

A Review of Neuromodulation in the Treatment of Cardiovascular Disease

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Introduction: The algorithmic use of neurostimulation to treat chronic pain is routine. However, it is underutilized in managing pain and other symptoms relating to cardiovascular dysfunctions. The goal of this article is to focus on the clinical results from using spinal cord stimulation (SCS) in the realm of cardiovascular medicine.

Material and Methods: The current literature was reviewed, summarized and tabulated. This manuscript contains results from systematic reviews, randomized clinical trials and observational study search results on PubMed spanning the last 30 years. The official positioning statement from the International Neuromodulation Society Neuromodulation Appropriateness Consensus Committee (NACC) was also highlighted.

Results: Evidence supports that SCS is a safe, reversible, minimally-invasive and efficacious modality to mitigate chronic symptoms of refractory angina pectoris and critical limb ischemia.

Discussion: Spinal cord stimulation is effective in providing relief, improve quality of life and functional mobility in patients living with ischemic pain of systemic arterial occlusive disease.

Conclusion: Spinal cord stimulation should be considered early in the treatment algorithm among individuals with inoperable ischemic pain.

Keywords: angina pectoris, critical limb ischemia, ischemic pain, congestive heart failure, Reynaud's syndrome, spinal cord stimulation

Introduction

The International Neuromodulation Society defined neuromodulation as, “the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body.” The concept of the therapeutic use of electricity in cardiology and pain medicine is not new. The first cardiac pacemaker was invented by John Hopps in the 1940s where a bipolar lead was threaded through the venous conduits to reach the atria to exert rate control.¹ Mirowski and colleagues installed the first implantable cardioverter defibrillator in 1980.² Paralleling the cardio-electrical medicine discovery, the first spinal cord stimulation (SCS) was introduced in 1967 for the treatment of intractable neuropathic pain in an oncological patient.³ Nearly a decade later, Cook and colleagues successfully demonstrated a novel SCS application in cardiovascular medicine.^{4,5} The authors showed that SCS improved microcirculation and ulcer healing among patients at risk for limb amputation where reconstruction surgery was impossible or failed.^{4,5} Significant technological advances have been made in the field of neuromodulation to pave the way for novel SCS indications that extend

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beyond pain management. In this review, we will present the current evidence of neuromodulation in managing cardiovascular diseases from the perspective of interventional pain medicine physicians. Recommendations from the Neuromodulation Appropriateness Consensus Committee (NACC) Guidelines will be discussed. We will selectively focus on neurostimulation use in managing ischemic cardiovascular pathologies and congestive heart failure (CHF). The purpose of this review is not only to summarize the effect of SCS in providing pain palliation, quality of life improvement among patients with cardiovascular pathologies, but also the disease progression modification and functional outcome through neuromodulation.

Cardiovascular Epidemiology/ Pathophysiology

Ischemia is caused by a disruption to the blood flow to a region of the body or an organ resulting in metabolic demand and supply asymmetry. Devoid of adequate blood supply and oxygenation, the tissues distal to the vessel occlusion may become hypoxic, damaged and painful.⁶ At the cellular level, hypoxia causes a reduction in intracellular cAMP availability and adenylate cyclase function resulting in an increase in the endothelial permeability and lysosomal extracellular migration leading to apoptosis and necrosis.^{7,8} The microcirculatory derangement in the muscular arterioles and capillaries occurs within minutes following ischemia. Microthrombosis forms within 3–4 hrs.⁹ In order to abolish an ischemic event, proper metabolic homeostasis and circulation must be restored. Paradoxically, even after the reopening of the vessels, the ischemic area may not regain its perfusion; this is also known as the no-reflow phenomenon. The no-reflow phenomenon perpetuates the ischemic insult by impeding flow from the surrounding tributaries.¹⁰ Additionally, reperfusion injury frequently occurs as a consequence of the reintroduction of blood flow. This often results in further tissue affliction and an intense inflammatory cascade.^{11–13} Reperfusion injury is closely associated with the no-reflow phenomenon.¹⁴

The morbidity and mortality of cardiovascular diseases are high. Approximately 6.5 million Americans are living with congestive heart failure. The survival rate is roughly 50% within 5 years of diagnosis. The healthcare-associated cost is estimated to reach 69.7 billion by the year 2030.¹⁵ Similarly, there are roughly 8.5 to 10 million Americans live with PAD and angina due to coronary artery disease (CAD) (half of a million new cases annually).¹⁶ Of those,

