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A Focused Review

Spinal Cord Stimulation for Refractory Angina Pectoris and Peripheral Vascular Disease

Timothy R. Deer, MD, and Louis J. Raso, MD

Spinal cord stimulation has been used in clinical practice for more than three decades. The primary use of this therapy has been in spine-related disorders. In recent years, the therapy has been used more extensively in diseases of the vascular system. Increasingly, interest has piqued in using this mode of treatment for refractory angina and ischemic pain secondary to peripheral vascular disease. In this publication, we review the current literature on these two indications and present case examples of both therapies.

Key words: Spinal Cord Stimulation, Angina Pectoris, Peripheral Vascular Disease

Neuromodulation can be defined as the electrical or chemical modification of the nervous system that changes the actual or perceived neurotransmission and response to a stimulus or condition. The first clinical use of these modes of treatment came in the 1960s when spinal electrodes were placed to treat patients who had failed lumbar surgery. These early devices were rudimentary and had a high failure rate because of the lack of programming options and the poor understanding of patient selection. Tremendous advances in these therapies have been made in the last decade. Current systems allow for multiple electrode selection, exponential programming options, and rechargeable batteries that allow for cost-effectiveness. Another significant advance in the past few years has been the developing of a better understanding of patient selection in regard to disease management and treatment. Established indications now include peripheral neuropathy, complex regional pain syndromes, post-herpetic neuralgia, and traumatic nerve injury. New interest has developed in pelvic pain, peripheral nerve entrapment syndromes and chronic abdominal pain of visceral origin. Impressive results have also been reported with the treatment of ischemic pain secondary to vascular disease and angina pectoris. In this review, we will discuss the efficacy mechanisms of action and indications for stimulation for these indications

From: The Center for Pain Relief, Charleston, West Virginia, 25301
Address Correspondence: Timothy R. Deer, MD, The Center for Pain Relief, 400 Court Street, Suite 304, Charleston, West Virginia, 25301
Email: DocTDeer@aol.com
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Angina

In refractory angina pectoris, the goal of Spinal Cord Stimulation (SCS) is the reduction in both frequency and severity of anginal attacks with an improvement in quality of life, and functional ability.

In 1999 the American Heart Association defined angina pectoris as a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back, or arm, typically aggravated by exertion or emotional stress (1). The syndrome is caused by an imbalance between the demand and the supply of oxygen to the heart. The decrease in blood supply to the heart is usually the result of vessel occlusion or vasospasm. An anginal attack is triggered by an increased demand for oxygen caused by physical activity, or other stresses. Heart disease remains the leading cause of death in the United States, and contributes extensively to healthcare costs to society.

The most common groups of patients with refractory angina pectoris have coronary artery disease that is not corrected by bypass grafting, stent placement, or aggressive medical management. Another group of refractory patients demonstrate normal coronaries on angiography but have significant intermittent anginal discomfort. This condition is sometimes referred to as "micro vascular angina" or "small vessel disease." On exercise electrocardiogram (EKG) the patients have typical exercise-triggered angina with ST segment depression. Since they generally fail to respond to conventional anti-anginal therapy, they remain a treatment dilemma. Some of the theories as to the cause of this syndrome include endothelial dysfunction, abnormal distribution and function of adenosine receptors, and estrogen deficiency (2). Both of these groups are treatment dilemmas for the cardiac treatment team.

Conventional Therapy For Coronary Artery Disease

Conventional therapy for coronary artery disease (CAD) is divided into invasive and non-invasive methods. Invasive methods employed when drug therapy fails include percutaneous transluminal intervention (PTI) and coronary artery bypass grafting (CABG). These therapies in patients with significant stenosis may result in increased survival and decreased cardiac morbidity.

