice cold water for the 2 minutes duration. A total of 4 baseline values were obtained during the protocol. The first baseline (BL1) was measured shortly after the 2 leads were implanted either in the T1-T2 or T5-T6 region as randomized and immediately prior to the initiation of the control CPT (SCS turned off). The second baseline (BL2) was measured prior to beginning the SCS at the first randomized spinal cord region; the third baseline (BL3) was measured prior to beginning the second randomized spinal cord region, and the fourth baseline (BL4) was measured after the SCS was turned off for approximately 5 minutes. The MAP and HR baseline values were obtained by measuring the mean over approximately a 2-minute period immediately prior to an intervention (CPT, SCS, or SCS+CPT). Similarly, the MAP and HR values during the CPT period of 2 minutes or SCS over the last 2 minute time period were averaged and used for comparisons and to calculate the percent change over baseline. The data was analyzed using a One Way Repeated Measures ANOVA, paired t-test or Wilcoxon signed rank test. A P value of < 0.05 was considered significant. All statistical analyses were performed using the SigmaStat version 3.1 (Systat Software Inc., Richmond, California).

Results

Effect of Control CPT on Hemodynamics and HR

The systolic and diastolic pressures increased significantly during the control CPT compared to baseline. SBP and DBP increased by 12.5±5.4 mmHg (P <0.001) and 7±4.3 mm Hg (P=0.002), respectively compared to baseline. The heart rate also increased significantly by 3.1±2.6 beats per minute (P =0.01) compared to baseline (Table 2). Fig. 3 shows changes in MAP at baseline and during the two minute CPT in the absence of SCS. Sympathetic activation by CPT increased MAP from a baseline value of 106 ±4.3 mmHg to 115.4±2.9 mmHg (P <0.001) in the absence of SCS.

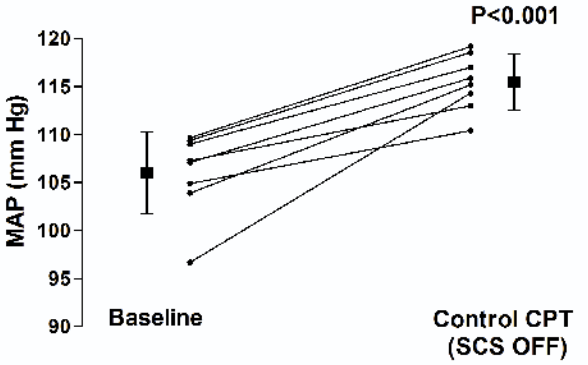

Fig.3. *Mean Arterial Pressure at baseline and during the 2 -minute Cold Pressor Test in the absence of SCS. Data are mean ± SD.*

Table 2. *Changes in systolic, diastolic, mean arterial pressure, and heart rate during only SCS and during SCS+ CPT. Values are mean±SD from 8 subjects.*

PROTOCOL	Mean Systolic Pressure	Mean Diastolic Pressure	Mean Arterial Pressure	Mean Heart Rate
BL1	141.9 ± 6.2	84.2 ± 4.6	106.0 ± 4.3	78.4 ± 12.5
CONTROL CPT	154.4 ± 4.2	91.3 ± 1.5	115.4 ± 2.9	81.5 ± 10.9
BL2	144.3 ± 8	85.3 ± 7.4	108.2 ± 7.5	76.0 ± 9.7
SCS @ T1/T2	148.6 ± 10.5	86.9 ± 7.3	110.2 ± 8.1	77.0 ± 9.8
SCS @ T1-T2+ CPT	156.6 ± 8.4	93.4 ± 6.8	117.4 ± 6.4	80.5 ± 13.3
BL3	148.6 ± 9.4	87.4 ± 7.2	110.7 ± 7.8	77.4 ± 13
SCS @ T5-T6	144.8 ± 10.7	84.0 ± 4.8	107.6 ± 7.4	74.7 ± 10.4
SCS @ T5-T6 + CPT	160.6 ± 10.9	95.8 ± 8	121.4 ± 9.2	78.9 ± 12
BL4	143.1 ± 9.8	83.1 ± 5.2	106.3 ± 6.4	77.6 ± 11.2

BL= baseline.