Table 1 Fontaine Classification of Limb Peripheral Arterial Disease Severity

	Stages	Symptoms
	I IIA IIB	Asymptomatic Pain free walking > 200m Pain free walking < 200m
CLI	IIIA IIIB IV	Pain at rest with ABI > 50 mm Hg Pain at rest with ABI < 50mm Hg Necrosis or gangrene

Abbreviation: CLI, critical limb ischemia.

only 12–20% are older than 60 years of age.¹⁷ Therefore, PAD also poses a significant negative socioeconomic burden from both unemployment and disability among the workforce.^{18,19} The typical symptoms of PAD in the lower extremities are achy pain, cramping in the buttocks, thighs, legs or toes that are aggravated by ambulation (claudication) and relieved by rest. The affected limb will have the appearance of hair loss, smooth shiny skin, numbness, decreased or absent pulses, muscle atrophy and reduced temperature upon palpation.²⁰ In more severe and chronic cases, pain may persist while at rest with non-healing ulcers that can develop.^{21,22} The stages of limb PAD are described by the Fontaine classification (Table 1) where critical limb ischemia (CLI) is considered the end stage of PAD as untreated CLI leads to limb loss and potential subsequent postamputation pain development.^{22,23} Of the 8.5 million Americans living with PAD, approximately 2 million have CLI (500–1000 new cases per million people per year) and the risks are associated with age, male, diabetes, and African American race.²⁴ The number of individuals living with CLI is projected to reach 2.8 million by 2020 or as high as 3.5 million after factoring in population prevalence of diabetes.²⁵ Additionally, CLI has a 50–60% and 70% mortality rate at 5 years and 10 years respectively because CLI is a mere clinical manifestation of lethal systemic PAD i.e. CAD.^{26–28} It has been reported that 7% of patients with intractable and inoperable CAD have significantly elevated mortality after 3 years.²⁹

Neuromodulation Mechanisms Pertain to Cardiovascular Disease Treatment

Although SCS has been in the repertoire for treating chronic pain syndromes in modern medicine, the exact mechanism by which SCS provides pain relief is yet to be elucidated. The earliest thoughts on the mechanism of

SCS was largely based on the gate control theory, proposed by Melzack and Wall, who suggested that by selectively stimulating the large diameter A-beta fibers one could inhibit pain transmission via the small A-delta and C fibers in the superficial dorsal horn.³⁰ However, clinical observation and animal investigations indicated that there were other significant mechanisms involving neurotransmitters, such as GABA, substance-P, and serotonin release due to SCS.³¹ Additionally, SCS was shown to trigger an upregulation of calcitonin gene-related peptide (CGRP), a potent endogenous vasodilator. The production of CGRP subsequently leads to downstream nitric oxide release and vascular smooth muscle relaxation, vasodilation and reduced vasospasms.^{32–34} Through the use of laser doppler flowmetry and neurotransmitter antagonists to reverse the effect of SCS in the rodent model, neuroscientists have been able to gain insight into SCS generated vascular resistance and ischemic pain treatments. SCS was observed to increase cutaneous blood flow by down-modulating the sympathetic nervous tone.^{35,36} This vasodilatory effect is confirmed by a mechanical shift mediated through sympathectomy or by pharmacologically diminishing or reversing the improved circulation brought on by SCS. It was observed that hexamethonium and chlorisondamine, both ganglioplegic agents, inhibited pre- and post-ganglionic transmissions.^{35,36} These findings suggested that SCS caused a vasodilatory effect at the level of post-ganglionic receptors by inhibiting alpha-1 adrenergic receptor activation. SCS was observed to promote GABA release, protein kinase B (AKT) and kinase (ERK) and phosphorylation in the superficial dorsal horn resulting in extremity vasodilation.³⁷ Similar to the above-mentioned study methodology, GABA-A, ERK and AKT antagonists were introduced to attenuate SCS induced vasodilation.^{32,38}

