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Dissociation between reduced pain and arterial blood pressure following epidural spinal cord stimulation in patients with chronic pain: A retrospective study

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Abstract

Acute pain and resting arterial blood pressure (BP) are positively correlated in patients with chronic pain. However, it remains unclear whether treatment for chronic pain reduces BP. Therefore, in a retrospective study design, we tested the hypothesis that epidural spinal cord stimulation (SCS) implantation to treat chronic pain would significantly reduce clinic pain ratings and BP and that these reductions would be significantly correlated. Pain ratings and BP in medical records were collected before and after surgical implantation of SCS at the University of Iowa Hospitals and Clinics between the years 2008 to 2018 (n=213). Reductions in pain rating [6.3 ± 2.0 vs. 5.0 ± 1.9 (scale:0-10), $P<0.001$] and BP [mean BP (MAP): 95 ± 10 vs. 89 ± 10 mmHg, $P<0.001$] were statistically significant within 30 days of SCS. Interestingly, BP returned toward baseline within 60 days following SCS implantation. Multiple linear regression analysis showed that sex ($P=0.007$), baseline MAP ($P<0.001$), and taking HTN meds ($P<0.001$) were significant determinants of MAP (model $R^2=0.33$). After statistical adjustments, MAP was significantly greater among women compared with men (-7.2 ± 8.5 vs. -3.9 ± 8.5 mmHg, $P=0.007$) and among patients taking HTN medications compared with patients not taking HTN medications (-10.1 ± 8.7 vs. -3.9 ± 8.5 mmHg, $P<0.001$), despite no group differences in pain. These findings suggest that SCS for chronic pain produces significant, albeit transient, reductions in BP. However, in

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Author Contributions

All authors of this research paper have directly participated in the study's conception and design, the drafting and revision of this paper, and final approval of the version to be published.

Conflict of Interest Disclosure

The authors have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter discussed in this manuscript. A patent is currently pending for use of epidural spinal cord stimulation to increase peripheral blood flow (S.W.H., M.T.H., G.L.P.).

contrast to our hypothesis, there was no association between reductions in pain and BP following SCS implant.

Keywords

pain; blood pressure; hypertension; spinal cord stimulation; neuropathic

Introduction

Chronic pain is associated with elevated arterial blood pressure (BP) and hypertension (HTN) [1–3]. The presence of HTN, and even high-normal BP, significantly increases the risk of coronary events and stroke and is a major healthcare burden [4]. Large epidemiological studies demonstrate that chronic pain is associated with a 23% increase in prevalence of HTN [2]. Similarly, controlled studies of chronic pain patients showed that diagnosis of HTN was present among 39% compared with 21% of tertiary care patients reporting no chronic pain [1]. However, despite the clear association between chronic pain and HTN, the mechanisms linking these two are not completely understood.

In healthy individuals, resting BP is inversely associated with acute pain sensitivity where elevated BP increases pain threshold and tolerance [5–8]. The central mechanisms by which elevated BP increases pain tolerance have been discussed previously [9–11] and include neural pathways such as stimulation of arterial baroreceptors which activate descending inhibitory pathways of pain. In this way, acutely and chronically elevated BP diminishes spinal nociceptive transmission, which is observed in genetically hypertensive rats [12], and produces decreased pain sensitivity. Indeed, decreased pain sensitivity can be reversed by lowering BP in genetically hypertensive rats [13–15], although some evidence suggests that decreased pain sensitivity in hypertensive humans may not be reversed following anti-hypertensive treatment [16]. There is also a role for endogenous opioid activity in hypertension-related reductions in pain sensitivity [13,15,17,18], including evidence of increased endogenous opioid activity associated with baroreceptor stimulation [19].

In contrast to healthy individuals, elevations in BP do not produce hypoalgesia (reduced pain sensitivity) in patients with chronic pain [2,7]. For example, in patients with chronic low back pain, higher BP is associated with lower pain threshold and greater pain intensity [7]. The reversal of the association between pain sensitivity and BP among patients with chronic pain may involve a dysfunctional interaction between systems regulating pain and BP [5–7,2]. There are known functional links between brain structures that contribute to regulation of pain perception and BP, such as the periaqueductal gray and rostral ventromedial medulla [20–22], that may become dysfunctional in states of chronic pain and affect activity of descending pain inhibition. Together, there is convincing evidence that patients with chronic pain exhibit dysfunction in central regulatory systems that is demonstrated by a parallel increase in pain sensitivity and resting BP. However, despite the large body of literature, it remains unclear whether treatment for chronic pain leads to a parallel reduction in BP.

Therefore, we sought to examine whether BP is reduced following treatment for patients with chronic pain, and to what extent reductions in BP are correlated with reductions in pain.