Effect of SCS at T1-T2 Region on Hemodynamics and HR:

Fig. 4 shows the effect of SCS at T1-T2 region on MAP and HR in 8 patients. Five out of 8 patients showed an increase in MAP and 6 out of 8 patients showed an increase in HR during SCS at T1-T2 region. Compared to baseline, SCS at the T1-T2 region significantly increased SBP by 4.3±5.1 mmHg (P<0.05; Table 2). However, DBP increased by only 1.5±3.3 mmHg (P=0.23; Table 2). SCS at this region resulted in a moderate insignificant increase in MAP by 2±3.8 mmHg and mean HR by 1±2.5 beats per minute (Figs. 4A & 4C; Table 2) compared to baseline. SCS at T1-T2 region during CPT also caused a slight increase in MAP by 2±6.6 mmHg and a drop in HR by 1±3.8 beats per minute respectively (Figs. 4B and 4D; Table 2) compared to control CPT (SCS turned off). None of these changes were significant.

Effect of SCS at T5-T6 Region on Hemodynamics and HR:

Compared to baseline, SCS at T5-T6 region decreased SBP and DBP by 3.8±9.8 mmHg (P =0.03) and 3.5±6.3 mmHg (P =0.16), respectively (Table 2). The effect of SCS at T5-T6 region on MAP and HR in 8 patients is shown in Fig. 5. Five out of 8 patients showed a decrease in MAP and in HR during SCS at T5-T6 region. SCS at the T5-T6 region resulted in an insignificant decrease in both MAP by 3.1±7.7 mmHg and mean HR by 2.7±4.3 beats per minute (Figs. 5A & 5C; Table 2), compared to baseline. SCS at the T5-T6 region during the CPT caused a significant increase in MAP by 5.9±7.1 mmHg (P<0.05) and a marginally significant (P =0.07) reduction in HR by 2.6±3.4 beats per minute, respectively (Figs. 5B and 5D; Table 2) compared to the control CPT (SCS turned off).