Neuromodulation Types and Complications

Regardless of the manufacturer software, a dorsal column SCS device consists of a lead(s), a pulse generator, and a wireless remote controller. The number of contacts ranges from 4 to 32. The power source is provided by an internally implanted or externally placed pulse generator (IPG) in most cases. Most commonly used leads are cylindrical and are placed into the epidural space percutaneous with real-time fluoroscopic visualization. On the other hand, paddle leads are flat and their placements are

performed by a neurosurgeon as an open laminotomy or partial laminectomy as required. The lead location can be placed according to the anatomic or neurologic target. For the treatment of pain syndrome of cardiovascular origin, both transcutaneous electrical nerve stimulation and SCS leads placed subcutaneously demonstrated benefits.^{39–41} Irrespective of the type of SCS device used, there is evidence that SCS is cost-effective despite an initial higher cost.⁴² In terms of SCS related complications, it was reported around 30–40%.⁴³ However, the complication rate is decreasing as surgical techniques and technology continue to mature.⁴⁴

The Rationale and Evidence for Using Neuromodulation for Cardiovascular Conditions

The mainstay therapy for PAD consists of medical therapy (weight reduction, smoking cessation counseling, cholesterol-lowering agents, cardiac rehabilitation, beta-blockers, nitrates, calcium channel blockers) and revascularization techniques, such as endovascular coronary catheterization and coronary artery bypass surgeries. Regardless of anatomical structure location, the goal is to maximize blood flow and oxygenation.⁴⁴ Although the first-line treatment options are efficacious, approximately 7% of the patients are non-responders.^{29,45} Following failed conventional and cardiac interventions, treatment options become limited as some patients may be excluded from undergoing more advanced surgeries due to their comorbidities. In cases where multiple small vessels are diseased, there are no clear endovascular procedural or surgical targets. In these cases, a historical umbrella term “cardiac syndrome X” was coined to describe potential causes of cardiac pain with all-encompassing pathophysiologies, including reduced coronary vasodilation, augmented sympathetic nervous activity, reduced pain threshold, abnormal endothelial function, esophageal dysmotility, and microvascular spasm.⁴⁶ Neurostimulation was noted as a reasonable option to mitigate the clinical symptoms of treatment-resistant PAD.⁴¹ As early as 2002, the Joint Study Group of European Society of Cardiology (the ESBY study), lead by Mannheimer et al reported that neurostimulation techniques are beneficial and should be considered early in the chronic refractory angina treatment algorithm.⁴⁷ SCS is particularly beneficial when the patient’s CLI severity is greater than Fontaine criterium III (pain at rest). More impressively, there is evidence that

demonstrates SCS augments capillary blood flow and skin temperature in the diseased limb thus facilitating skin ulcers less than 3 cm in diameter among patients with an adequate collateral reserve and potentially to prevent amputation.^{5,48,49}

Kinfe et al searched the PubMed database that pertained to SCS in the management of PAD and chronic refractory angina pectoris compared to conventional

therapies. Their search was limited to prospective and randomized controlled trials studying the effect of SCS compared to medical therapy on PVD on pain control (Table 2). The authors specifically examined the number of patients that achieved minimal clinically important difference (MCID), defined as a reduction of 3 points on the visual analog pain scale (VAS). Their search yielded seven studies. The authors further stratified their findings into

Table 2 Literature Search Results Performed by Kinfe et al⁵⁰: Randomized Clinical Trials and respective Studies

Randomized Clinical Trials and Prospective Studies	
Investigators	Study Parameters and Outcomes
Jivegård et al. ⁵²	Participants: CLI and DM (N=51) Year/Duration: 1995/18 months Setting: Multicenter, Sweden Outcome: SCS group had better pain relief and limb salvage ($p<0.05$) particularly in inoperable limb ischemia and arterial hypertension.
Hautvast et al. ⁵³	Participants: Refractory angina pectoris (N = 25) Year/Duration: 1998/6 weeks Setting: Single center, The Netherlands Outcome: SCS group had significant improvements in the following outcomes: exercise tolerance, time to angina, attack episodes, ischemic episodes, sublingual nitrates consumption, quality of life, and pain.
Spincemaile et al. ⁵⁴	Participants: CLI (N=120) Year/Duration: 2000/24 months Setting: Multi center, The Netherlands Outcome: Individuals treated with SCS had significantly improved mobility, energy efficiency and required less opioid and non-opioid analgesic medications.
Lanza et al. ⁵⁵	Participants: Refractory angina pectoris (N=10) Year/Duration: 2004/ 6 weeks Setting: Single center, Italy Outcome: SCS provided better limb salvage in patients with moderately preserved microcirculation.
Sgueglia et al. ⁵⁶	Participants: Treatment-resistant and inoperable CLI (N=19) Year/Duration: 2007/36 months Setting: Single center, Italy Outcome: SCS cohorts had fewer anginal episodes of shortened duration with reduced immediate release nitrates use. Significant improvement in functional status, exercise-induced angina and ST segment changes were observed in the SCS group but not in controls.
Eddicks et al. ⁵⁷	Participants: Refractory angina pectoris (N=12) Year/Duration: 2007/16 months Setting: Single center, Germany Outcome: The experimental arm showed reduced anginal attacks, improved quality of life, and functional capacity compared to their placebo cohorts.
Lanza etl al. SCS-ITS trial ⁵⁸	Participants: Refractory angina pectoris (N=25) Year/Duration: 2011/3 months Setting: Single center, Italy Outcome: Paresthesia based SCS was superior to sham stimulation. There were no difference detected between subthreshold and sham stimulation groups.

