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Cardiovascular Effects of Spinal Cord Stimulation: The Highs, the Lows, and the Don't Knows

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ABSTRACT

Background and Objectives: There are many potential etiologies of impaired cardiovascular control, from chronic stress to neurodegenerative conditions or central nervous system lesions. Since 1959, spinal cord stimulation (SCS) has been reported to modulate blood pressure (BP), heart rate (HR), and HR variability (HRV), yet the specific stimulation sites and parameters to induce a targeted cardiovascular (CV) change for mitigating abnormal hemodynamics remain unclear. To investigate the ability and parameters of SCS to modulate the CV, we reviewed clinical studies using SCS with reported HR, BP, or HRV findings.

Materials and Methods: A keyword-based electronic search was conducted through MEDLINE, Embase, and PubMed data bases, last searched on February 3, 2023. Inclusion criteria were studies with human participants receiving SCS with comparison with SCS turned off, with reporting of either HR, HRV, or BP findings. Non-English studies, conference abstracts, and studies not reporting standalone effects of SCS when comparing SCS with non-SCS interventions were excluded. Results were plotted for visual analysis. When available, participant-specific stimulation parameters and effects were extracted and quantitatively analyzed using ordinary least squares regression.

Results: A total of 59 studies were included in this review; 51 studies delivered SCS invasively through implanted/percutaneous leads. Eight studies used noninvasive, transcutaneous electrodes. We found numerous reports of cervical, high thoracic, and mid-to-low thoracolumbar SCS increasing resting BP, and cervical/mid-to-low thoracolumbar SCS decreasing BP. The effect of SCS location on HR and HRV was equivocal. We were unable to analyze stimulation parameters owing to inadequate parameter reporting in many publications.

Conclusions: Our findings suggest CV neuromodulation, particularly BP modulation, with SCS to be a promising frontier. Further research with larger randomized controlled trials and detailed reporting of SCS parameters will be necessary for appropriate evaluation of SCS as a CV therapy.

Keywords: Blood pressure, heart rate, heart rate variability, review, spinal cord stimulation

INTRODUCTION

Spinal cord stimulation (SCS)[1,2] has been reported to affect blood pressure (BP), heart rate (HR), and HR variability (HRV) in individuals with and without cardiovascular diseases, and for various indications.[3,4] Increasingly, SCS has been reported to normalize abnormal BP in conditions such as autonomic dysreflexia (AD), which increases BP, and orthostatic hypotension (OH), which decreases BP, resulting from spinal cord injuries (SCI).[5,6]

The cardiovascular (CV) system relies on the activation of reflex pathways in response to stimuli detected by receptors such as baroreceptors, chemoreceptors, and nociceptors.[7] These receptors modulate sympathetic/parasympathetic balance of the autonomic nervous system that can be impaired by neurological conditions and other diseases.[8,9]

Historically, cardiac sympatho-vagal balance was measured by HRV spectrum analysis in which high-frequency power components (HF) were believed to reflect vagal tone, low-frequency

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power components (LF) reflecting sympathetic activity, and the ratio (LF/HF) a representation of the balance.[8] However, this interpretation of LF/HF ratio has been disproven given the poor relationship between sympathetic nerve activation and LF power.[10,11] Despite this, HRV analysis continues to be reported as approximations of sympatho-vagal activity.

Invasive SCS can be delivered by inserting an electrode into the spinal cord (intraspinal SCS; ISCS) or placing electrodes over the dura mater (epidural SCS; ESCS) introduced percutaneously or surgically.[12,13] Noninvasive SCS is achieved transcutaneously (TSCS) with surface electrodes placed on the back over the midline or paraspinal area.[14] After electrode placement over targeted spinal cord segments, stimulation parameters (intensity, frequency, pulse width, waveform) that elicit desired physiologic effects are determined.

Unfortunately, the most effective SCS approach to induce specific CV changes remains unclear. There is no consensus on the spinal cord segments to be targeted and the stimulation parameters to be used for modulating BP, HR, and HRV at rest and in response to activation of reflex pathways. We endeavored to review SCS literature in humans to identify specific spinal segments and stimulation parameters that elicit CV effects in various conditions with and without disrupted CV control. The identification of spinal segments and parameters can enable efficient determination of patient-specific protocols for managing CV dysfunctions.

MATERIALS AND METHODS

Search Strategy

A literature search of the MEDLINE, Embase, and PubMed data bases was conducted via Ovid on June 26, 2023. The Boolean combination keywords used to identify scientific publications involving the use of SCS in humans with HR, HRV, or BP findings were ((“spinal cord stimulation” OR “spinal cord epidural stimulation” OR “dorsal column stimulation" OR “epidural spinal electrical stimulation”) OR ((“electric stimulation” OR “electrical neuromodulation”) AND “spinal cord”)) AND “human” AND (“heart rate” or “tachycardia” or “bradycardia” or “blood pressure” or “hypotension” or “hypertension” or “cardiovascular” or “cardiac” or “heart” or “rate pressure product”). A manual search of cited references in relevant articles also was performed.

Eligibility Criteria

Inclusion criteria were established using the Population, Intervention, Comparison, Outcome framework.[15,16] Studies analyzed required human subjects (population) to have received SCS (intervention), compared with no SCS (comparison), and report on HR, HRV, or BP findings. Case studies and series were included to maximize the evidence base.[17] Non-English studies and conference abstracts were excluded. Studies that compared SCS with non-SCS interventions without analysis of the standalone effects of SCS were excluded. In cases where several publications presented data from the same patient cohort, those publications were incorporated only if they provided distinct intervention and/or outcome measures. Two authors (Marco Law and Rahul Sachdeva) independently reviewed each study for eligibility criteria.

Data Extraction

Data extracted included study design, sample size, participants’ demographics, indication for SCS, stimulation type, stimulation parameters, protocol, and CV outcomes. For analysis, study indications were grouped into one of pain (includes chronic pain, neuropathic pain, and persistent spinal pain syndrome (PSPS, formerly failed back surgery syndrome), angina (includes refractory angina pectoris and cardiac syndrome X [CSX]), neurotrauma/neurodegenerative conditions (SCI, multiple sclerosis [MS], Parkinson’s disease, multiple system atrophy [MSA]), or healthy controls (no clinical indication for SCS). Targeted spinal cord levels and effect on BP, HR, and HRV were plotted for visual analysis.

Statistical Methods

Ordinary least squares regression was performed on the stimulation parameters of 27 individuals with complete parameter reporting and BP outcomes using Python 3.9.7 and StatsModels 0.14.0 (Python Software Foundation, Wilmington, DE).[18] Independent variables were frequency, pulse width, and voltage. The dependent variable was BP change (increase or decrease).

RESULTS

The data base search identified 2226 studies. After initial screening, 178 studies underwent full-text review. Two independent screenings (Rahul Sachdeva and Marco Law) based on the abstract resulted in similar studies with 99% agreement, except for three abstracts. This was resolved via discussion with the senior author (Andrei Krassioukov). A total of 59 studies were ultimately included (Supplementary Data Fig. S1). A summary of the results is presented in Table 1.