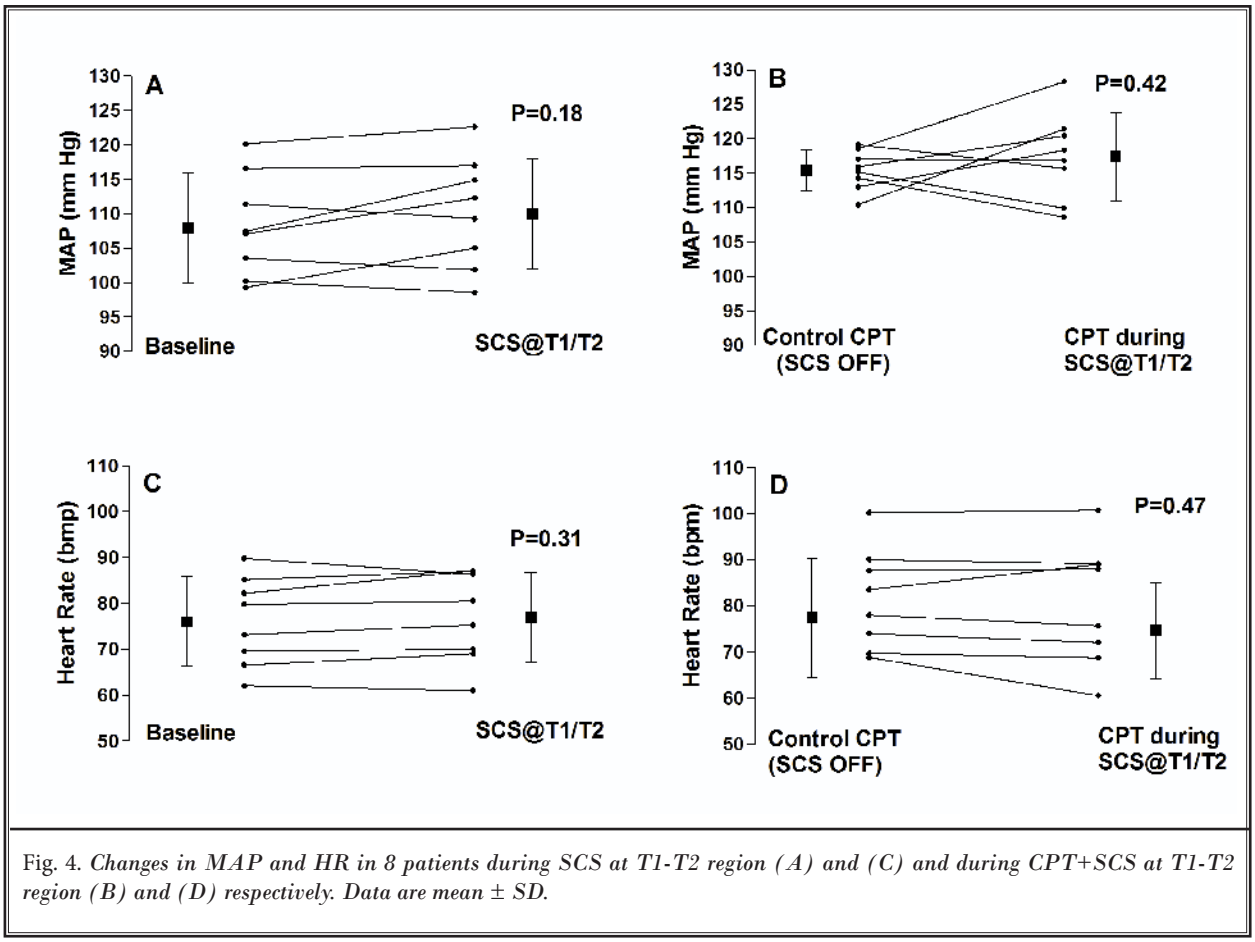

Fig. 4. *Changes in MAP and HR in 8 patients during SCS at T1-T2 region (A) and (C) and during CPT+SCS at T1-T2 region (B) and (D) respectively. Data are mean ± SD.*