Non-invasive or drug therapy involves treating the disease processes at different locations in a multi-purpose effect. To decrease the oxygen demand, beta-blockers and calcium channel blockers are prescribed. To increase the oxygen supply, nitrates and calcium channel blockers are employed. To improve endothelial function, statins and ACE inhibitors are used. Coumadin and anti-platelet drugs are used to avoid clotting in the coronaries.

Defining Refractory Angina Pectoris

Despite employing all of the above therapies, in a number of patients the goal of controlling angina is not achieved. Reducing anginal pain is helpful in improving function and quality of life, but it is also important since the increased sympathetic tone caused by pain may lead to a worsening of myocardial ischemia.

Refractory angina pectoris is designated to identify patients in whom anginal pain is not controlled by both anti-anginal medication and revascularization procedures (3, 4). Patients usually have a long history of coronary artery disease, were previously treated with multiple CABG and PTI procedures, have a mean age of 63 years, and have a reduced left ventricular ejection fraction. It is estimated that 100,000 patients in the United States and Europe meet this criteria. These patients have a poor quality of life and require numerous hospital admissions to control pain.

Pain Pathways Involved In Angina Pectoris

Pain transmitted from the heart during an episode of angina begins in the adventitia of the coronary arteries and the myocardium. These pain afferents, along with sympathetic nerve branches, transmit to the upper four thoracic parasympathetic ganglia. The pain afferents continue until they reach the segments in the spinal cord. During angina, the activated fibers activate the sympathetic afferent fibers that enter the T1-T6 spinal cord segments.

Effects Of Neuromodulation On Angina And Ishemia

Randomized studies on SCS have demonstrated a reduction in anginal complaints, decreased use of short-acting nitrates, and a perceived improvement in quality of life, along with an increased exercise capacity. The beneficial effects last for at least 1 year in 80% of patients, with the increased exercise capacity and improved quality of life being reported in 60% of patients for up to 5 years.

A reduction in ischemia occurs during the anti-anginal effects. This is demonstrated on both exercise stress testing and ambulatory EKG monitoring. Chauhan demonstrated an increase in coronary flow velocity during Neuromodulation(5). There is a decrease in myocardial oxygen consumption with a possible redistribution to tissue with impaired blood flow (6, 7, 8).

The issue of SCS depriving the patient of anginal "warning signals" has always been a concern. Even though SCS elevates the anginal threshold, patients report reductions of perceived pain experiences, but data suggests they can still feel significant cardiac events. There remains an intact pain perception during an acute myocardial infarction. In a retrospective study of 517 patients, no increase in mortality was noted, and patients were aware of significant ischemic events determined by Holter monitoring (9).

Mannheimer and colleagues compared SCS with coronary bypass surgery in patients who only experienced symptomatic relief from bypass surgery (10). At 6 months, no statistical difference in symptom relief between bypass and SCS was evident. In the SCS population, there was a lower mortality and cerebrovascular morbidity. SSCS is obviously more cost-effective and at 5-year follow-up, there was no difference in mortality (11).

SCS does not appear to influence heart rate variability. It is thought to stabilize intracardiac neuronal function, help prevent the occurrence of reperfusion arrhythmias, and possibly prevent sudden cardiac death. No studies have ever reported an influence on left ventricular function by SCS in either a positive or negative effect.

Mechanism Of Action

Many theories have been introduced to explain how SCS raises the anginal threshold. SCS initially was believed to work through the autonomic nervous system. The evidence for this theory was lacking, when results showed that SCS had no effect on heart rate or on epinephrine metabolism. The current theory is that SCS affects the balance between myocardial oxygen supply and demand. Theories as to how SCS accomplishes this include recruitment of collaterals, angiogenesis, or a complex preconditioning to reduce the effects of ischemia. Mannheimer and colleagues randomized patients with refractory angina to normal controls or as a group stressed with right atrial pacing (6). The SCS patients achieved angina at a higher threshold, but all patients ultimately reported angina. SCS activates efferent and afferent neural projections at the cardiac level. This activation releases various endogenous chemicals (endorphins, norepinephrine, and neurokinins). The net effect of this release is stabilization of the myocardium during an ischemic episode. These benefits develop no tolerance to the stimulation

and as a result the benefits are maintained for years, based on the studies noted above.

