



Spinal cord stimulation for angina pectoris and peripheral vascular disease

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Spinal cord stimulation (SCS) has been used with success to treat neuropathic pain in the United States and worldwide. Its use to treat angina pectoris and peripheral vascular disease (PVD) in patients deemed inoperable is widespread in Europe but not in the United States.

Patients afflicted with inoperable vascular insufficiency suffer greatly from pain, and their disease process may also limit their lifestyle. Since the uses and outcomes of SCS for inoperable cardiac and vascular disease was reviewed 8 years ago [1], a considerable amount of literature has been published on the topic.

Appropriate considerations when addressing this topic include the indications for SCS, physiologic and anatomic effects of SCS, pain relief obtained, persistence of any benefits with long-term follow-up, use of adjuvant medications for symptom control, SCS-driven changes in quality of life, and any effect on morbidity and mortality.

The scope of the disease process is significant. In patients with advanced limb vascular insufficiency, tissue loss is a clear concern. In the United States, approximately 60,000 amputations are performed each year [2]. In addition, the 5-year mortality in elderly patients with lower limb vascular insufficiency exceeds 50% [3]. Because many patients are burdened by advanced coronary artery disease (CAD) resulting in angina pectoris that is deemed inoperable or by advanced PVD resulting in claudication and rest pain that is also deemed inoperable, any benefit from SCS would be welcome.

Mechanisms of action

Several theories seek to explain the mechanism of action of SCS in advanced PVD [4]. One theory holds that electrical stimuli inhibit the transmission of

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nociceptive impulses from the dorsal horn to the brain by means of the spinothalamic tract. A second hypothesis holds that antidromic stimulation of the spinal cord causes nerve fibers to release mediators that result in vasodilatation, such as substance P, prostacyclin, and calcitonin gene-related peptide (CGRP). A third theory suggests the involvement of neurotransmitters, such as vasoactive intestinal peptide, serotonin, substance P, CGRP, gamma-aminobutyric acid (GABA), prostaglandins, and nitric oxide. A fourth theory suggests that SCS affects the autonomic nervous system and inhibits sympathetically-maintained vasoconstriction by means of alpha-1 adrenergic and nicotinic ganglionic receptors.

Investigators who have attempted to elucidate the effects of SCS on pain perception in angina suggest that the activation of wide dynamic range neurons, a decrease in the release of excitatory amino acids (such as glutamate and aspartate) by means of a GABA increase in the dorsal horn or the inhibitory effects of adenosine and facilitation of beta-endorphin release, are all mediated by SCS [5]. Given the postulated role of the thalamus in modulating cardiac ischemic pain, positron emission tomography scans show a relative increase in regional cerebral blood flow in the vicinity of the dorsomedial part of the thalamus with SCS [5].

Some have concluded that SCS-mediated reductions in pain and sympathetic tone in patients with angina improve the myocardial oxygen supply-demand ratio by reducing oxygen demand and increasing oxygen supply [5]. This is supported by the consideration that diseased myocardial vessels are already functioning at their maximal capacity and cannot accommodate an increase in blood flow.

Particulars related to SCS

One item of interest that is not always mentioned in studies is the continuous versus cyclical use of SCS in the prophylaxis and treatment of ischemic pain. One investigation had patients with angina undergo more stimulation during attacks of pain than for prophylaxis [6]. In another study, patients used SCS three times per day for 1 hour with additional elective use during angina attacks [7]. In practice, the patient implanted with SCS for angina pectoris often uses a comfortable low-intensity stimulation for several hours per day for preventive purposes [8].

Another variable to consider in the use of SCS for ischemic vascular disease is the question of appropriate SCS settings—a factor that, once again, is not always indicated in the relevant studies. Common parameters consist of an amplitude of 1.0 to 5.0 volts, a frequency of 70 to 120 Hertz, and a pulse width of 200 to 300 microseconds [9].