To address these specific questions, we performed a retrospective study in which electronic medical records were surveyed among a large sample of patients that received epidural spinal cord stimulator (SCS) implantation for chronic pain. Epidural SCS is commonly used to treat patients with chronic pain originating in the peripheral nervous system (neuropathic pain) [23,24]. Although SCS has been routine therapy for several decades, no studies have directly assessed BP responses to SCS in patients with chronic pain. We hypothesized that clinic pain ratings and BP would be significantly reduced following SCS implantation and that reduced pain would be a significant determinant of the reduction in BP.

Methods

This study conformed to the Declaration of Helsinki and was approved by the Institutional Review Board at the University of Iowa (Project#: 201805969).

Data collection:

Review of electronic medical records (EMR) was performed on patients at the University of Iowa Hospitals and Clinics (UIHC) that underwent surgical implantation of SCS to treat chronic pain originating in the lower back and/or limbs between the years 2008 to 2018 with no criteria for exclusion. EMR were analyzed using TriNetX (TriNetX, Inc., Cambridge, MA), which is a research network that provides access to de-identified patient statistics directly from health care information systems [25]. The EMR utilized at UIHC are managed by Epic health care information system (Epic Systems Corporation, Verona, WI). Waiver of informed consent was granted by the institutional review board (IRB) for this retrospective study as only statistical summaries of de-identified information without protected health information is received via TriNetX [26]. Patient confidentiality was protected by assigning numerical identifiers to each record and by only collecting information necessary to answer the research question. The data query included sex, date of birth, date of SCS implantation surgery, all entries of pain ratings and systolic and diastolic BP within 90 days before and after the date of SCS implantation surgery, and all entries of prescription medications for BP. The length of time that patients had been taking HTN medications was unknown because the duration of prescription drug use was not retrievable via TrinNetX. However, prescriptions for HTN medication likely did not change at the time of surgery because treatment for HTN was not part of the standard of care. Pain intensity was scored using the Visual Analogue Scale for pain (VAS) [27], which is a 0-10-point scale (0 = no pain, 10 = worst pain possible). Test-retest reliability of the VAS has been established [28,29] and demonstrates sensitivity to detect changes in pain [30,31]. BP was measured in the clinic using an automated oscillometric arm cuff in the seated position for the purpose of patient care.

Spinal cord stimulation:

The epidural SCS system consists of a lead wire with up to 16 electrodes implanted posterior to the dorsal columns of the spinal cord outside the dura mater and an implantable impulse generator and battery to deliver electrical current. [32,23,33] The final electrode position on the dorsal column is typically determined by induction of paraesthesiae in the same area of pain with electrodes in proximity of T6-T10 or C2-C5 depending on symptoms. No

patients received dorsal root ganglion (DRG) stimulation. SCS electrode implant locations and programming configurations for cases of chronic pain have been described in detail [33]. The SCS device is controlled via a hand-held wireless remote, which has the capability to turn the device on and off and adjust programs that determine the waveform, pulse frequency, pulse width, and amplitude. Patients are instructed in the use of the SCS device and allowed to adjust the stimulation program and level of stimulation (voltage) within a preset range as needed to treat their pain. The time duration and level of stimulation outside of the clinic was not controlled for in this study because of the heterogeneity in pain symptoms among patients.

Data analysis:

Review of medical records indicated 611 patients from UIHC received SCS surgical implants between the years 2008 and 2018. Of the 611 patients that received SCS implants, 213 patients had one or more records of pain rating and BP within 90 days prior to SCS implantation (baseline) and one or more records of pain rating and BP within 30 days following SCS implant. Pain ratings and BP values entered into electronic medical records within 90 days prior to SCS implantation were averaged for each patient to represent baseline. The rationale for averaging pain ratings and BP within 90 days prior to SCS was to minimize the influence of any potential aberrant entries and to obtain the most representative values for each patient. Analyses excluded data on the day of the SCS implant. Given that pain and BP were assessed for patient care, the day and time of pain ratings and BP measurements were not standardized, i.e., patients had different numbers of pain ratings and BP recordings that were taken on different days. Therefore, pain ratings and BP values were averaged for each patient before and after the SCS implant. MAP was calculated as $[(1/3) \cdot (\text{systolic BP} - \text{diastolic BP})] + \text{diastolic BP}$.