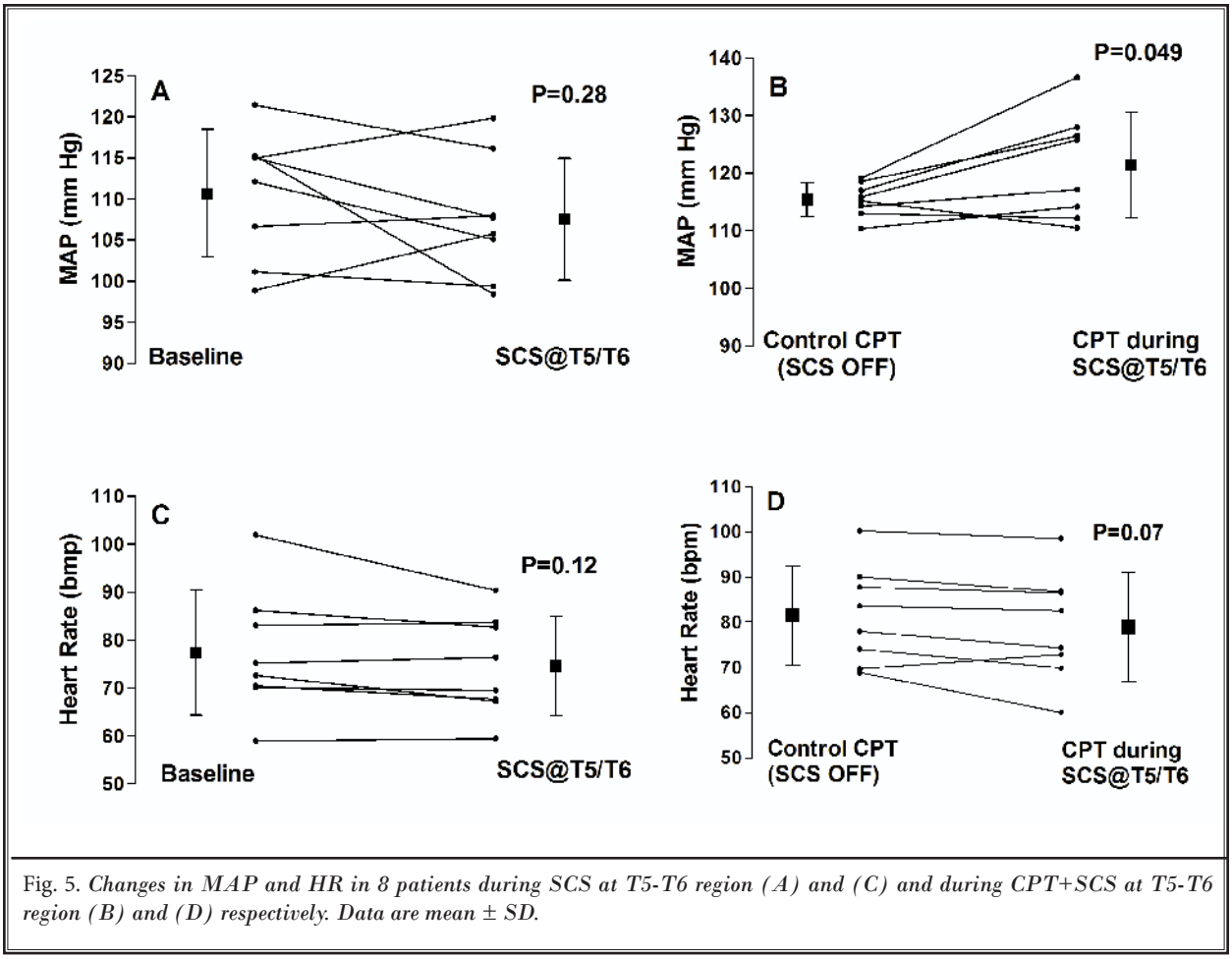

Fig. 5. *Changes in MAP and HR in 8 patients during SCS at T5-T6 region (A) and (C) and during CPT+SCS at T5-T6 region (B) and (D) respectively. Data are mean ± SD.*

Discussion

This study demonstrated that brief periods (8 – 10 minutes) of SCS at either the T1-T2 or T5-T6 region did not significantly alter the MAP or HR. However, SCS at the T1-T2 region caused a slight increase in HR and MAP, which is not consistent with previous data in the literature. Sympathetic fibers innervate the heart from the level of the superior cervical ganglion from spinal levels T1 through T4 while T5-T6 spinal regions provide sympathetic fibers to blood vessels (13). Several studies have shown that the peripheral resistance of the vasculature decreases with SCS (4,7), in turn decreasing the afterload the ventricles must pump against. Thoracic SCS has been shown to decrease firing of neurons of the spinothalamic tract and suppress the excitatory capacity of intrinsic cardiac neurons (3). Thoracic SCS has also been shown to activate sensory afferent fibers (3) and it is likely that the stimulation intensity used in our study would induce activation of the dorsal column. Thoracic SCS (in the region where sensory afferents project) may produce excitatory stimulation to higher centers in the brain stem and hypothalamus, mimicking sympathetic activation. This then would produce a reflex parasympathetic outflow to the heart.

Issa et al (6) have recently demonstrated in canines that 15 minutes of thoracic SCS significantly decreased sinus rate by 7.5 bpm, increased the PR interval by 11 ms, and reduced systolic blood pressure by 9.8 mmHg. These findings may be due to autonomic modulation as the findings from this study are consistent with en-

hancement of vagal tone and/or withdrawal of sympathetic tone with SCS. 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. The results we obtained during stimulation of the T1-T2 spinal cord region, however, do not support this contention. Levin and Hubschmann (14) studied the effect of SCS for 20 minutes in a patient with multiple sclerosis and showed that there was a moderate decrease in blood pressure during SCS at the T5-T6 region.

Foreman et al. (3) proposed that intrinsic cardiac neuron activity is modulated by SCS, most specifically the input of intrathoracic sympathetic nerves to the heart and showed that SCS suppressed activity generated by intrinsic afferent sensory cardiac neurons. Several previous studies have shown that SCS modulates the autonomic nervous system. Olgin et al (5) showed that, in a canine model, SCS slowed the sinus rate and prolonged conduction time through the AV node, and that effect appeared to be mediated by the vagus nerve. Our study showed that SCS appears to enhance parasympathetic activity or decrease sympathetic tone in the T5-T6 region compared to the T1-T2 region of the spinal cord. Although only SCS at T5-T6 region resulted in a moderate drop in MAP by 3.1±7.7 mmHg, SCS at the T5-T6 region during concomitant CPT increased MAP significantly by 5.9±7.1 mm Hg compared to the control CPT (SCS off). This increase in MAP could have stimulated the baroreceptors in the carotid sinus. Afferent baroreceptor activity at the Nucleus Tractus Solitarius (NTS) region in the brain stem is known to influence the vasomotor center which regulates the sympathetic nervous system. Thus an active NTS during CPT+SCS at the T5-T6 region could have inhibited the sympathetic outflow and stimulated the parasympathetic outflow resulting in a modest drop of HR by 2.6±3.4 beats per minute. Cui et al (19) studied baroreceptor modulation of muscle sympathetic nerve activity (MSNA) and HR in 10 normal subjects during the CPT and showed that baroreceptors were capable of modulating MSNA and HR during the CPT.