Possible explanations for the anti-anginal, decreased ischemic effect include an increased coronary flow, a direct pain blocking effect, and a reduced oxygen consumption. Studies have shown that afferent stimulation with SCS gave rise to a reduction in oxygen consumption during ischemia (6). SCS also improves myocardial lactate production. The final pathways for the effects of SCS are the intracardiac neurons. Foreman showed that SCS modulates the firing of these neurons (12). Other research has shown that even during coronary occlusion, SCS continued to suppress the activity of intracardiac neurons (13).

In the studies reviewed, the most common complications included infection, lead migration, and device failure. Each of these complications occurred in less than one percent of the participants and no permanent sequelae were recorded.

It is clear from the above discussion that SCS is an effective therapy in patients with refractory angina. It is patient-controlled and reversible. It has a low complication rate and does not mask a serious cardiac event. The mechanism of action is complicated and SCS acts at numerous sites.

Peripheral Vascular Disease

Ischemia

When blood flow to tissue drops below an acceptable level, the metabolism of that tissue switches from aerobic to anaerobic. If the level continues to drop, cell death may ensue. If necrosis occurs, then the patient experiences the pain of ischemia or claudication. Critical limb ischemia in non-diabetic patients is defined as pain at rest or the presence of tissue necrosis. It is important to identify a therapy that can treat the pain of limb ischemia so amputation can be avoided. SCS has shown promise to be an ideal therapy to improve outcomes, including limb salvage, in this group of patients.

Pain secondary to critical limb ischemia is most likely a combination of nociceptive and neuropathic pain. In many patients opioids do not improve the neuropathic component of this ischemic event. SCS may be effective for the neuropathic component of ischemic pain. With tissue breakdown and necrosis, nerve endings are exposed with the patient experiencing symptoms of neuropathy. The exact effects of SCS on the pathology and pain associated with ischemia are still not known. Some of the proposed theories are anti-nociception, A-delta and C fiber modulation, or an anti-ischemic effect related to the sympathetic nervous system. The purpose of all therapy with regard to peripheral vascular disease is decreased pain and limb salvage. Patients with ischemic ulcers of 3 centimeters or more have a poor limb salvage rate regardless of therapeutic modality (14, 15). A large number of patients undergo amputation within three months of being diagnosed with critical limb ischemia.

The first reports of potential benefits of SCS in this patient population were more than two decades ago when Cook reported that SCS resulted in autonomic changes and warming in the extremity. The mechanism of action was theorized to be improved blood flow.16 The mechanisms underlying the effects of SCS on pain due to ischemia in the extremities, whether resulting from occlusive vascular disease or vasospasm, are different from those acting in neuropathic pain. A relief of the net ischemia by rebalancing oxygen need and supply is the most likely mechanism. SCS induces vasodilatation in a situation involving low sympathetic vasoconstrictor tone occurring with antidromic activation and stimulation-induced sympathetic inhibition that may occur in a limb with high levels of sympathetic activation. Thus there is a dual mechanism creating an overall effect that leads to improved perfusion and reduced pain.

Controlled Studies:

In 1994, the first randomized controlled study was performed in Belgium on 38 patients with ischemic rest pain and found there was no statistically significant difference regarding amputation (17). SCS provided pain relief, an increased ability to walk, improved function, and an improved quality of life (18). Jivegard reported on the effects of SCS in 51 patients with inoperable severe lower limb ischemia. He followed the patients for 18 months and reported on the amputation-free survival. SCS was superior to the control group 62% vs. 45%, which was statistically significant ($p>0.05$) (19).