To begin to examine temporal changes in pain ratings and BP following SCS implantation, values entered into electronic medical records were averaged into increments of 30 days (within 1-30 days, 31-60 days, and 61-90 days following SCS implant). However, the number of available electronic medical records for each patient that included pain ratings and BP beyond 30 days following SCS implant was markedly reduced. Twenty-one patients that had 1 pain rating at all time points, and 46 patients had 1 BP measurement at all time points. Therefore, the primary analysis focused on the change in pain ratings and BP from baseline to 30 days following SCS implant, although additional examination of records beyond 30 days was performed among patients with measurements at all time points. Also, since day-to-day pain ratings can be variable, weighted means were determined to limit the skew produced by outlier values. When determining the weighted mean for each patient, the contribution of each pain rating to the mean was inversely proportional to the deviation from the mean. For example, the mean of three pain ratings 9, 9, and 1, is 6.3, but the weighted mean is 6.6 because the contribution of the pain rating 1 is less relative to 9 and 9. Importantly, weighted means did not change the overall results.

Statistical analysis:

Bivariate regression analysis and Pearson's correlation coefficient were used to test the strength of associations between pain ratings, age, and BP. Multiple linear regression was

used to examine whether any of the independent variables (age, sex, pain rating, BP, and taking HTN meds) were significant determinants of changes in pain and BP following SCS implant. Repeated measures one-way analysis of variance (ANOVA) was used to examine changes in pain ratings and BP following SCS implant and the Holm-Sidak method was used for pairwise comparisons. Analysis of covariance (ANCOVA) was used to determine differences between groups (men vs. women, patients taking HTN medications vs. not taking HTN medications) after adjusting for confounders (age, sex, pain rating, BP, and taking HTN meds). Data are presented as mean $\pm$ SD.

Results

Patient characteristics:

Patient characteristics including baseline pain scores, BP, and prescription medications, are described in Table 1. On average, patients had elevated BP based on recently established thresholds for BP stratification [34]. Cases were primarily failed back surgery syndrome (FBSS) with a minority of cases being complex regional pain syndrome (CRPS), all displaying neuropathic features responsive to SCS.

Pain ratings before SCS implant (baseline):

Pain ratings (0-10-point scale) before SCS implant were similar ($P=0.97$) when calculated as a mean (6.3 ± 2.0) (Table 1) and weighted mean (6.3 ± 2.0) for each patient. Results from multiple linear regression analysis (independent variables: age, sex, MAP, and taking HTN meds) showed that only age ($P=0.009$) and MAP ($P=0.003$) were significant determinants of pain rating (model $R^2=0.08$, $P=0.001$) (Table 2). When considering weighted means for pain ratings, similar results were observed in the multiple linear regression analysis, including statistical significance for age ($P=0.011$) and MAP ($P=0.007$) (model $R^2=0.08$, $P=0.002$). Higher pain rating was inversely associated with age (bivariate correlation analysis: $R=-0.21$, $P=0.003$) (Figure 1A) and positively associated with MAP (bivariate correlation analysis: $R=0.21$, $P=0.002$) (Figure 1B). The positive association between pain rating and MAP was driven primarily by the association between pain rating and diastolic BP ($R=0.25$, $P<0.001$) rather than systolic BP ($R=0.10$, $P=0.136$).

Pain ratings following SCS implant:

Pain rating was significantly lower within 30 days following SCS implant ($P<0.001$) (Figure 2, left panel). Similar results were observed when considering weighted means (6.3 ± 2.0 vs. 5.0 ± 1.9 , $P<0.001$). When considering all time points (i.e., baseline and within 30, 60, and 90 days following SCS implant) and patients with pain ratings at all time points ($n=21$), a statistically significant change in pain rating was not observed ($P=0.32$) (Figure 2, right panel). Similar results were observed when considering weighted means (Baseline: 6.9 ± 1.4 ; 30 days: 6.1 ± 2.0 ; 60 days: 6.2 ± 2.3 ; 90 days: 6.6 ± 1.6 , $P=0.32$).

Results from multiple linear regression analysis (independent variables: age, sex, baseline pain rating, baseline MAP, MAP, and taking HTN meds) among all patients ($n=213$) showed that only baseline pain rating ($P<0.001$) and age ($P<0.001$) were significant determinants of the reduction () in pain rating within 30 days following SCS implant

(model $R^2=0.45$, $P<0.001$) (Table 2). Similar results were observed when considering weighted means for pain rating for each patient (model $R^2=0.46$, $P<0.001$), including statistical significance for baseline pain rating (weighted means) ($P<0.001$) and age ($P<0.001$). Thus, in contrast to our hypothesis, the reduction in pain rating following SCS implant was not associated with the reduction in BP. The reduction in pain rating was associated with greater baseline pain rating and advanced age.