Indications for SCS of the selected studies were angina (n = 20 [34%]), SCI (n = 18 [30%]), pain (n = 11 [19%]), cardiac dysrhythmias (n = 2 [3%]), atypical Parkinson disease (n = 1 [2%]), heart failure (n = 1 [2%]), MS associated symptomologies (n = 1 [2%]), and multiple system atrophy (n = 1 [2%]). One study (2%) evaluated SCS in participants without CV symptoms being treated for a variety of conditions, and three studies evaluated SCS in individuals with no indications for SCS using percutaneous ESCS (n = 1 [2%]) or TSCS (n = 2 [3%]).

ESCS was used in 50 studies (85%), TSCS in eight studies (13%), and ISCS in one study (2%). Most studies were pre-post design (n = 39 [66%]), with the remainder being case reports (n = 7 [12%]), case series (n = 6 [10%]), nonrandomized controlled trial (n = 1 [2%]), retrospective cohort study (n = 2 [3%]), and randomized controlled trials (n = 4 [6%]).

Association Between Spinal Cord Segments and Resting BP

Of the 25 studies (Supplementary Data Table S1) that reported resting BP, seven (28%) reported no effect of SCS on BP,[36–41] whereas the remaining 18 (72%) reported state-dependent effects.[5,19–23,27,29,34]

Stimulation applied to most spinal cord segments has been reported to modulate resting BP (Fig. 1). Decrease in resting BP was reported in four pain studies with cervical (C3–C7) and mid-to-low thoracic (T5–T12) stimulation.[28,32–34] In one retrospective study, both LF and HF SCS of unspecified cervical segments and T7-to-T12 spinal cord segments were found to only decrease systolic BP (SBP) in individuals with preimplant hypertension >140 mm Hg.[34] In another study, reductions in SBP, diastolic BP (DBP), and mean arterial pressure (MAP) were only transient, returning to baseline within 60 days.[32] Although pain is an obvious confounder, one study reported significant reductions in BP after SCS that were not

Table 1. Summary of Literature Search Results.

Measure	SCS indication	Increase	Decrease	No change/inconclusive
Resting BP	Angina, arrhythmia, healthy, heart failure, neurotrauma, neurodegenerative, pain	15 studies (Aslan et al[19], Ditterline et al[20,21], Gorgey et al[22], Harkema et al[23], Holwerda et al[24], Mikhaylov et al[25], Naar et al[26], Nightingale et al[27], Perese et al[2], Schultz et al[28], Singh et al[29], Squair et al,[5,30] Ter Laan et al[31])	4 studies (Holwerda et al,[32] Lopez et al,[33] Memar et al,[34] Schultz et al[28])	7 studies (Keller et al[35], Lanza et al[36,37], Levin et al[38], Martin et al[39], Norrsell et al[40], Saraste et al[41])
Resting HR	Angina, arrhythmia, healthy, heart failure, neurodegenerative, neurotrauma, pain	5 studies (Andersen et al[42], Aslan et al[19], Inanici et al[14], Mannheimer et al[43], Norrsell et al[40])	6 studies (Goudman et al,[44,45] Harkema et al[23], Meglio et al[3], Perese et al[2], Ter Laan et al[31])	18 studies (Anselmino et al[46], De Jongste et al[47,48], Di Pede et al[49], Ditterline et al[20,21], Ferrero et al[50], Hautvast et al[51], Holwerda et al[24], Kalmar et al[52], Keller et al[35], Lanza et al[36], Levin et al[38], Martin et al[39], Mikhaylov et al[25], Naar et al[26], Schultz et al,[28] Singh et al[29])
Resting HRV	Angina, heart failure, neurotrauma, pain	5 studies (Anselmino et al[46], Goudman et al[44], Grimaldi et al[53], Kalmar et al[52], Moore et al[4])	1 study (Ditterline et al[21])	7 studies (Andersen et al[42], Black et al[54], De Jongste et al[48], Di Pede et al,[49] Hautvast et al[51], Naar et al[26], Schultz et al[55])
BP Dysregulation	Neurotrauma, neurodegenerative, healthy	11 studies (Aslan et al,[19] 2018 Darrow et al[56], Ditterline et al[21], Gorgey et al[22], Harkema et al[57], Mazzone et al[58], Phillips et al[59], Squair et al[5,30],	3 studies (Richardson et al[13], Sachdeva et al[6], Samejima et al[62])	0 studies

(Continues)

Table 1. *Continued*

Measure	SCS indication	Increase	Decrease	No change/inconclusive
		West et al[60], Yamasaki et al[61])		
Angina Stress	Angina	4 studies (De Jongste et al[47], Eliasson et al[63], Mannheimer et al[43], Sgueglia et al[64])	1 study (Norrsell et al[40])	7 studies (Jessurun et al,[65] Lanza et al[36,37], Lanza et al, Mannheimer et al,[66] Norrsell et al[67], Sanderson et al,[68,69] Saraste et al[41])
ANS Activation in Intact Autonomic Regulation	Healthy, pain	1 study (Schultz et al[28])	1 study (Meglio et al[3])	2 studies (Schultz et al[28,55])

associated with reduction in pain, and a recent retrospective study found no relation between clinical records of pain and BP.[32,34]

SCS-dependent increase in resting BP was reported in individuals with pain, neurotrauma/neurodegenerative conditions, and arrhythmia, and in healthy controls. Spinal cord segments associated with increased resting BP spanned from C1 to C7, T1 to T3, and T6 to S4. An exception to this was in angina studies in which no BP effects were reported with stimulation to C8-to-T3 spinal cord segments.[36,37,40,41] In three pain studies, high cervical (C1–C5), high thoracic (T1–T3), and low thoracic to lumbosacral (T12–S4) spinal cord segment stimulation increased resting BP.[2,24,28] One study reported increase in resting BP with T1-to-T4 SCS in heart failure.[26] In seven SCI studies and one MSA study in individuals experiencing BP manifestations such as OH, persistent low resting BP, or AD, SCS at low-thoracic and lumbosacral spinal segments (T11–S4) consistently increased resting BP.[5,19–23,27,30] In one study in children with SCI, SCS to spinal cord segments C6 to C7, T12 to L2, and S1 to S4 indicated no changes to SBP or DBP.[35] In another study, SCS to C4 to C6, C7 to T1, and T11 to L2 only increased DBP and MAP.[29] One MS study investigated the effect of SCS on resting BP and showed no effect of midthoracic (T4–T8) stimulation on resting BP.[38] One cardiac arrhythmia study showed TSCS at high thoracic (T1–T2) spinal cord segments increased BP.[25] In healthy controls, one study showed TSCS of the C3-to-C5 spinal cord segments can increase BP whereas stimulation of T3-to-T5 segments in another study did not find BP effects.[31,39]

Association Between Spinal Cord Segments and Resting HR

A total of 29 studies reported resting HR findings; 18 (62%) reported no SCS-dependent effect on HR; six (21%) reported decreased HR with SCS, and five (17%) reported increased HR with SCS (Supplementary Data Table S2). Irrespective of indication, the effect of stimulation at most spinal cord segments on resting HR was equivocal (Fig. 2).