Claeys and Horsch studied 86 patients randomized to maximum medical management versus SCS. Forty-five patients received SCS and 41 had optimal medical therapy. Limb survival at one year was 68% in the SCS patients and 65% of patients in optimal medical therapy resulting in no statistical difference (20).

In a 1999 Dutch study, 120 patients were evaluated over a 5-year period. Forty (67%) of 60 SCS patients and 41 of 60 (68%) standard treatment patients were living at the end of the study. Limb survival after 2 years was 60% in the SCS group and 46% in the conservative therapy group, which was statistically significant ($p>0.05$) (21).

Experimental Data

It has been suggested that SCS may have a beneficial effect on microcirculation in certain patients and that tissue capillary oxygen pressure (TcpO2) can be used to distinguish responders from non-responders. Early data found that SCS increased TcpO2 following 9 +/- 4 days of SCS. Patients who experienced a 20% or more increase in Tcp02 had excellent responses to both pain reduction and limb salvage (22).

Kumar treated patients with severe ischemia, who showed no significant improvement after 6 months of conservative therapy. Excellent (>75%) pain relief and a substantial increase in TcpO2

after trial stimulation showed a significant positive correlation with long-term success. Patients with a TcpO2 of less than 10mmHg following stimulation, tended to undergo an amputation within the first 3 months. The best results were in patients with severe claudication and rest pain without trophic changes in the foot (23).

Based on available literature, SCS reduces ischemic limb pain and the need for medication for analgesia. The mechanism of action is believed to be a modulation of sympathetic and parasympathetic balance although this has not been determined conclusively. The selection criteria of a baseline TcpO2 >20mmHg and ischemic ulcers of less than 3 cms in measurement seems to be the most important prognostic factors. In patients meeting these criteria, some have suggested that prolonged trialing is not necessary and can be done at the time of the permanent implant. In patients with diseases related to vasospasm, the mechanism of action is unclear and no definitive evidence studies have been performed.

Case Presentation

Angina

A 58-year-old white male presented with anginal pain at rest despite previous surgical revascularization. Repeat radioisotope stress testing showed persistent myocardium at risk. Angiography showed no lesions amenable to repeat surgery or cardiac stenting. The patient was treated with maximum medical therapies by a board-certified cardiologist, but was still unable to walk more than 20 feet or complete one standard flight of steps.

Spinal cord stimulation trialing was performed with one octrode lead at C7-T1 at midline, and a second octrode lead at T1-T2 5mm left of midline (Fig. 1). Hand-held computer programming resulted in excellent stimulation in the distribution of the angina. The patient had marked improvement in symptoms at 48 hours and an internal programmable generator was permanently implanted (Genesis, Advanced Neuromodulation Systems, Plano, Texas). In the following 6 months, the patient was able to reduce his nitrate consumption by 60%, participate in cardiac rehabilitation, and improve his exercise tolerance to one mile by continuous treadmill endurance testing. The patient was using the simple program of a guarded cathode at electrodes 4, 5 and 6 on the left-sided lead and a guarded cathode at electrodes 3, 4, 5 on the midline lead. Preferred frequency was 80hzs, and amplitudes were less than 3 mAmps. The patient found that he achieved the best outcome by using the system in a continuous fashion