Clinic BP following SCS implant:

Significant reductions were observed in systolic BP (-6 ± 15 mmHg), diastolic BP (-7 ± 9 mmHg), and MAP (-7 ± 10 mmHg) within 30 days following SCS implant compared with baseline (Figure 3, left panels). If using more stringent inclusion criteria, such as 3 BP measures in medical records at baseline and within 30 days following SCS implant ($n=64$), results were not significantly different for systolic BP (-9 ± 12 mmHg, $P=0.27$), diastolic BP (-7 ± 8 mmHg, $P=0.31$), and MAP (-7 ± 9 mmHg, $P=0.25$) compared with the selected inclusion criteria of 1 BP measure at baseline and within 30 days following SCS implant described above. Interestingly, systolic BP, diastolic BP and MAP were significantly greater at 60 days following SCS implant compared with 30 days among patients that had BP measures in medical records at all time points ($n=46$) (Figure 3, right panels). These results demonstrate a transient reduction in BP that returns towards baseline within 60 days following SCS implant.

Results from multiple linear regression analysis (independent variables: age, sex, baseline pain, pain, baseline MAP, and taking HTN meds) showed that sex ($P=0.007$), baseline MAP ($P<0.001$), and taking HTN meds ($P<0.001$) were significant determinants of MAP within 30 days following SCS implant (model $R^2=0.33$, $P<0.001$) (Table 2). By using partial regression plots, Figure 4 contrasts the (lack of) association between MAP and pain (Panel A) and the negative association between MAP and baseline MAP (Panel B) while holding the remaining independent variables constant in the multiple linear regression analysis. Similar results were observed when considering systolic BP (model $R^2=0.31$) and diastolic BP (model $R^2=0.31$) as dependent variables in place of MAP, except that sex was not a significant determinant of systolic BP ($P=0.089$).

Sex differences in clinic BP following SCS implant:

Since sex was a significant determinant of the change in BP following SCS implant, further analyses were performed among men and women separately. Sex comparisons at baseline are described in Table 1. Like results observed when men and women were combined (i.e., Figure 3), MAP was significantly reduced within 30 days following SCS implant among men (Figure 5A, left panel) and women (Figure 5B, left panel). When considering all time points (i.e., baseline and within 30, 60, and 90 days following SCS implant) and patients with BP measurements at all time points, MAP was significantly greater within 60 days following SCS implant compared with 30 days among men and women (Figure 5A,B, right panels). Among women, similar results were observed when considering systolic BP ($P<0.001$) and diastolic BP ($P<0.001$) for the analysis of all time points. Among men, similar results were observed for diastolic BP ($P=0.025$) for the analysis of all time points, although there was no significant change when considering systolic BP ($P=0.11$).

There were no significant differences between women and men in systolic BP (Women, -7.3 ± 15.3 vs. Men, -4.7 ± 14.4 mmHg, $P=0.216$), diastolic BP (Women, -6.2 ± 9.2 vs. Men, -4.5 ± 8.9 mmHg, $P=0.170$), and MAP (Figure 4C, left panel) within 30 days following SCS implant. However, when controlling for potential confounding variables (baseline pain, pain, age, baseline MAP, and taking HTN meds) using analysis of covariance (ANCOVA), results showed that MAP within 30 days following SCS implant was significantly greater among women compared with men ($P=0.007$) (Figure 4C, right panel). Only baseline MAP ($P<0.001$) and taking HTN medications ($P<0.001$) were significant covariates, consistent with results from multiple regression analysis among the entire cohort. Similarly, ANCOVA showed that diastolic BP within 30 days of SCS implant was significantly greater among women compared with men (adjusted means $\pm$ SD: Women, -7.0 ± 7.8 vs. Men, -3.7 ± 7.8 mmHg, $P=0.002$), and systolic BP tended to be greater among women compared with men, but did not reach statistical significance (adjusted means $\pm$ SD: Women, -7.5 ± 12.6 vs. Men, -4.5 ± 12.6 mmHg, $P=0.089$). Overall, these results suggest a greater reduction in BP following SCS implant among women compared with men, particularly when controlling for confounding variables.

HTN medications and clinic BP following SCS implant:

Since taking HTN medications was a significant determinant of the change in BP following SCS implant, separate analyses were performed among patients taking HTN medications ($n=60$) and not taking HTN medications ($n=153$). Pain ratings were not different between patients taking and not taking HTN medications (6.1 ± 2.0 vs. 6.3 ± 2.0 , $P=0.53$). Baseline systolic BP was significantly greater among patients taking HTN medications compared with patients not taking HTN medications (137 ± 16 vs. 132 ± 14 mmHg, $P=0.033$), although there was no significant difference in diastolic BP (74 ± 10 vs. 77 ± 10 mmHg, $P=0.067$) and MAP (95 ± 10 vs. 95 ± 10 mmHg, $P=0.854$). Within 30 days following SCS implant, MAP was significantly lower among patients taking HTN medications (Figure 6A, left panel) and patients not taking HTN medications (Figure 6B, left panel) compared with baseline. When considering all time points (i.e., baseline and within 30, 60, and 90 days following SCS implant) and patients with BP measurements at all time points, MAP was significantly greater within 60 days following SCS implant compared with 30 days among patient taking HTN medications (Figure 6A, right panel) and not taking HTN medications (Figure 6B, right panel). Among patients taking HTN medications, similar results were observed when considering systolic BP ($P=0.002$) and diastolic BP ($P=0.001$) for the analysis of all time points. Among patients not taking HTN medications, similar results were observed when considering diastolic BP ($P<0.001$) for the analysis of all time points, whereas systolic BP within 30 days of SCS implant was significantly lower compared with baseline and 90 days ($P=0.019$).