A third factor to consider is whether to perform a “trial” of SCS with a percutaneous lead (as is commonly done in treating neuropathic pain) or to simply do a “trial on the table,” and implant the pulse generator or receiver in the operating room once adequate paresthesia coverage of the painful area is obtained. The single-session implant is supported by one study in which 96% of

the cases done in a two-session protocol actually underwent implantation after a temporary external SCS trial [10]. In this study, the only patients who developed infection underwent the two-step procedure.

A final area of consideration is where to place the electrode in the epidural space. An accepted approach for treatment of angina pain is to puncture the epidural space at the T6 level and to advance the electrode to the level of T1 to T2 [6]. Electrode placement for pain from ischemia for PVD has been described in locations ranging from T8 to L1, and one study showed that stimulation at a higher level (T8 to T10) tended to cause vasoconstriction, while stimulation at T12 tended to cause vasodilatation [11].

The location of the pulse generator or the receiver ranged from below the costal arch to the abdomen, the iliac fossa, or the upper outer quadrant of the buttocks.

Spinal cord stimulation and angina

Angina pectoris is a condition of chest and sometimes arm and jaw pain caused by an imbalance in myocardial oxygen supply and demand. This imbalance is often secondary to atherosclerotic CAD but may also be a function of coronary vasospasm. Myocardial vascular supply may be enhanced by percutaneous transluminal angioplasty or coronary artery bypass grafting (CABG). The subset of the victims of frequent angina attacks who are not candidates for interventional coronary artery efforts and are medically managed with beta-blockers, calcium-channel blockers, and nitrates may be candidates for SCS.

Thus, one study's SCS inclusion criteria included frequent activity-limiting angina, persistence of angina despite optimal medical therapy, stable angina pattern, electrocardiographic or exercise test evidence of ischemia, CAD judged unsuitable for revascularization, and no contraindications for SCS (these would normally include conditions such as gross abnormalities in spinal anatomy and coagulopathy) [10]. In addition, patients must be able to manage the SCS device [6].

Studies examining the feasibility of SCS in "inoperable" angina pectoris have looked at several outcomes. One prospective, randomized study showed that SCS significantly reduces the frequency of angina attacks compared with controls [7]. The "electrical stimulation versus coronary artery bypass surgery" study (ESBY) showed that patients randomized to receive SCS had an 83.7% self-estimated treatment effect and a statistically significant decrease in the frequency of angina attacks [6]. A prospective study of 104 patients who underwent SCS implantation secondary to severe refractory angina pectoris showed a statistically significant diminution in angina episodes at rest, angina episodes with activity, and total angina episodes [10]. Patients enrolled in a prospective study who received SCS showed a statistically significant improvement in Canadian Cardiovascular Society angina class, with improvement of more than or equal to one class in 80% and of more than two classes in 42% [10].

In addition to its analgesic properties, SCS has anti-ischemic effects. A controlled study showed that SCS not only significantly increased time to angina during exercise testing but also significantly reduced ST segment depression at maximal exercise to a statistically significant degree [7]. The ESBY study, on the other hand, showed that those randomized to CABG had significantly fewer ischemic episodes as measured by ST analysis compared with the SCS group despite the fact that both groups had significantly fewer angina attacks [8]. This seems consistent with the finding that, despite its proven anti-anginal benefits, SCS does not deprive the patient of warning signals of actual myocardial ischemia, which is a function of lactate accumulation within the myocardium.

One index of efficacy for SCS is patient consumption of nitrates. A group randomized to SCS consumed significantly fewer nitrates than at baseline, with no difference found upon comparison with a group randomized to CABG [6]. Two prospective studies corroborated this finding [7,10].

A potential practical benefit of SCS would be its effect on a patient's quality of life. One prospective, randomized study showed statistically significant improvements over baseline in activities of daily life and social activity scores in patients who received SCS for angina [7]. The Nottingham Health Profile (NHP) assesses patients on 6 dimensions: energy, pain, emotional reactions, sleep, social isolation, and physical mobility. The ESBY study showed that patients randomized to SCS showed a greater than 30% improvement in NHP scores compared with baseline, which was significant and comparable to the improvement shown by patients randomized to CABG [12]. These results were consistent at follow-up of 4.8 years.