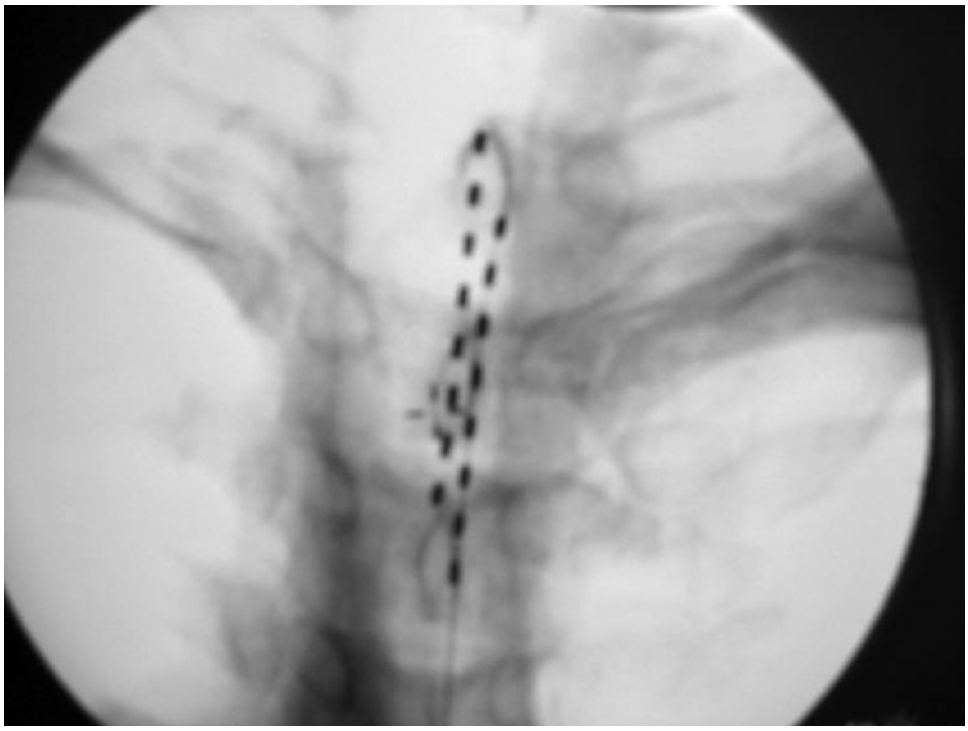

Fig. 1 *Trialing was performed with one octrode lead at C7-T1 at midline, and a second octrode lead at T1-T2 5 mm left off midline.*

Case Two

Peripheral Vascular Disease

A 46-year-old white female presented with a history of small vessel disease of the upper and lower extremities. Rheumatologic work-up suggested an atypical form of lupus. On vascular studies she had evidence of small vessel disease that was not amenable to surgical correction. The patient was treated with anti-platelet medications, and coumadin without success. She developed small ischemic lesions on both of her second, third and fourth upper phalanges (less that 0.5 cms). She also developed rest pain of her feet, which worsened with activity. A surgical digital sympathectomy of her upper extremities was attempted without success. Sympathetic nerve blocks of the stellate ganglion and lumbar plexus produced no improvement. Dual octrode leads were placed at C3, 4 and 5 in a staggered array just off midline. (Fig. 2)

Excellent stimulation was obtained using a simple cathode (electrode 5) and anode (electrode 7) pattern on both leads. Within 48 hours of initiating the trial, the patient had improved capillary refill, improved surface temperatures (2 degrees Celsius), and markedly reduced pain. The system was permanently implanted on Day 7 and stimulation was satisfactory. (Eon, Advanced Neuromodulation Systems, Plano, Texas). A trial was performed for the lower extremity ischemia 2 weeks later using octrode leads at T11 and T12. (Fig. 3)

Excellent stimulation was obtained at low amplitudes resulting in decreased pain and improved exercise tolerance. A permanent system was implanted without adverse events (Eon, Advanced Neuromodulation Systems, Plano, Texas). Over the next 3 months, all lesions healed, all evidence of ischemic disease resolved on exam, and the patient markedly reduced her oral opioids. The patient found a need to use continuous stimulation. On a few occasions, the patient turned the system off for more that 3 hours and experienced a return of her ischemia. This suggests an ongoing