Decrease in resting HR was reported in pain studies, in neurotrauma/neurodegenerative conditions, and in healthy controls. Although cord segments associated with SCS-dependent decrease in resting HR generally spanned from C1 to C6, C8 to T3, and T4 to S5, numerous studies reported contradicting findings. In pain studies, SCS-dependent decrease in resting HR was reported with stimulation of C1-to-C5, T1-to-T2, and T8-to-L2 segments in three studies.[2,44,45] In three other pain studies, stimulation of the same spinal cord segments did not modulate resting HR.[24,28,52] In one SCI study, stimulation of the T12-to-S4 segments lowered resting HR in one of four participants.[23] This contrasted with three SCI studies reporting no effect and one reporting increased resting HR in individuals with orthostatic intolerance with stimulation to C5, T11, or T12-to-S4 segments.[19–21,35] In one study in children with SCI, stimulation of C4-to-C6, C7-to-T1, and T11-to-L2 spinal cord segments did not alter resting HR.[29] One study comprising participants with pain or neurotrauma/neurodegenerative conditions specifically investigating the effect of SCS on HR reported an SCS-dependent decrease at rest with stimulation to segments spanning C5 to C6, C8 to T3, and T4 to S5.[3] In healthy controls, an SCS-dependent decrease in resting HR with stimulation to C3-to-C5 segments was reported in only one study.[31]

SCS-dependent increase in resting HR was reported in angina and neurotrauma/neurodegenerative studies. For angina, stimulation of T1-to-T3 segments caused an SCS-dependent increase in resting HR in two studies and increased average HR after one year

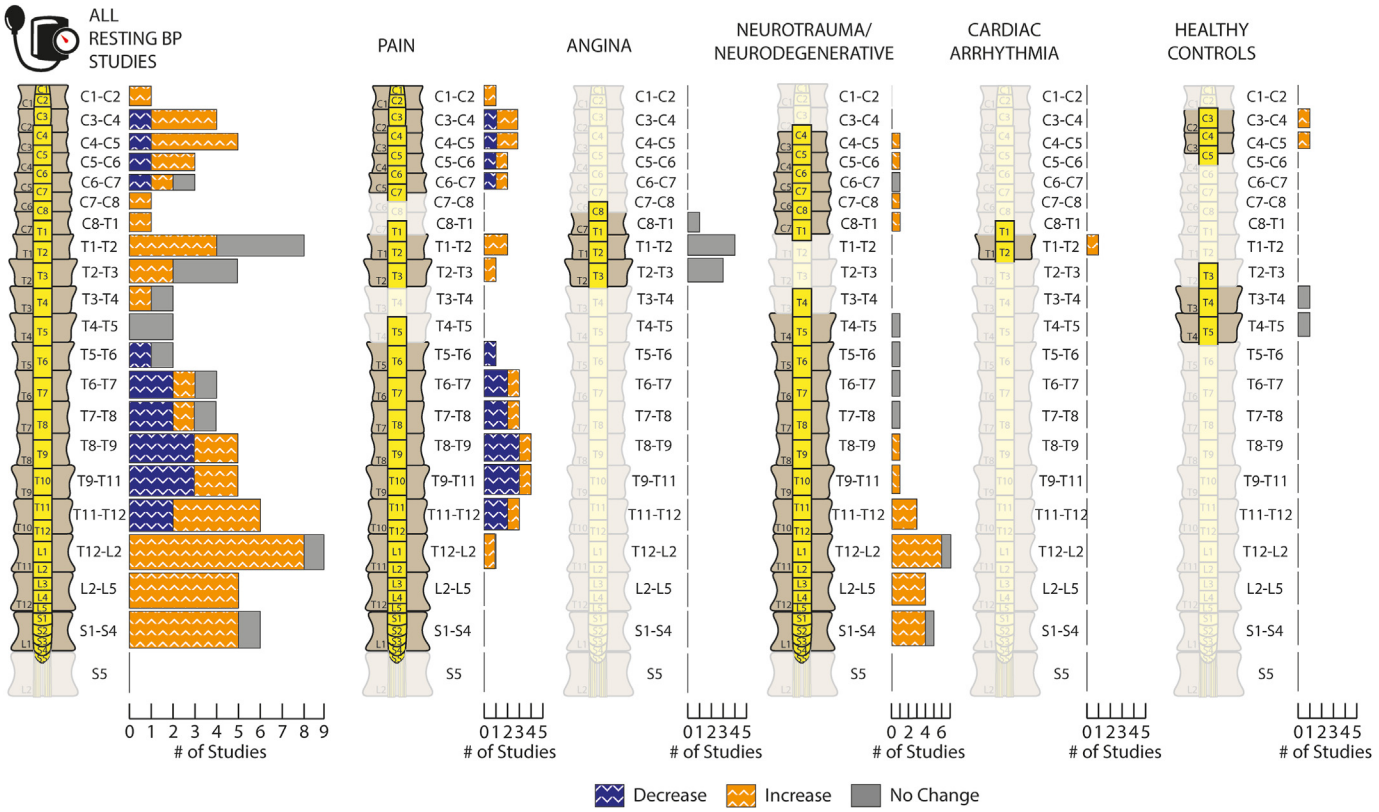

Figure 1. Stimulated spinal cord segments and effect on resting BP. Number of studies with electrode placements covering each vertebral level, the corresponding spinal cord segments, and the reported effects on BP at rest for all SCS indications ($n = 24$), pain (chronic $n = 2$, neuropathic $n = 2$, PSPS $n = 2$), angina (refractory $n = 2$, CSX $n = 2$), neurotrauma/neurodegenerative (SCI $n = 7$, MS $n = 1$, MSA $n = 1$), cardiac arrhythmia ($n = 1$), and healthy controls ($n = 2$). [Color figure can be viewed at www.neuromodulationjournal.org]

of implantation in one study.[40,42,43] In contrast, six studies reported no SCS-dependent effect with stimulation to the same segments.[36,46–49,51] In neurotrauma/neurodegenerative conditions, SCS-dependent increase in resting HR was reported in two2 SCI studies. In one individual with SCI presenting with chronic bradycardia, midcervical cord stimulation (C4–C5/C6–C7) above and below the level of injury corrected and maintained resting HR.[14] In individuals with orthostatic intolerance due to SCI, an increase in resting HR was observed with lumbosacral stimulation of the T12-to-S4 spinal cord segments.[19]

Although the SCS-dependent effects on HR control are equivocal, SCS-dependent rhythm control was revealed in a case series with two individuals experiencing cardiomyopathies. In these individuals, stimulation of the C6 spinal cord segment reduced the number of episodes of ventricular tachycardia.[53]

Association Between Spinal Cord Segments and HRV at Rest

HRV findings were reported in 13 studies (Supplementary Data Table S3), seven of which (54%) reported no SCS-dependent HRV effects. The remaining studies found various changes in LF and HF or the LF/HF ratio. Figure 3 illustrates stimulated spinal cord segments and the reported effects on HRV at rest.