Abbreviations: RCT, randomized clinical trial; CLI, critical limb ischemia; SCS, spinal cord stimulation.

short- (1–2 months), medium- (3–11 months) and long-term (greater than 12 months) term follow up results.⁵⁰ Totalling 7 studies (short-term: 148 patients, medium-term: 272 patients, and long-term: 239 patients), individuals with refractory angina pectoris who received SCS obtained a mean reduction in VAS of 1.6 (short-term), 3.2 (medium-term), 3.4 (long-term) versus 0.3 (short-term), 1.5 (medium-term) and 0.3 (long-term) among patients that were treated conservatively. Similarly, comparing SCS and conservative treatment cohorts with PAD, the VAS decrease was 1.1, 1.9 and 2.8 versus 1.4, 2.0 and 2.1. The author concluded that the effects of SCS on pain reduction increased over time as the amount of VAS decrease in both PAD and refractory angina pectoris groups either achieved or trended towards MCID as the SCS treatment duration lengthened.⁵⁰ Deoganonkar and coworkers reviewed 11 studies examining the effect of SCS in treating clinical signs and symptoms of CLI from 1983 to 2013.⁵¹ The summary from that analysis is listed in Table 3A and B. Consistent with the other studies, Deoganonkar et al concluded that SCS is both safe and efficacious in alleviating the symptoms of CLI. SCS was also shown to improve limb survival, physical activity tolerance, and quality of life. The author also cautioned that patient selection is paramount and SCS should only be carefully considered as a limb salvage therapy after pharmacologic and revascularization interventions are first considered in reversing the underlying ischemic causes.⁵¹

NACC Guideline Recommendations

In the same year, Deer and colleagues from The neuromodulation Appropriateness Consensus Committee (NACC) from the International Neuromodulation Society published a consensus statement on the use of spinal cord and peripheral nervous system neuromodulation which is also known as the NACC guidelines among pain medicine practitioners.⁴⁴ The NACC recommends that PAD should be first treated with conventional medical and revascularization therapies in the majority of the patients who are good surgical candidates. However, in patients that cannot tolerate medication side effects, angioplasty or coronary bypass surgeries, SCS is not only effective in mitigating the signs and symptoms of CLI but it also decreases amputation risks and improves outcomes. However, it was noted that using SCS as a limb salvage means incurring a significantly higher cost.^{68,69}

Ischemic Pain Syndrome Recommendations

The European Peripheral Vascular Disease Outcome Study (SCS-EPOS), a multicentered prospective study, demonstrated in patients with non-reconstructable CLI and transcutaneous oxygenation (TcPO₂) reserve of at least 20 mm Hg, but 10–30 mm Hg increase in response to SCS. SCS treatment of non-reconstructable critical leg ischemia was shown to provide a significantly better limb survival rate compared to conservative treatment.⁵⁹ Ubbink et al conducted a systematic review and meta-analysis comparing SCS with conventional medical management (CMM) to CMM alone with patients with inoperable CLI. Their results demonstrated SCS coupled with CMM improved limb salvage, ischemic pain, and several clinical outcomes.⁶⁸ SCS is particularly efficacious in patients with Fontain II classification without trophic changes in the foot.⁶² In patients without arterial hypertension where limb amputation is inevitable, SCS was shown to lower the amputation levels.⁵²