During epidural SCS, the current may spread into the lateral columns of the spinal cord and inhibit sympathetic outflow. It is possible that the observed trend in reduction of MAP and HR during the stimulation of the T5-T6 spinal region may be due to inhibition of the sympathetic activity. SCS in the T5-T6 region may reduce sympathetic outflow by attenuating efferent sympathetic activity and inducing vasodilation of the peripheral microcirculation. Thoracic SCS has also been shown to cause peripheral vascular vasodilation mediated by nitric oxide (15) and release of the vasodilator calcitonin gene-related peptide-CGRP (8). The slight rise in heart rate evoked by SCS at the T1-T2 region could have been due to a direct stimulation of sympathetic preganglionic efferent fibers that exit the cord in the ventral roots. However, we consider this possibility unlikely since the stimulus voltage was below the threshold for efferent motor neuron stimulation, and probably also below the threshold for efferent sympathetic stimulation, since these fibers are usually less excitable than the large motor neurons in the ventral roots.

Preliminary studies indicate that SCS has a positive effect on myocardial ischemia. Several studies performed during acute pain showed that treatment with SCS reduced ST-segment depression and promoted increased exercise tolerance, decreased the need for nitrates and increased perfusion of myocardial tissue. Studies in patients with refractory angina pectoris have also reported reduction of objective signs of myocardial ischemia, including exercise-induced ST-segment depression and spontaneous transient ischemic episodes on Holter monitoring with SCS (2,16-18). SCS has also been reported to exert long-term anti-ischemic effects (18). Sanderson et al (20) assessed severe angina pectoris patients with right atrial pacing during SCS. Pacing was started at a rate of 100 bpm and increased in increments of 10 bpm. BP was measured during pacing, with SCS first turned off, then on and off again, with a 30 minute interval. The systolic BP decreased from 135 mmHg (SCS off) to 124 mm Hg (SCS on) at maximum heart rate (150 bpm).

This study has several important limitations. The interventions were not totally randomized. Not all patients were able to keep their hand in ice water for 2 minutes. SCS was applied for short duration of about 8 – 10 minutes, while in most clinical studies it is maintained for much longer time periods. All patients received light sedation during the implantation procedure. This could have altered their MAP and HR. All patients were having neuropathic pain at the time of study and this could have influenced the results as well. Another limitation is the lack of power due to the small sample size.

Conclusion

This study demonstrated that SCS at either the T1-T2 or T5-T6 region did not significantly alter MAP or HR compared to baseline. At the T5-T6 region, only SCS reduced the mean arterial blood pressure to a moderate extent, consistent with the previously known antisympathetic effect of SCS in animals. However, during an elevated sympathetic tone induced by CPT, SCS at the T5-T6 region increased MAP significantly. The T1-T2 spinal region is targeted routinely in drug refractory angina pectoris patients and the results of this study raise the possibility that the relief of angina due to stimulation at the T1-T2 might be unrelated to changes in HR or MAP induced by SCS. The rise in HR and MAP in response to SCS at T1-T2 region is not consistent with previous data in experimental animals. Acute SCS did not result in adverse cardiovascular responses and proved to be safe.