SCS-dependent decreases in LF were reported in only one study each for pain, angina, and SCI indications. A decrease in LF was reported with stimulation to T8-to-T12 spinal cord segment in one pain study.[44] One angina study reported an SCS-dependent decrease in LF but did not specify the spinal cord segments being stimulated.[4] An SCS-dependent increase in LF was reported in only one SCI study, with stimulation of T12-to-S4 spinal cord segments.[21]

SCS-dependent decrease in HF was reported in only one pain study with stimulation to C4-to-C7 and T9-to-L5 spinal cord segments.[52] SCS-dependent increase in HF was reported in one pain study with stimulation to T8-to-T12 and one SCI study with stimulation to T12-to-S4 spinal cord segments.[21,44]

SCS-dependent decreases in the LF/HF ratio were reported in a few pain and angina studies with stimulation to C5-to-T1 and T7-to-T11 spinal cord segments. One angina study reported a decrease in the LF/HF ratio with stimulation of C5-to-T1 segments.[46] In one pain study, SCS-dependent decrease in the LF/HF ratio was reported with stimulation to T7-to-T11 spinal cord segments.[44] The above findings were contradicted by other studies reporting no effect on the LF/HF ratio with stimulation to the same segments.[49,52,54]

Effect of SCS on CV Function in Response to BP Dysregulation

Supplementary Data Table S4 summarizes studies of stress tests in individuals with BP dysregulation. SCS yielded consistent results in correcting hypotensive abnormalities by increasing BP (Fig. 4a). SCS delivered between T9-to-S4 spinal cord segments increased BP during orthostatic stress tests (OSTs) in all SCI studies ($n = 7$) and decreased OH-associated tachycardia in four studies.[5,19,21,22,56,57,59–61] One study reported significant reductions in heart rate response during OST with L2-to-L5 SCS.[70]

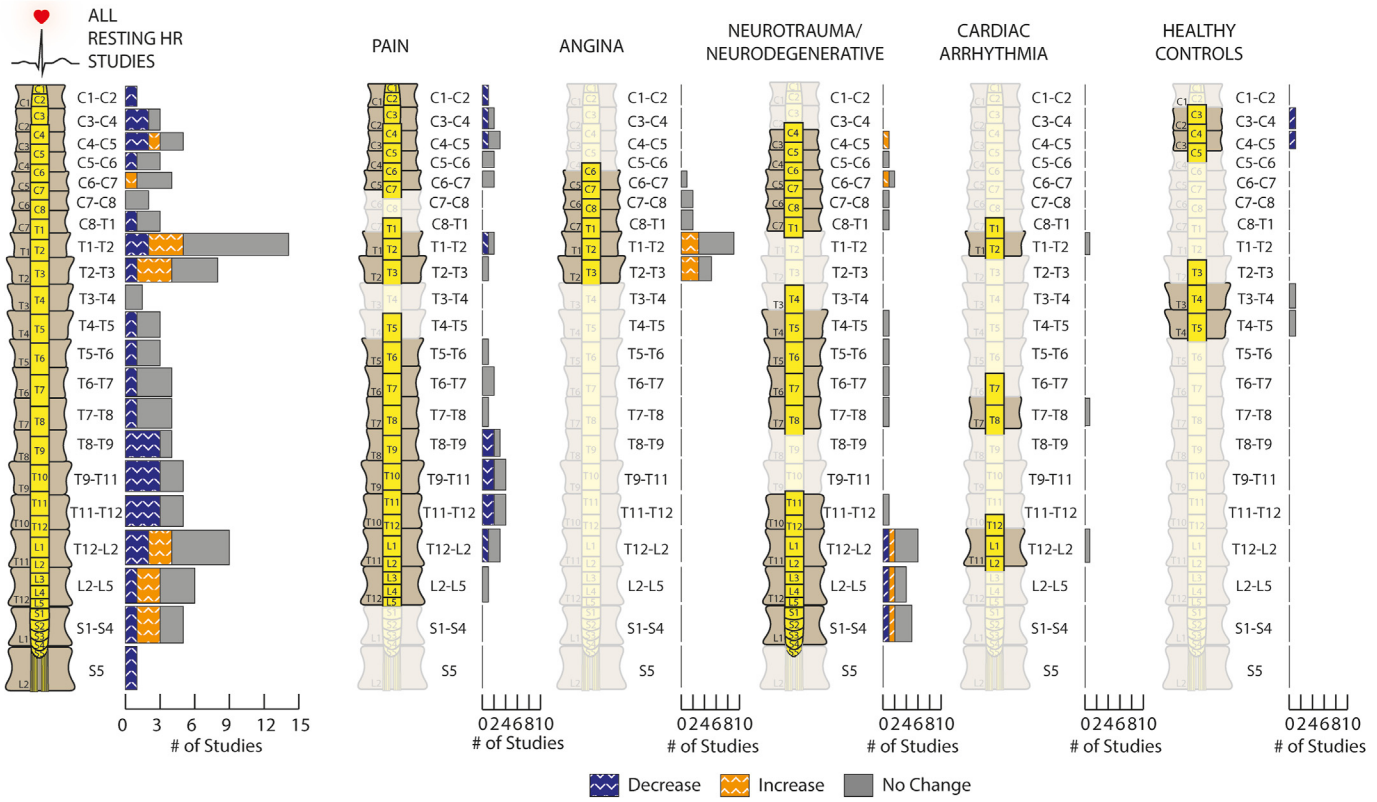

Figure 2. Stimulated spinal cord segments and effect on resting HR. Number of studies with electrode placements covering each vertebral level, the corresponding spinal cord segments, and the reported effects on HR at rest, for all SCS indications (n = 29), for pain (chronic n = 2, neuropathic n = 2, PSPS n = 2), angina (refractory n = 9, CSX n = 1), neurotrauma/neurodegenerative (SCI n = 7, MS n = 1), cardiac arrythmia (n = 1), and healthy controls (n = 2). [Color figure can be viewed at www.neuromodulationjournal.org]

SCS at T7-to-T9 spinal cord segments also has been reported to increase SBP, DBP, and MAP during OSTs.[59] Beyond the immediate corrective effect of SCS, daily SCS at T11 to S4 delivered as a training intervention was reported to recondition the CV system such that OSTs did not cause decreases in BP in the absence of ESCS.[21,57] More recently, a neuroprosthesis using a closed-loop controller providing continuous stimulation to T12-to-L5 spinal cord segments was shown to reduce BP errors during OST by dynamically adjusting stimulation intensity.[5] A similar modulatory effect in reducing SBP decrease during OST was reported in one individual with MSA using a neuroprosthesis.[30] In one individual with atypical parkinsonism experiencing OH, stimulation of the C1-to-C5 spinal cord segments during OST increased both BP and HR.[58]

Three SCI studies reported SCS to mitigate the pathologic rise in BP during episodes of AD (Fig. 4b). One case series found the initiation of SCS to the L2-to-S5 spinal cord segments to eliminate AD episodes in four of five individuals (80%) and allowed the discontinuation of antihypertensives in two individuals.[13] TSCS of T7-to-T9 spinal cord segments associated with increasing BP during OH also decreased BP during AD and reduced the reflex bradycardia associated with AD in one case report.[6] A reduction of AD-associated increase in BP and reflex bradycardia also was reported in a case series applying ESCS to T11-to-L5 spinal cord segments.[62]