Raynaud's Syndrome (RS) Recommendations

Although RS is a rare diagnosis, RS can be debilitating as it primarily affects fingers. RS is characterized by cyanotic discoloration, burning, paresthesia, and allodynia (perceiving a non-noxious stimulus as painful). The symptoms typically worsen in response to cold or stress. RS can be a stand-alone condition or a part of larger systemic disorder, such as scleroderma, CREST syndrome or lupus. The underlying disease mechanism is thought to originate from increased vasospastic tone and activity in the distal extremities resulting in ischemic pain. Even though the current available literature on SCS for RS pain is limited to case series,^{70–76} the largest study consisted of 1048 patients followed longitudinally for a decade and 40 with severe symptoms treated with SCS.⁷⁷ The results showed a responder rate of 60% (24/40) with 45% (18/40) and 15% (6/40) reporting excellent and good outcomes respectively. The patients that were treated with SCS within 5 years of RS diagnosis did better. The benefit of early SCS intervention was echoed by Devulder et al.⁷⁸ The authors also noted the best results were obtained from placing the SCS lead at T1. Based on the current pooled evidence, the NACC recommends that SCS should be selectively and judiciously offered to patients with RS within the first 12 weeks of painful ischemic pain.⁴⁴

Table 3 (A) Randomized Clinical Trials and Prospective Studies reviewed by Deoganonkar et al⁵¹ **(B)** Literature Search Results Performed by Deogaonkar et al⁵¹: Retrospective Studies and Case Series

A	
Randomized Clinical Trials and Prospective Studies	
Investigators	Study Parameters and Outcomes
Amann et al. ⁵⁹ (SCS- EPOS)	Participants: CLI (N=71) Year/Duration: 2003/12 months Setting: Multi center, multiple European Countries Outcome: SCS cohorts had significantly better pain relief and limb survival rate (33%).
Ubbink et al. ⁶⁰	Participants: CLI (N=120) Year/Duration: 1999/>18 months Setting: Multi center, The Netherlands Outcome: SCS provided better limb salvage in patients with moderately preserved microcirculation.
Petrakis and Sciacca ⁶¹	Participants: Treatment-resistant and inoperable CLI (N=150) Year/Duration: 1999/>6 months Setting: Single center, Italy Outcome: SCS group reported significant pain reduction. Improved skin blood flow was also observed in the SCS group.
Kumar et al. ⁶²	Participants: Nonreconstructable CLI (N=39) Year/Duration: 1997/21 months Setting: Single center, Canada Outcome: SCS improved tissue oxygenation, pulse volume, blood flow velocity, micro- and macro-circulation.
Claeys and Horsch ⁶³	Participants: Fontaine classification IV CLI and DM (N=81) Year/Duration: 1996/12 months Setting: Single center, Germany Outcome: Individuals treated SCS+prostaglandin significantly improved significantly in foot ulcer healing and oxygenation.
Jivegård et al. ⁵²	Participants: CLI and DM (N=51) Year/Duration: 1995/18 months Setting: Multi center, Sweden Outcome: SCS group had better pain relief and limb salvage ($p<0.05$) particularly in inoperable limb ischemia and arterial hypertension.
B	
Retrospective Studies and Case Series	
Tallis et al. ⁶⁴	Participants: Medical and surgical therapy resistant CLI (N=10) Year/Duration: 1983/NA Setting: Single center, The United Kingdom Outcome: All participants had physical activity tolerance increase. Most had pain, ulcer healing and cutaneous/muscle blood flow improvement.
Horsch et al. ³⁶	Participants: CLI (N=258) Year/Duration: 2004/18 months Setting: Single Center, Germany Outcome: Among inoperable lower extremity PVD individuals (TcPO ₂ <10mm Hg), limb survival improved significantly when treated with SCS.
Brummer et al. ⁶⁵	Participants: Inoperable CLI with end stage renal disease (N=8) Year/Duration: 2006/12 months Setting: Single center, Italy Outcome: All patients showed significant pain, QoL, limb survival gain, especially among Fontaine stage II and IV participants.
Reig et al. ⁶⁶	Participants: Inoperable CLI (N=8) Year/Duration: 2009/20 years Setting: Single center, Spain Outcome: 88% of the SCS group demonstrated good pain relief and ulcer healing.

(Continued)

Table 3 (Continued).