When examined using ANCOVA and controlling for potential confounding variables (baseline pain, pain within 30 days following SCS, age, sex, baseline MAP), there was a significantly greater MAP within 30 days following SCS implant among patients taking HTN medications compared with patients not taking HTN medications ($P<0.001$) (Figure 6C). Only sex ($P=0.007$) and baseline MAP ($P<0.001$) were significant covariates. Similar results were observed when considering systolic BP (adjusted means $\pm$ SD: HTN meds,

-11.8 ± 13.0 vs. No HTN meds, -3.9 ± 12.8 mmHg, $P < 0.001$) and diastolic BP (adjusted means $\pm$ SD: HTN meds, -9.3 ± 7.9 vs. No HTN meds, -3.9 ± 7.8 mmHg, $P < 0.001$) as dependent variables in place of MAP, except that sex was not a significant covariate for systolic BP ($P = 0.089$).

The influence of HTN medications on MAP following SCS implant was examined among men and women separately (Figure 6D). Results from ANCOVA controlling for confounding variables (baseline pain, pain within 30 days following SCS, age, baseline MAP) showed that MAP within 30 days following SCS implant was significantly greater among men taking HTN medications compared with men not taking HTN medications ($P = 0.004$) (Figure 6D, left panel). Only baseline MAP was a significant covariate ($P < 0.001$). Similar results were observed when considering systolic BP ($P < 0.001$) and diastolic BP ($P = 0.001$). The same analysis among women showed that MAP within 30 days following SCS implant was significantly greater among women taking HTN medications compared with women not taking HTN medications ($P < 0.001$) (Figure 6D, right panel). Only baseline MAP was a significant covariate ($P < 0.001$). Similar results were observed when considering systolic BP ($P < 0.001$) and diastolic BP ($P = 0.004$). These results suggest no major difference between men and women in the influence of HTN medications on BP within 30 days following SCS implant.

Finally, there were no significant differences ($P = 0.78$) in MAP within 30 days following SCS implant among patients taking 1 HTN medication (-11.6 ± 9.1 mmHg, $n = 23$), 2 HTN medications (-8.7 ± 8.9 mmHg, $n = 20$), 3 HTN medications (-9.4 ± 9 mmHg, $n = 9$), and 4+ HTN medications (-9.7 ± 8.8 mmHg, $n = 8$). Data reported are means adjusted for covariates (ANCOVA), which include baseline pain, pain within 30 days following SCS, age, sex, and baseline MAP. Only baseline MAP was a significant covariate ($P < 0.001$). Similar results were observed for systolic BP ($P = 0.377$) and diastolic BP ($P = 0.620$). Although duration of HTN medication use and adherence could not be determined, it is unlikely that changes in BP following the SCS implant are a result of immediate changes in HTN medications because patients did not receive new HTN medication prescriptions at the time of SCS implantation.

Discussion

The present study examined whether BP is reduced following SCS implant in patients with chronic pain and the extent to which reductions in BP are related to reductions in pain. Three important and novel findings were observed. First, BP was significantly reduced following the SCS implant in addition to reduced pain ratings. However, in contrast to our hypothesis, reductions in pain ratings and BP following SCS implant were not related. Second, when controlling for confounding variables (ANCOVA), women demonstrated significantly greater reductions in BP following SCS implantation compared with men, despite no sex difference in the reduction in pain following SCS. Similarly, those taking HTN medications demonstrated significantly greater reductions in BP following SCS implantation compared with those not taking HTN medications, despite no difference in the reduction in pain following SCS. Together, these findings demonstrate transient reductions in BP following

SCS implantation. However, although SCS may mediate reductions in BP in addition to reductions in pain ratings, changes in BP and pain ratings were not associated.