References

1. Shealy CN, Mortimer TJ, Reswick JB: Electrical inhibition of pain by stimulation of the dorsal columns: Preliminary clinical report. *Anesth Analg* 1967; 46:489-491.
2. Schoebel FC, Frazier H, Jessurun GAJ, De Jongste MJL, Kadipasaoglu KA, Jax TW, Heintzen MP, Cooley DA, Strauer BE, Leschke M: Refractory angina pectoris in end-stage coronary artery disease: Evolving therapeutic concepts. *Am Heart J* 1997; 134:587-602.
3. Foreman RD, Linderoth B, Ardell JL, Barron KW, Chandler MJ, Hull SS, TerHorst GJ, DeJongste MJL, Armour JA. Modulation of intrinsic cardiac neurons by spinal cord stimulation: implications for its therapeutic use in angina pectoris. *Cardiovascular Research* 2000; 47:367-375.
4. Tanaka S, Barron KW, Chandler MJ, Linderoth B, Foreman RD. Low intensity spinal cord stimulation may induce cutaneous vasodilation via CGRP release. *Brain Res* 2001; 896:183-187.
5. Olgin JE, Takahashi T, Wilson E, Vereckei A, Steinberg H, Zipes DP. Effects of thoracic spinal cord stimulation on cardiac autonomic regulation of the sinus and atrioventricular nodes. *J Cardiovasc Electrophysiol* 2002; 13:475-481.
6. Issa ZF, Zhou X, Ujhelyi MR, Rosenberger J, Bhakta D, Groh WJ, Miller JM, Zipes DP. Thoracic spinal cord stimulation reduces the risk of ischemic ventricular arrhythmias in a postinfarction heart failure canine model. *Circulation* 2005; 111:3217-3220.
7. Linderoth B, Herregodts P, Meyerson BA. Sympathetic mediation of peripheral vasodilation induced by spinal cord stimulation: Animal studies of the role of cholinergic and adrenergic receptor subtypes. *Neurosurgery* 1994; 35:711-719.
8. Croom JE, Foreman RD, Chandler MJ, Barron KW. Cutaneous vasodilation during dorsal column stimulation is mediated by dorsal roots and CGRP. *Am J Physiol* 1997; 272(2 Pt 2):H950-957.
9. Tanaka S, Komori N, Barron KW, Chandler MJ, Linderoth B, Foreman RD. Mechanisms of sustained cutaneous vasodilation induced by spinal cord stimulation. *Auton Neurosci* 2004; 114:55-60.
10. Hagbarth KE, Hallin RG, Hongell A, Torebjork HE, Wallin BG. General characteristics of sympathetic activity in human skin nerves. *Acta Physiol Scand* 1972; 84:164-176.
11. Delius W, Hagbarth KE, Hongell A, Wallin BG. General characteristics of sympathetic activity in human muscle nerves. *Acta Physiol Scand* 1972; 84:65-81.
12. Belani KG, Buckley JJ, Poliac MO. Accuracy of radial artery blood pressure determination with the Vasotrac. *Can J Anaesth* 1999; 46(5 Pt 1):488-496.
13. Netter, FH. *Atlas of Human Anatomy. 2nd Edition*. Novartis Publishing, East Hanover, New Jersey, 1997, pp 167.
14. Levin BE, Hubschmann OR. Dorsal column stimulation: Effect on human cerebrospinal fluid and plasma catecholamines. *Neurology* 1980; 30:65-71.
15. Croom JE, Foreman RD, Chandler MJ, Koss MC, Barron KW: Role of nitric oxide in cutaneous blood flow increases in the rat hindpaw during dorsal column stimulation. *Neurosurgery* 1997; 40:565-570.
16. Andersen C: Does heart rate variability change in angina pectoris patients treated with spinal cord stimulation? *Cardiology* 1998; 89:14-18.
17. Mannheimer C, Eliasson T, Augustinsson LE, Blomstrand C, Emanuelsson H, Larsson S, Norrsell H, Hjalmarsson A. Electrical stimulation versus coronary artery bypass surgery in severe angina pectoris. The ESBY Study. *Circulation* 1998; 97:1157-1163.
18. Di Pede F, Lanza GA, Zuin G, Alfieri O, Rapati M, Romano M, Circo A, Cardano P, Bellocci F, Santini M, Maseri A. Immediate and long-term clinical outcome after spinal cord stimulation for refractory stable angina pectoris. *Am J Cardiol* 2003; 91:951-955.
19. Cui J, Wilson TE, Crandall CG. Baroreflex modulation of muscle sympathetic nerve activity during cold pressor test in humans. *Am J Physiol Heart Circ Physiol.* 2002; 282:H1717-1723.
20. Sanderson JE, Brooksby P, Waterhouse D, Palmer RB, Neubauer K. Epidural spinal electrical stimulation for severe angina: A study of its effects on symptoms, exercise tolerance and degree of ischemia. *Eur Heart J* 1992; 13:628-633.