Ubbink and Vermeulen ⁶⁷	Participants: Inoperable CLI (N=450) Year/Duration: 2013/12 months Setting: Review, The Netherlands Outcome: Individuals treated with SCS +CM vs CM alone, SCS+CM achieved better limb salvage, pain control and lower pain medication requirement. No ulcer rate healing differences were found.
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Abbreviations: RCT, randomized clinical trial; CLI, critical limb ischemia; SCS, spinal cord stimulation; PVD, peripheral vascular disease; TcPO₂, transcutaneous partial oxygen pressure; QoL, quality of life; CM, conservative management.

Chronic Refractory Angina Recommendations

The evidence supporting the SCS in managing chronic refractory angina is well defined and comprehensive. The ESBY study (Electrical Stimulation versus Coronary Artery Bypass Surgery in Severe Angina Pectoris) randomized 104 patients with severe refractory angina pectoris to coronary artery bypass grafting or SCS. At five years, the survival rate or quality of life were equitable.⁷⁹ SCS resulted in significantly fewer angina attacks, hospital admission, immediate-release nitrate consumption, improved exercise capacity and quality of life outcome measures. Several authors noted that the improved circulation may be due to the fact that the patients treated with SCS had enhanced exercise tolerance, thus facilitating new collateral vascular circuitry formation.^{49,80,81} Due to the rigor in refractory angina pectoris neurostimulation research and continually improved evidence level, the NACC was able to provide the highest recommendation level: “A” as defined by the US Preventive Service Task Force as “extremely recommendable (high-level evidence that the measure is effective and benefits outweigh the harms).” Concordantly, SCS as a method for treating refractory angina pectoris has been accepted by the European Society of Cardiology and American Heart Association/American College of Cardiology.⁸² In summary, SCS could be an option for patients with severe refractory angina pectoris and serious comorbidities who could not receive invasive bypass grafting technique because of unacceptable surgical complication risks and other contraindications. Since the NACC guideline publication, Pan et al performed a systematic review and meta-analysis consisting of only randomized clinical trials with the primary indication towards refractory angina pectoris, focusing on pain parameters, and long-term functional outcomes. The individual studies are summarized in Table 4. The study results showed that SCS was effective and safe in enhancing exercise capacity, quality of life, well-being and diminishing nitroglycerin needs.

Additionally, Canadian Cardiovascular grading and pain reductions were also noted.⁸³

Congestive Heart Failure Recommendations

The effect of SCS on the cardiovascular system is known among neuromodulators. Depending on the location of the spinal stimulation, corresponding vasodilatory effects were observed.^{44,93} The following lead locations and physiological effects are summarized from the evidence presented in the NACC guidelines: Increasing cerebral blood flow, vasomotor tone, neurochemical mediators and reducing sympathetic activities have been achieved with SCS leads placed at C1/C2. Increased upper extremity circulation is achieved with lower cervical cord (C3-6) stimulation. Similarly, lower extremity and pedal vasodilation is attained with lower thoracic and upper lumbar spinal (T11-L3) stimulation. T1-T3 stimulation 24 hrs daily was successful in relieving chronic congestive heart failure,⁹⁴ while T2-4 at 12 hrs/day was not efficacious in the DEFEAT-HF study lead by Zipes et al.⁹⁵ Despite the outcome discrepancies, methodological differences, and respective study limitations, the authors cautioned drawing premature conclusions on negating the role of SCS in congestive heart failure management.⁹⁵ The United States Food and Drug Administration (FDA) has just released premarket approval for the first neuromodulatory device for CHF treatment in the United States.⁹⁶

Conclusion

Spinal cord stimulation is effective in providing relief, improved quality of life, and functional mobility in patients living with ischemic pain of systemic arterial occlusive disease. Spinal cord stimulation should be considered early in the treatment algorithm among individuals with inoperable ischemic pain. As researchers, engineers and physicians continue to challenge the current technological limitations, novel stimulation parameters with new anatomical targets may provide increased efficacy in the use of neuromodulation within the cardiovascular field.