Potential mechanisms mediating reductions in clinic BP following SCS

We hypothesized that reductions in pain following SCS would reduce BP given the association between chronic pain and elevated BP reported in the literature [1–3]. However, the significant reduction in BP observed within 30 days following SCS was not associated with the reduction in pain. Therefore, we speculate that SCS modulates pain sensitivity and BP through separate pathways. SCS may influence neural pathways involved in cardiovascular control in addition to inhibiting ascending pathways that convey nociceptive information. In regard to BP, studies suggest that SCS modulates activity of neurons within the intermediolateral column, which mediates sympathetic innervation of the body [35]. In support of this, previous work by Foreman and Linderorth have shown decreased sympathetic outflow with SCS in an animal model [36]. Also, studies in humans indicate that acute SCS can transiently reduce sympathetic outflow to the periphery [33]. It is possible that SCS activation of afferent sensory fibers in the dorsal columns stimulate GABAergic interneurons and inhibit sympathetic preganglionic neurons and peripheral release of norepinephrine [36].

Influence of HTN medications on clinic BP following SCS

The reductions in BP among patients receiving HTN medications (~28% of patients) was markedly greater compared with patients not receiving HTN medications. This was surprising since there was no significant difference between groups in the reduction in pain ratings following SCS. BP before SCS (baseline) was the only significant determinant of the reduction in BP following SCS implantation. That is, higher BP before SCS predicted larger reductions in BP. It is tempting to speculate that SCS and HTN medications may work synergistically to achieve reductions in BP. However, the reduction in BP following SCS was not significantly different between groups of patients taking 1, 2, 3, or 4+ HTN medications. Also, when examining separate HTN drug categories (renin-angiotensin system, calcium channel blockers, diuretics, adrenergic receptor blockers) and the associated reductions in BP, there were no significant differences between categories (data not shown in results). However, there are some limitations to these analyses because measures of adherence and compliance to HTN medications could not be obtained via our database [25]. Together, the results suggest that baseline BP was the prominent determinant of the reduction in BP following SCS, i.e., larger reductions in BP with higher baseline BP, and is likely reflected by HTN medications status. Prospective studies controlling for HTN medication use are needed to determine the interaction between SCS and HTN medications and the BP response among patients with chronic pain.

Sex differences in clinic BP following SCS

When controlling for potential confounding variables (baseline pain, pain, age, baseline MAP, and taking HTN meds), women exhibited significantly greater reductions in BP following SCS compared with men. These results were surprising given findings from large clinical studies showing that hypertensive women exhibit similar [37] or lower [38] rates of BP control in response to cardiovascular drug treatment compared with men. However, no studies have directly examined BP responses to SCS and potential sex differences. Evidence

suggests women have a lower pain threshold and a greater response to analgesics, both pharmacological and nonpharmacological, compared with men [39–41]. These data would predict larger BP responses to SCS if pain relief modulates the BP response. However, there was no sex difference in the reduction in pain following SCS, which is in accordance with previous studies demonstrating no sex difference in pain relief for conditions commonly indicated for SCS, including failed back syndrome, peripheral vascular disease, peripheral neuropathy, and other etiologies of chronic retractable pain [42]. Moreover, evidence suggests that the relation between BP and pain may be similar in men and women [43], further supporting the notion that reduced pain did not fully account for the reductions in BP. Together, these findings suggest that the mechanism(s) involved in the larger reductions in BP in response to SCS among women compared with men may involve pathways unrelated to pain such as neural control of the cardiovascular system.

Strengths and limitations

A major strength of the present study is examination of a substantial volume of already existing medical records (real world clinical data) to test the novel hypothesis. However, the frequency of clinic BP measurements were variable and not at the same time points for each patient. The variability in the frequency of clinic BP measurements limits the resolution needed to determine temporal changes in BP following SCS implant with high resolution. Also, the duration and intensity of stimulation and level of implant in spinal cord were not controlled. Since each patient has their own specific duration and intensity of stimulation and level of implant in spinal cord that produces optimal pain relief, the feasibility of controlling for stimulation parameters and achieving reductions in pain for a large group of patients is limited. On the other hand, allowing patients to use individual stimulation parameters for pain reduction provided the unique opportunity to address the hypothesis that reductions in pain would drive reductions in BP. In addition, although the Visual Analogue Scale for pain (VAS) has proven to be reliable [28,29] and demonstrates sensitivity to detect changes in pain [30,31], the detection of changes in pain in the present study may have been limited because the VAS does not adequately cover the full domain of neuropathic pain. Clinical measures specific to neuropathic pain and subgroups of neuropathic pain may have increased sensitivity [44]. Consequently, we cannot completely rule out that BP was reduced following SCS as a result of reduced pain that was not detected with the VAS. Finally, although the overall study design and the quantity of data captured was robust, the retrospective nature of the study places limitations on interpreting causality and warrants future prospective studies to determine the extent to which SCS reduces BP among patients with chronic pain and HTN.