It is useful to look at follow-up data to see if the benefits of SCS persist. One study showed that at 1-year patients prospectively randomized to SCS showed second-order improvement in time to angina, exercise time, and ST-segment depression at maximal exercise and linear improvement in quality of life variables [7]. Similarly, the 2-year follow-up data from the ESBY study confirmed that 84% of patients reported symptomatic improvement in terms of reduced frequency and severity of angina attacks [13]. That this is not a placebo effect can be seen by the fact that the patients' symptoms recur with battery depletion or system dysfunction and are ameliorated by restoration of the system [1].

Despite its many benefits, long-term studies do not reveal any survival benefits of SCS for angina pectoris. A 2-year prospective study found no difference in cardiac or non-cardiac deaths between those who responded and those who did not respond to SCS [10]. The 5-year mortality of 27.9% in the ESBY study was similar between those who received SCS and those who received CABG, once again with no difference in the percentage of cardiac deaths [12]. The ESBY study showed that cardiac events between those randomized to SCS versus CABG were similar, but those receiving CABG suffered significantly more cerebrovascular events (stroke being a recognized complication of bypass) [6].

It is reasonable to ask if SCS is cost-effective. In one study, patients prospectively assigned to SCS decreased their rate of hospitalizations from

80% in the 6 months preceding implantation to 28% in the 6 months following implantation. Not surprisingly, this study also showed a strongly statistically significant decrease in the number of days spent in the hospital secondary to angina chest pain [10]. A 2-year follow-up of the 104 patients randomized in the ESBY study shed light on cost savings issues [13]. The cost of the primary intervention is clearly higher in the CABG group, while that of follow-up interventions (eg. battery or lead replacement) is higher in the SCS group. Nonetheless, the SCS group showed a strongly significant cost savings overall and, once again, a decrease in hospital days secondary to cardiac morbidity. Patients receiving SCS in the ESBY study spent an average of 5 days in the hospital associated with their implantation, and the subsequent decrease in the amount of time required for this procedure may lead to further cost savings.

Spinal cord stimulation and peripheral vascular disease

As mentioned earlier, SCS use for PVD deemed to be surgically inoperable has been only slowly embraced in the United States, despite its prevalence in Europe. An ischemic limb is considered unreconstructable only if it is impossible to perform angioplasty or bypass grafting [4]. In addition to its potential use to treat extremity pain due to vascular insufficiency, SCS has been examined for possible effects on walking distance, healing of ischemic leg ulcers, quality of life, limb salvage, and days of hospitalization for PVD.

Most of the studies reviewed use similar selection criteria. To be included, patients must have recurring ischemic rest pain (usually of 2 weeks or more duration) and unreconstructable disease of the lower extremity (ie, lack of suitable vessels, ankle/brachial indices <0.4 , or great toe pressures <30 mm Hg) [4,14]. Inclusion criteria usually limit ischemic ulcers to a diameter of no more than 3 cm^2 , since larger ulcers show a propensity not to heal [4]. The severity of PVD is often assessed with the Fontaine classification: stage I is asymptomatic, stage II has intermittent claudication, stage III has pain at rest, and stage IV has pain at rest and ulcers [2].

In multiple studies, SCS improved pain for patients with PVD deemed inoperable. A review of European literature revealed that 70% to 80% of patients achieved significant ($>75\%$) pain relief [9]. Because 70% of these patients achieved sustained relief that was lost immediately on lead displacement or generator depletion, the beneficial effect was unlikely caused by the placebo effect. A prospective, randomized study found pain scores significantly lower at 2 and 18 months in the SCS group compared with a control group receiving standard analgesic therapy [15]. In a series of 10 SCS patients, 9 achieved pain relief; this study underscored the finding that patients with Fontaine stage III disease fared better than those with stage IV disease [11]. A dissenting opinion was offered by another prospective trial, where patients randomized to SCS and to standard analgesic therapy showed significant decreases in pain scores with no difference

between the groups [3]. This trial included patients with stage IV disease, and the report did not mention the parameters of SCS (amplitude, frequency, pulse width, electrode location) but did note a significant decrease in narcotic and non-narcotic analgesic use among the SCS group.