Table 4 Randomized Clinical Trials and Prospective Studies Included in the Systematic Review Conducted by Pan et al.⁸³

Randomized Clinical Trials and Prospective Studies	
Investigators	Study Parameters and Outcomes
Mannheimer et al. ⁸⁴	Participants: Refractory angina pectoris (N = 20) Year/Duration: 1988/6 months Setting: Single center, Sweden Outcome: SCS improved performance on bicycle ergometer test by decreasing ST segment depression and recovery time.
Hautvast et al. ⁵³	Participants: Refractory angina pectoris (N = 25) Year/Duration: 1998/6 weeks Setting: Single center, The Netherlands Outcome: SCS group had significant improvements in the following outcomes: exercise tolerance, time to angina, attack episodes, ischemic episodes, sublingual nitrates consumption, quality of life, and pain.
Greco et al. ⁸⁵	Participants: Refractory angina pectoris (N = 46) Year/Duration: 2000/24 months Setting: Single center, Italy Outcome: SCS significantly reduced angina episodes, increased exercise tolerance noted during stress test. The improvements were sustained at 24 months.
Jessurun et al. ⁸⁶	Participants: Refractory angina pectoris (N=24) Year/Duration: 1999/ 6 weeks Setting: Single center, The Netherlands Outcome: TENs improved the perfusion reserve ratio evaluated by using positron emission tomography scan.
Vulink et al. ⁸⁷	Participants: Refractory angina pectoris (N=26) Year/Duration: 1999/12 months Setting: Single center, The Netherlands Outcome: Individuals with SCS had significant improvement in pain and quality of life at 3 months. Social, mental and physical scores on quality of life improved after 1 year.
de Jongste et al. ⁸⁸	Participants: Refractory angina pectoris (N=17) Year/Duration: 2004/12 months Setting: Single center, The Netherlands Outcome: SCS significantly improved exercise capacity and quality of life.
McNab et al. SPiRit trial ⁸⁹	Participants: Refractory angina pectoris (N=60) Year/Duration: 2006/12 months Setting: Single center, The United Kingdom Outcome: SCS and percutaneous myocardial laser revascularization groups had similar outcomes. However, SCS cohorts had significant improvement Canadian Cardiovascular Society grading change.
Eddicks et al. ⁵⁷	Participants: Refractory angina pectoris (N=12) Year/Duration: 2007/16 months Setting: Single center, Germany Outcome: The experimental arm showed reduced anginal attacks, improved quality of life, and functional capacity compared to their placebo cohorts.
Bondesson et al. ⁹⁰	Participants: Refractory angina pectoris (N=121) Year/Duration: 2008/12 months Setting: Single center, Sweden Outcome: Both enhanced external counterpulsation and SCS significantly reduced nitrate usage.
Dyer et al. SPiRit trial ⁹¹	Participants: (N=20) Year/Duration: 2008/24 months Setting: Single center, The United Kingdom Outcome: SCS and percutaneous myocardial laser revascularization achieved similar improvement. SCS was less cost-effective at the time of the study.

(Continued)

Table 4 (Continued).

Lanza et al. SCS-ITA trial ⁵⁸	<p>Participants: Refractory angina pectoris (N=25)</p> <p>Year/Duration: 2011/3 months</p> <p>Setting: Single center, Italy</p> <p>Outcome: Paresthesia based SCS was superior to sham stimulation. There were no difference detected between subthreshold and sham stimulation groups.</p>
Zipes et al. ⁹²	<p>Participants: (N= 46)</p> <p>Year/Duration: 2012/6 months</p> <p>Setting: Multi center, The United States of America and Canada</p> <p>Outcome: Both high and low frequency SCS reduced anginal frequency. Total exercise time and time to anginal onset were prolonged. There were no inter-group differences detected.</p>

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Dr. Deer is a consultant for Axonics, Abbott, Nalu, Saluda, Stingenics, Flowonix, Comerloc, SPR Therapeutics, Vertos, Vertiflex, Spinethera, Jazz. He is a minor equity holder for Saluda, Nalu, Spinethera, Stingenics, Vertiflex, Vertos, and Bioness, and received research funding from Mainstay. In addition, Dr. Deer has a patent Abbott pending. Dr. Jason Pope serves as a paid consultant for Abbott, Flowonix, Jazz Pharmaceuticals, Stingenics, SPR Therapeutics, Medtronic, Nevro, Tersera, Vertos, and Saluda. Dr. Krishnan Chakravarthy is a consultant to Abbott, Bioness, Medincell, SPR Therapeutics, Nalu, Oska Wellness, Medtronic. He is a minor equity holder in Nalu and Oska Wellness. Dr. Yang has no conflict of interest to declare. The authors report no other conflicts of interest in this work.

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