Effect of SCS in Response to CV Demand During Angina

Although studies have shown consistent antianginal effects with the use of SCS, the effects do not appear to be related to alterations to CV parameters (Supplementary Data Table S5). Of the 11 angina studies that applied SCS to the T1-to-T3 spinal cord segments corresponding to dermatomes associated with angina, most studies reported no significant changes to HR and BP during exercise or dopamine stress test (n = 8 [73%]). One prospective randomized controlled study of 24 participants with refractory angina also reported no difference between symptom-limited HR and SBP.[65] Only three of eight studies (36%) reported increased SBP during peak exercise and maximum workload,[47,63,64] and only one study reported an increase in HR during angina.[64] During atrial pacing in three studies (Fig. 4d), SCS increased pacing tolerance in one study and in one of two studies, reduced arterial BP at a pacing rate that had triggered angina when stimulation was withheld.[40,43,67]

Effect of SCS in Response to ANS Activation in Those With Intact Autonomic Control

Three studies reported mixed SCS-dependent HR or BP effects during autonomic nervous system activation in individuals without autonomic dysregulation (Supplementary Data Table S6). One study involving participants with mixed indications for SCS found stimulation of C5-to-C6, C8-to-T3, and T4-to-S5 spinal cord segments to limit the increase in HR induced by sympathetic activation and chemical parasympathetic inhibition.[3] During sympathetic activation with the cold pressor test (CPT), individuals being treated for pain showed no SCS-dependent effect on HR during stimulation of T1-to-T3 or T5-to-T7 spinal cord segments.[28,55] The same pain

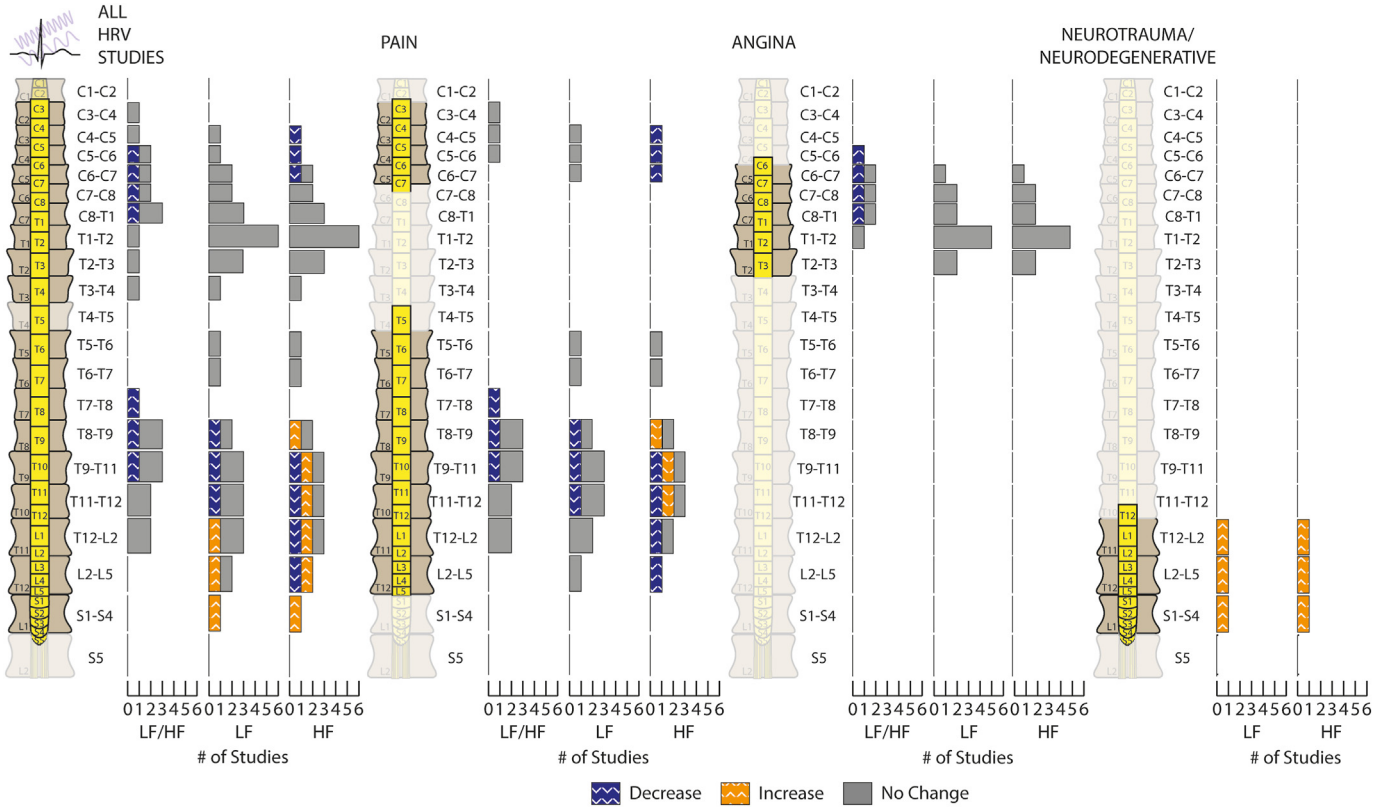

Figure 3. Stimulated spinal cord segments and effect on HRV. Number of studies with electrode placements covering each vertebral level, the corresponding spinal cord segments, and the reported effects on LF/HF, LF, and HF HRV components at rest for all SCS indications (n = 13, includes cardiac arrhythmia [n = 1], and heart failure [n = 1]), pain (chronic n = 1, neuropathic n = 1, PSPS n = 2), angina (refractory n = 6), and neurotrauma/neurodegenerative (SCI n = 1). [Color figure can be viewed at www.neuromodulationjournal.org]

studies reported conflicting effects of T5-to-T7 SCS on MAP during CPT, with one study reporting an increase whereas the other did not find any significant change. Stimulated spinal cord segments and effects on SNS activation are illustrated in Figure 4e.

Selection, Reporting, and Effects of Electrical Parameters on CV Parameters

Irrespective of delivery method (ie, ISCS, ESCS, TSCS), stimulation parameters (intensity, frequency, pulse width) were reported fully in only 37 of 59 studies (63%), and partially (≥one parameter) in 11 studies (19%). The remaining 11 studies (19%) did not specify any parameters. In all studies, intensity was increased until the desired therapeutic effects were elicited or a threshold of discomfort was reached. Reasoning for selected stimulation frequencies and pulse width was not discussed in any of the studies. By method of SCS delivery and indication for stimulation, only 29 of 50 of ESCS studies (58%) reported all stimulation parameters; the least detailed reporting was from angina studies, with only five of 20 studies (25%) reporting all parameters. In contrast, 18 of 21 neurotrauma/neurodegenerative studies (86%) and nine of 11 pain studies (82%) reported full stimulation parameters. Reported parameters overlapped greatly (Fig. 5). Owing to limited reporting, no combinations of ESCS parameters to elicit specific BP, HR, or HRV outcomes were identified. Reporting of TSCS parameters was more consistent—seven of eight studies (88%) reported all parameters.