Perspectives

A dysfunctional interaction between pain and cardiovascular regulatory systems exists among patients with chronic pain that results in a positive correlation between chronic pain and resting BP [5–7,2]. Results from the present study demonstrate a divergence between pain and resting BP following SCS. This is important because the association between chronic pain and HTN [1–3] may elevate the risk of coronary events and stroke [4]. Reductions in BP following SCS were particularly robust among patients taking HTN medications (systolic BP: –13 mmHg) compared with those not taking HTN medications

(systolic BP: -4 mmHg). In controlled clinical trials such as the HOPE-3 study, a reduction in systolic BP of -5.8 mmHg using pharmacological therapy in persons at intermediate risk was associated with a 28% lower incidence of major cardiovascular events compared with placebo [45]. Therefore, the observations in this retrospective study suggest a clinically meaningful reduction in BP among chronic pain patients using SCS. Clinical studies also indicate that 1 in 50 patients beginning HTN treatment would need 4 or more medications within 1.5 years of follow-up [46]. This is particularly concerning given the strong association between chronic pain and elevated BP [1–3]. Our findings suggest that clinically meaningful reductions in BP among patients with chronic pain may be more readily achieved with HTN medications in combination with SCS.

Conclusion

In summary, findings from this retrospective study suggest that SCS produces significant, albeit transient, reductions in BP among patients with chronic pain. Also, despite parallel reductions in pain ratings, we did not observe an independent correlation between reductions in BP and pain following SCS implant. Interestingly, women demonstrated significantly greater reductions in BP following SCS implant compared with men, and patients taking HTN medications demonstrated significantly greater reductions in BP following SCS implant compared with patients not taking HTN medications. These results provide a strong basis and rationale for controlled, prospective studies that further examine the efficacy of SCS to reduce BP among patients with chronic pain.

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Figure 1.

Bivariate correlation analysis between pain rating and age (Panel A) and mean arterial pressure (MAP) (Panel B) before epidural spinal cord stimulator (SCS) implant (n=213). Pain intensity was scored using the Visual Analogue Scale for pain (0-10, 0 = no pain, 10 = worst pain possible) and averaged over 90 days for each patient prior to SCS implant to represent baseline. Similarly, MAP was averaged over 90 days for each patient to represent baseline. Dashed lines indicate 95% confidence intervals.

Figure 2.

Box and whisker plots of pain ratings among patients with chronic pain before epidural spinal cord stimulator implant (baseline) and within 30 days following SCS implant (left panel), and among patients with pain ratings at all time points (baseline and within 30, 60, and 90 days following SCS implant) (right panels). Boxes show the median and ends of boxes define the 25th and 75th percentiles, and whiskers define 10th and 90th percentiles. Comparison between time points was performed using repeated measures one-way analysis of variance (ANOVA). Pain intensity was quantified using the Visual Analogue Scale for pain (0-10, 0 = no pain, 10 = worst pain possible). *P<0.05 vs. baseline.

Figure 3.

Box and whisker plots of systolic blood pressure (BP) (Panel A), diastolic BP (Panel B), and mean arterial pressure (MAP) (Panel C) among patients with chronic pain before epidural spinal cord stimulator implant (baseline) and within 30 days following SCS implant (left panels), and among patients with BP measurements at all time points (baseline and within 30, 60, and 90 days following SCS implant) (right panels). Boxes show the median and ends of boxes define the 25th and 75th percentiles, and whiskers define 10th and 90th percentiles.

Comparison between time points was performed using repeated measures one-way analysis of variance (ANOVA). * $P < 0.05$ vs. baseline. # $P < 0.05$ vs 30 days.

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Figure 4.

Partial regression plot between the change () in pain rating and mean arterial pressure (MAP) within 30 days following SCS implantation adjusted for age, sex, baseline pain rating, baseline MAP, and taking hypertensive (HTN) medications (Panel A) and partial regression plot between baseline MAP and mean arterial pressure (MAP) within 30 days following SCS implantation adjusted for age, sex, baseline pain rating, pain, and HTN medications. Variables on the horizontal axes and vertical axes are adjusted for these predictor variables, resulting in standardized values greater than zero and less than zero. The

regression coefficients (β) represent the association between the predictor variable (x-axis) and the outcome (y-axis, MAP) while holding the other predictors constant. Dashed lines indicate 95% confidence intervals.

A) Men **B) Women** **C) Δ MAP within 30 days** **Figure 5.**

Box and whisker plots of mean arterial pressure (MAP) among men (Panel A) and women (Panel B) with chronic pain before epidural spinal cord stimulator implant (baseline) and within 30 days following SCS implant (left panels), and among men and women with pain ratings at all time points (baseline and within 30, 60, and 90 days following SCS implant) (right panels). Boxes show the median and ends of boxes define the 25th and 75th percentiles, and whiskers define 10th and 90th percentiles. Comparison between time points was performed using repeated measures one-way analysis of variance (ANOVA). * $P < 0.05$

vs. baseline. [#] P<0.05 vs 30 days. Panel C shows the change () in MAP in men and women within 30 days following SCS implant (left panel) and MAP in men and women within 30 days following SCS implant while covarying for baseline pain, pain, age, baseline MAP, and taking HTN medications (analysis of covariance, ANCOVA) (right panel), [†] P<0.05 vs. men.