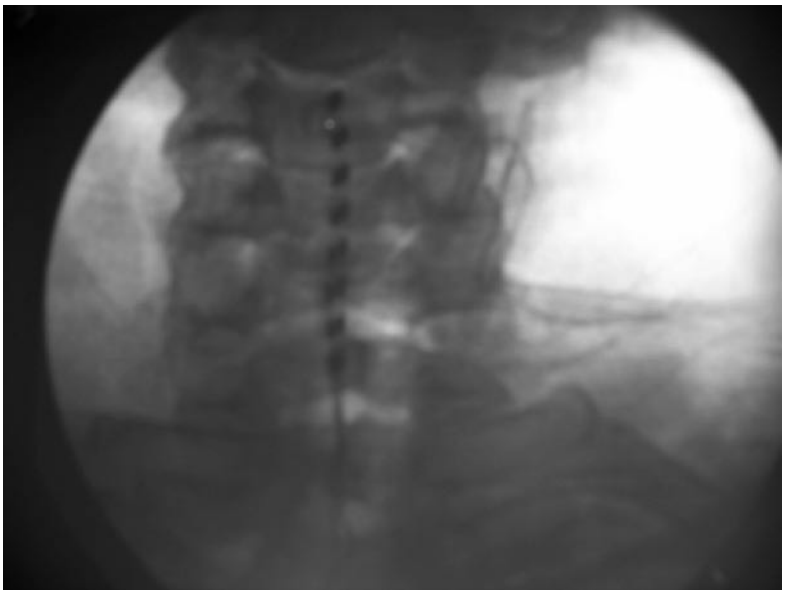

Fig.2. *Dual electrode leads were placed at C3, 4, and 5 in a staggered array just off midline*

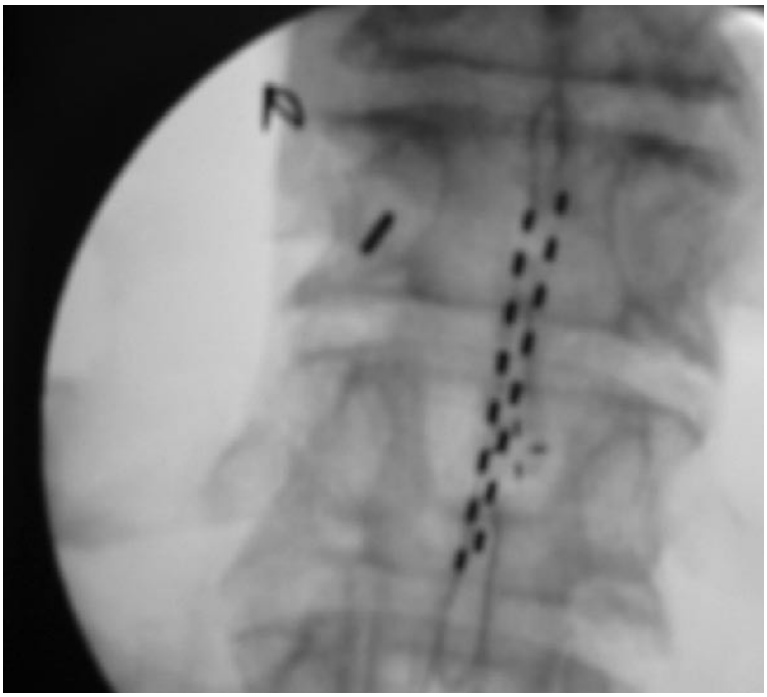

Fig.3. *A trial was performed for the lower extremity ischemia 2 weeks later using octrode leads at T11 and T12.*

mechanism of action with no change in the overall disease state in this case.

Conclusions

Spinal cord stimulation is an exciting area of medicine that allows many patients to have improved quality-of-life and reduced pain. The use of these devices in diseases of the cardiovascular system is an appropriate therapy and should be considered more often in these patients.

Author Affiliation:

Timothy R. Deer, MD
Medical Director
The Center for Pain Relief
Clinical Professor of Anesthesiology
West Virginia University School of Medicine
400 Court Street, Suite 304
Charleston, West Virginia, 25301
DocTDeer@aol.com

Louis J. Raso, MD
Medical Director
Interventional Pain Management
Jupiter, Florida 33469

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