Despite most studies inadequately reporting parameters, we were able to extract participant-specific stimulation intensity (in volts), frequency (in hertz), and pulse width along with participant-specific results from nine studies.[5,13,23,24,27,49,57,60,62] A total of 27 BP and HR data points were extracted. No appreciable trends were observed regarding stimulation parameters and HR effects. However, as seen in Figure 6, shorter pulse widths appear to decrease BP whereas longer pulse widths increase BP. This was confirmed by ordinary least squares regression of the available data reporting statistically significant pulse width and frequency coefficients (Supplementary Data Table S7).

DISCUSSION

This review indicates that SCS is a viable option for modulating CV function, with most notable documented effects in individuals with neurotrauma (eg, SCI) or neurodegenerative conditions (eg, MS, Parkinson's disease) for correcting hemodynamic instabilities. From a mechanistic standpoint, a recent review from our group suggests that the acute (real-time) effects of SCS in modulating CV function are likely mediated through activation of somato-autonomic reflexes.[71] SCS stimulates multiple dorsal roots and preferentially recruits large-diameter fibers.[72] Experiments involving dorsal rhizotomy indicate that activation of dorsal roots causes modulation of sympathetic preganglionic neurons, without direct activation of dorsal column, intraspinal, or dorsal horn neurons.[5] The SCS-dependent selective excitation or inhibition of sympathetic preganglionic neurons allows increase or decrease, respectively, in BP.

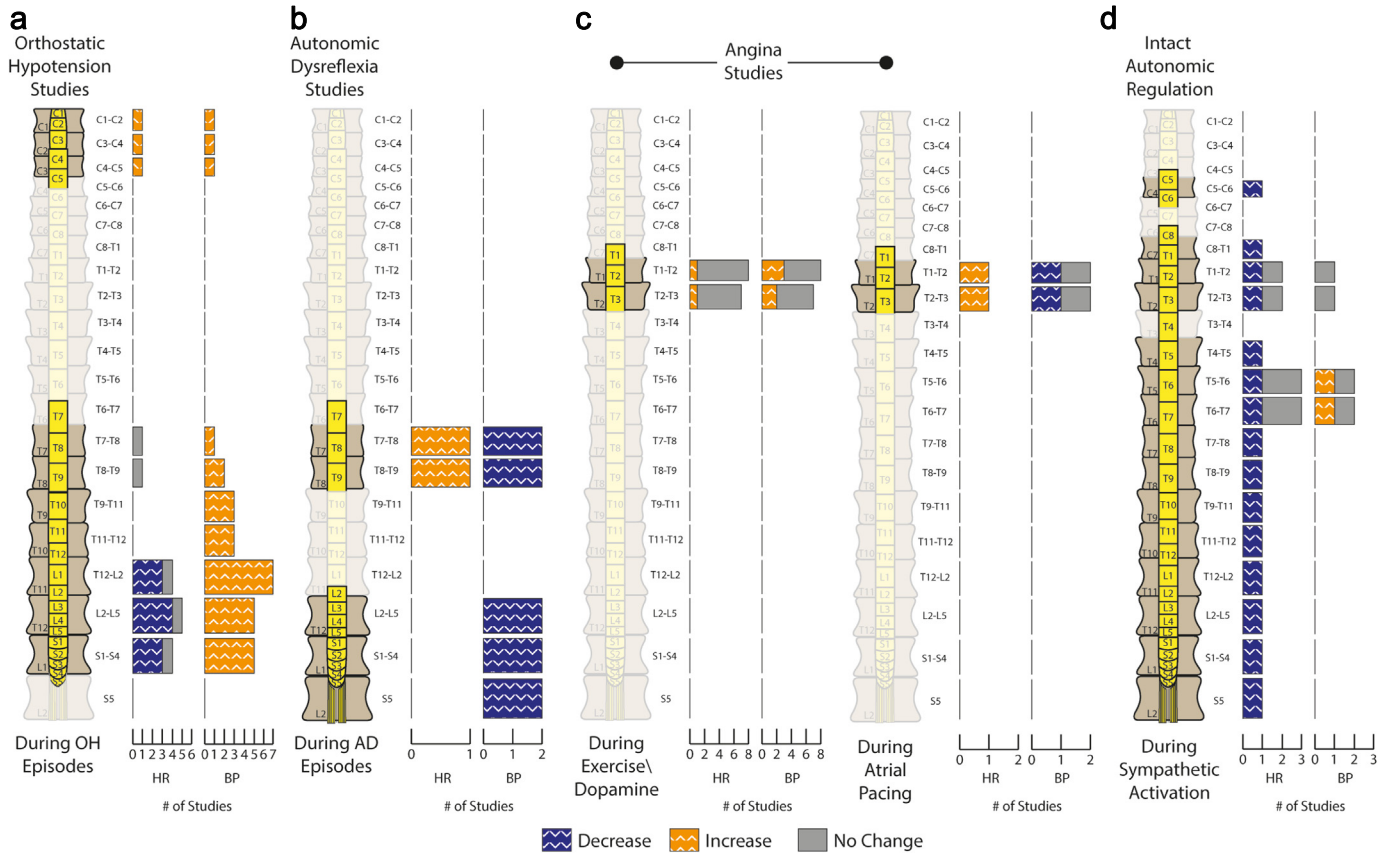

Figure 4. Stimulated spinal cord segments and CV effect during stress tests. Stimulated spinal cord segments and reported effects during physiological stress and activation of reflex pathways. Number of studies with electrode placements covering each vertebral level, the corresponding spinal cord segments, and the reported effects of SCS on HR and BP during OH (n = 11) (panel a), episodes of AD (n = 3) (panel b), exercise/dopamine stress tests (n = 8) (panel c, left), atrial pacing (n = 3) in individuals treated with SCS for angina (panel c, right), and sympathetic nervous system activation in individuals with intact autonomic regulation (panel d). [Color figure can be viewed at www.neuromodulationjournal.org]

SCS at Rest

SCS across a variety of spinal cord segments appears to modulate resting BP. We identified a trimodal distribution of spinal cord segments (cervical, high thoracic, and mid-to-low thoracolumbar) that was associated with an increase in resting BP and a bimodal distribution of spinal cord segments (cervical and mid-to-low thoracolumbar) associated with decrease in BP at rest. It is important to note that these findings are limited owing to the site of electrode application being determined on the basis of the initial clinical indication for SCS that may not have been for CV modulation. For example, angina studies (n = 20) placed electrodes over the T1-to-T3 spinal cord segments, likely owing to viscerosomatic convergence of cardiac visceral spinal afferent fibers and cardiac nociceptive afferent fibers along a propriospinal pathway with branches in the upper thoracic region.[73]

SCS across nearly all spinal cord segments is reported to decrease resting HR, and midcervical, high thoracic, and low thoracolumbar/sacral stimulation appear to increase resting HR, but these findings are equivocal. Most studies failed to report resting HR change during SCS. Similarly, the effect of SCS on LF/HF, LF, and HF is largely equivocal across most reported spinal cord segments. Stimulation to cervicothoracic spinal cord segments largely appears to have no effect on HRV components, whereas thoracolumbar/sacral stimulation appears to have mixed and conflicting effects on HRV. These findings are affected by indication-specific spinal cord segment targets.