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Figure 6.

Box and whisker plots of mean arterial pressure (MAP) among patients with chronic pain taking hypertensive (HTN) medications (Panel A) and not taking HTN medications (Panel B) before epidural spinal cord stimulator implant (baseline) and within 30 days following SCS implant (left panels), and among patients with blood pressure measurements at all time points (baseline and within 30, 60, and 90 days following SCS implant) (right panels). Boxes show the median and ends of boxes define the 25th and 75th percentiles, and whiskers define 10th and 90th percentiles. Comparison between time points was performed

using repeated measures one-way analysis of variance (ANOVA). Panel C shows changes () in MAP in patients with chronic pain not taking HTN medications and taking HTN medications while covarying for baseline pain, pain, age, sex, and baseline MAP (analysis of covariance, ANCOVA). Similarly, Panel D shows changes () in MAP in men (left panel) and women (right panel) with chronic pain that were not taking HTN medications and those that were taking HTN medications while covarying for baseline pain, pain, age, and baseline MAP (analysis of covariance, ANCOVA). † $P < 0.05$ vs. no HTN medications.

Table 1.

Subject characteristics

Variable	All patients	Men	Women	P-value
Number of patients, n	213	97	116	--
Age, years	60 ± 14	62 ± 13	59 ± 15	0.117
Min-max age, years	29-91	29-89	29-91	--
Systolic BP, mmHg	133 ± 14	134 ± 15	132 ± 14	0.251
Diastolic BP, mmHg	76 ± 10	78 ± 10	75 ± 9 *	0.006
MAP, mmHg	95 ± 10	97 ± 11	94 ± 10 *	0.036
History of heart surgery, n (%)	7 (3)	4 (4)	3 (3)	0.810
History of vascular disease, n (%)	9 (4)	7 (7)	2 (2)	0.101
Pain rating (before SCS)	6.3 ± 2.0	6.2 ± 2.0	6.3 ± 2.0	0.498
Prescription medications				
Benzodiazapines, n (%)	57 (27)	23 (24)	34 (29)	0.445
Anticonvulsants, n (%)	87 (41)	40 (19)	47 (41)	0.973
Opioids, n (%)	209 (94)	95 (96)	114 (99)	0.744
ACE inhibitors, n (%)	34 (16)	12 (12)	22 (19)	0.262
ARBs, n (%)	12 (6)	4 (4)	8 (7)	0.565
Beta-blockers, n (%)	30 (14)	13 (13)	17 (15)	0.949
Ca ²⁺ channel blockers, n (%)	13 (6)	5 (5)	8 (7)	0.809
Diuretics, n (%)	35 (16)	11 (11)	24 (21)	0.099
Alpha-adrenergic blockers, n (%)	1 (1)	1 (1)	0 (-)	0.928
Non-selective adrenergic blockers, n (%)	7 (3)	3 (2)	4 (3)	0.810
Central alpha-adrenergic inhibitor, n (%)	3 (1)	1 (1)	2 (2)	0.876

Values are means ± SD. P-values are t-test results between men and women (Chi-square testing for categorical data).

* P<0.05 vs. men.

MAP, mean arterial pressure; SCS, epidural spinal cord stimulator; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

Table 2.

Multiple regression analysis

Dependent variables:	Baseline pain rating		Pain rating (30 days)		MAP (30 days)	
	β	P-value	β	P-value	β	P-value
Independent variables:						
Age	-0.19	0.009	-0.23	<0.001	-0.04	0.557
Sex (men vs. women)	-0.05	0.437	-0.04	0.447	0.16	0.007
Baseline pain rating	--	--	-0.66	<0.001	-0.11	0.151
Baseline MAP	0.20	0.003	-0.09	0.156	-0.49	<0.001
Pain rating (30 days)	--	--	--	--	-0.08	0.296
MAP (30 days)	--	--	-0.07	0.296	--	--
Taking HTN meds	0.01	0.932	-0.08	0.182	-0.28	<0.001
Model variance (R ²):	0.08	0.001	0.45	<0.001	0.33	<0.001

Men: n=97, Women: n=116. Beta (β) values are standardized coefficients. Delta (Δ) values for pain rating and mean arterial pressure (MAP) are changes from baseline within 30 days following epidural spinal cord stimulation (SCS) implant. HTN, hypertension; Meds, medications.