Spinal Cord Stimulation During Stress States

The present findings suggest the effect of SCS on CV system to be state and pathology dependent, inducing corrective effects on HR and BP only during pathologic states. In pathologic states such as dysrhythmia (ventricular tachycardia and bradycardia), SCS reduced the number of episodes and increased HR, respectively.[14,53] In studies in which participants did not have pathologic hemodynamic states, SCS did not cause aberrant changes.

Current evidence supports using SCS for modulating pathological increases (AD) and decreases (OH) in BP with mid-to-low thoracolumbar SCS and possibly high cervical SCS. During orthostatic stress, transient decreases in BP are normally corrected through near-instantaneous baroreceptor activation and subsequent constriction of lower body blood vessels. SCS at various low thoracic and lumbosacral spinal cord segments (Fig. 4) has been shown in OH studies to increase BP during orthostatic stress and thus does not support the recently reported mechanism of "haemodynamic hotspots" for BP modulation.[5] Lumbosacral SCS targets the spinal cord region without sympathetic preganglionic neurons and likely stimulates interneuron-based relays, causing blood

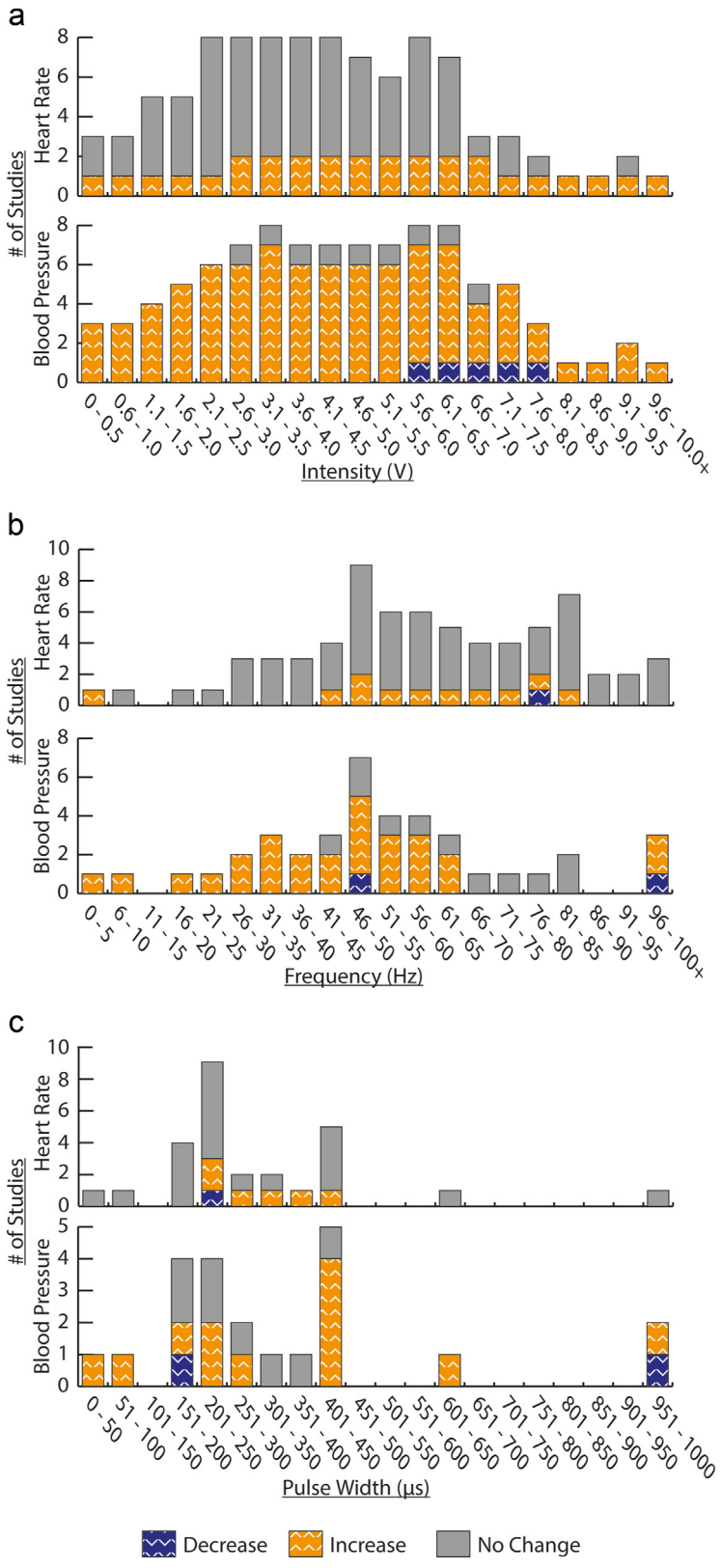

Figure 5. Stimulation parameters for ESCS studies and effects on resting HR and BP. Number of ESCS studies reporting resting HR and BP findings and the associated stimulation parameters intensity (panel a), frequency (panel b), and pulse width (panel c). [Color figure can be viewed at www.neuromodulationjournal.org]

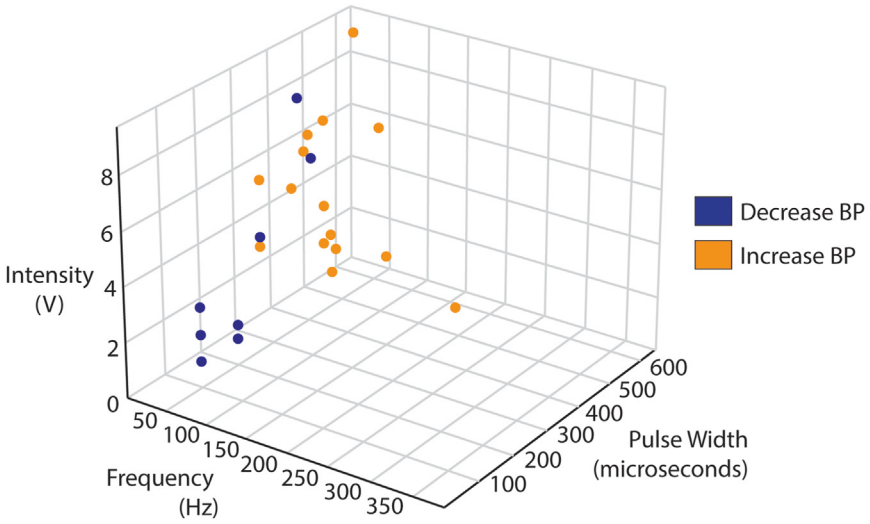

Figure 6. Three-dimensional plot of frequency, pulse width, voltage, and the associated BP effects on 27 participants. Ordinary least squares regression was performed, with frequency (coefficient −0.0067, $p = 0.004$), pulse width (coefficient −0.0051, $p < 0.005$), and voltage (coefficient 0.0095, $p = 0.886$) as independent variables. Clusters of BP effect are visualized. [Color figure can be viewed at www.neuromodulationjournal.org]

vessel constriction and BP normalization.[74] The use of a neuroprosthetic baroreflex system has been shown in case reports of SCI and MSA to immediately increase BP during orthostatic stress in near-real time, effectively mitigating the OH severity.[5,30,59]

SCI at or above the T6 spinal segment commonly manifests as AD. Pathologic increase in BP results from the activation of thoracolumbar sympathetic preganglionic neurons and downstream vasoconstriction after a noxious stimulus (eg, distended bladder or bowel) without appropriate supraspinal control. TSCS of the thoracolumbar spinal cord segments also was able to reduce the increase in BP during AD, postulating that stimulation activates local large-diameter afferents and gate-controls the noxious stimuli.[6,59] Similarly, lumbosacral eSCS also has been reported to mitigate AD, likely owing to the ESCS-driven inhibition of long ascending propriospinal neurons.[62] Although only three studies have reported AD-correcting effects of SCS, these studies support continued research and development of SCS-based treatment of AD.[6,13,62]

In those without CV pathology, the effects of SCS are less convincing. Antianginal effects of SCS of the T1-to-T3 spinal cord segments indicated in published literature seem unlikely to be due to alterations in CV thresholds during stress tests used to determine the threshold for anginal episodes and indirectly assess how well the CV system responds to the increase in CV demand. Although SCS delayed angina onset, it did not increase HR or BP at maximum workload or peak exercise. SCS may blunt the effects on HR during sympathetic activation and parasympathetic inhibition with stimulation across a variety of spinal cord segments, but evidence is limited to one dedicated study.[3] During sympathetic activation in individuals without autonomic dysregulation, no conclusions can be reasonably drawn owing to the small number of studies reporting conflicting HR or BP effects.

Stimulation Parameters and CV Response

No definite stimulation parameters were identified to elicit specific CV responses. Many studies fail to report complete stimulation parameters in their methods. However, analysis in a few participants suggests short pulse widths reduce BP and longer pulse widths increase BP, and higher intensities are associated with increase in BP.

In most studies, intensity was experimentally determined by incrementally increasing until a desired effect or subjective end point is reached, and the choice of frequency and pulse widths was based on clinical indication. For example, angina studies used 45 to 100 Hz; pain studies used 50 Hz, and AD used 30 to 65 Hz. Although a potential mechanism for pain relief and AD suppression may be due to low frequencies modulating neuronal gate control and blocking noxious stimuli, the mechanism by which it increases BP in OH is unclear.[6]

One additional factor influencing parameter selection is the mode of current delivery; TSCS favored longer pulse widths (~1 millisecond) whereas ESCS pulse widths tended to be <500 μs. Lee et al found pulse width programming to increase and steer spatial selectivity of dorsal column fiber recruitment.[75] This also might explain the pulse-width dependent change in BP (Fig. 6); however, more research is needed to substantiate these findings. A higher pulse width with TSCS may have been necessary for adequate penetration through the skin and stimulating the spinal cord.

Limitations

A major limitation of this review is the variety of studies (with respect to indications, study design, sample sizes, and confounders) that were included. The strength of evidence between different study types (eg, case reports versus randomized controlled trials) was not analyzed—most studies were pretest-posttest studies, case reports, and case series, with only four small randomized controlled trials identified. In addition, sample sizes of most studies were small, particularly in the more recent studies of SCS in individuals with SCI.

Regarding reporting of methods, many studies failed to provide full stimulation parameters, thus rendering quantitative and visual identification of parameter combinations impossible. For the same

reasons, we were unable to analyze other parameters such as electrode configuration, current direction, and pulse waveform, all of which can affect outcomes.[2,5] For future studies, it may be relevant to compare outputs of SCS devices in Coulombs, a measurement that was not reported in most studies.

Finally, there are several possible explanations for discrepancies in outcomes between various SCS indications. Medications, particularly those that have negative inotropic or chronotropic effects such as antiischemic agents, likely alter BP, HR, and HRV in ways that may dampen or eliminate the effects of SCS and contribute to inconclusive outcomes. Unfortunately, owing to inconsistent reporting of concurrent medications being used by participants (eg, angina studies reported whether antianginal medications were continued, but medications were not reported for most non–angina studies), this effect was not analyzed. Regarding HRV, two studies acknowledged the possibility of SCS-induced artifacts in the power spectrum affecting the HRV calculations.[44,48] This could potentially be addressed using a low-pass filter before downsampling.

CONCLUSION

This review focused on evaluating the effect of SCS location on BP, HR, and HRV, in addition to the stimulation parameters required to elicit these effects. We attempted to identify several potential global and indication-specific spinal cord regions that, when stimulated, alter HR or BP at rest, in addition to regions that modulate CV reflex activations during physiological stress. Current literature shows that SCS can increase and decrease BP at rest, and that these effects can be elicited using a variety of stimulation parameters at a variety of spinal cord segments. Published literature also supports the use of SCS for modulating pathological increases and decreases in BP by appropriately increasing and decreasing BP. Current evidence for SCS modulating HR and HRV remains unclear.

Unfortunately, we were unable to identify definitive patterns in stimulation parameters that elicited specific directional effects owing to inadequate reporting. As it stands, effects of SCS on the CV system can be achieved with a variety of parameter combinations. Future studies should aim to increase sample size and indications for stimulation to better detect global and indication-specific CV effects across all spinal cord segments and evaluate the impact of various stimulation parameters on CV response. Moreover, stronger evidence in the form of randomized controlled trials with complete stimulation parameter reporting will be required to make more concrete conclusions.

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Authorship statements

Marco Law was responsible for conceptualizing the project, developing the methods, literature search and review, data collection, analyses, creating visualizations, and drafting the original manuscript. Rahul Sachdeva performed literature review and assisted with writing and editing the final version of the paper. David Darrow provided feedback on multiple drafts of the manuscript. Finally, Andrei V. Krassioukov managed project administration, allocated necessary resources, and helped to finalize the written work. All four authors have carefully reviewed and approved the final manuscript, which reflects their collective efforts and insights on this important topic.

Conflict of interest

The authors reported no conflict of interest.

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1016/j.neurom.2023.07.010.

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COMMENTS

Law et al have provided an excellent working summary of studies looking at the effects of spinal cord stimulation on cardiovascular parameters. This is a rapidly expanding field and greatly enhanced by groups such as the University of California Los Angeles team looking at mechanisms and interactions between the nervous system and the cardiovascular system. It is apparent that there is much more work to be done in harnessing the autonomic effects of SCS (and indeed other therapies such as DRG stimulation that we have shown also to have profound autonomic effects). This study provides a good starting point.

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The authors conducted a review to present the cardiovascular effects of SCS in human studies. Lately, the interest in cardiovascular effects and specifically heart rate variability in relation to pain has drastically increased. In-depth statistical analyses to evaluate whether heart rate variability is a biomarker for pain intensity and the implementation of wearables to collect output parameters of the autonomic nervous system in real time are among th eexamples of the increased interest in cardiovascular effects. Presumably, the interest in the autonomic nervous system will only increase, so this work provides a great visual overview of what is currently known about the topic.

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