The issue of the outcome among patients with stage IV disease is relevant with respect to claudication. In the aforementioned series of 10 patients, claudication distance increased significantly in 5 of 5 with stage III but only 1 of 5 with stage IV disease [11]. Some investigators have suggested that special attention be paid to stage II patients, whose claudication distance may become reduced to the point where they develop pain at rest [2]. The theory arising from this study is that the sooner SCS is applied, the better the expected outcome.

Several investigators have examined the impact of SCS on microcirculatory blood flow to shed light on SCS's effects. Microcirculatory blood flow can be assessed by way of capillaroscopy (visualization of skin capillaries in hand and foot nailbeds), measurement of transcutaneous oxygenation, or a Doppler laser flow study [2]. Approximately 90% of distal skin blood flow normally passes through subpapillary, thermoregulatory vascular beds that bypass the nutritional capillaries through arteriovenous anastomoses [16]. A prospective study showed that patients with good outcomes from SCS and baseline transcutaneous partial pressures of oxygen (TcPO₂) less than 30 mm Hg showed significant increases in TcPO₂ in the symptomatic leg [14]. The study found that a combination of excellent (>5%) pain relief and increase in TcPO₂ of 10 mm Hg or more above baseline values correlated significantly with long-term (patients were followed up to 36 months) pain relief. A small study found SCS increased skin capillary blood flow measured by laser Doppler flowmetry in affected and unaffected limbs, with the greater response in the unaffected limb being presumably secondary to relative preservation of vasomotor responsiveness in the limb with less disease [11].

An additional area of outcome investigation is ulcer healing and tissue loss. In one study, trophic ulcers healed at a rate of approximately 20% with SCS and tended to show evidence of healing if TcPO₂ rose to a level greater than 25 mm Hg [14]. Two randomized, controlled trials showed no significant benefit with regard to limb salvage from SCS versus medical therapy, although the amputation rate tends to be lower among patients without than with hypertension [3,15]. A retrospective analysis showed that co-existing diabetes leads to a poorer prognosis of SCS for limb salvage, with 34% of diabetics treated with SCS requiring amputation, as opposed to 28.5% of non-diabetics [2].

A final area of interest when discussing SCS and PVD is the outcome of the therapy on quality of life. A group randomized to SCS and medical treatment versus medical treatment alone was evaluated for up to 18 months by means of the NHP, the EuroQol questionnaire, and the mobility subscore of the Sickness Impact Profile [3]. The overall scores for quality of life improved significantly with no difference between groups. The mobility and energy subscores of the NHP for non-amputated patients, however, were significantly higher in the SCS patients. This study also found that amputation had a negative effect on mobility but led to substantial pain relief.

Complications

Several studies have addressed the issue of complications in the use of SCS for angina pectoris and PVD. In a study of angina, 2 of 17 patients experienced electrode migration requiring intervention within 12 months [7]. Electrode migration and associated changes in paresthesia are treated by reprogramming the stimulator or by surgical revision. In a prospective study of 104 patients, 6 developed site infections [10]. A total of 6 patients in this series had to be explanted, 4 for pocket site infections, 1 for pain at the generator site (abdominal), and 1 because of electrode dislodgement. The ESBY study had three electrode displacements that required re-operation but no intraspinal infections [13]. The average life span of the pulse generator was at 3.3 years, and 17 of 57 pulse generators had to be replaced within 5 years.

A retrospective review of SCS for the treatment of chronic critical limb ischemia reported a total technical complication rate of up to 15% [4]. Lead dislocation usually occurred within the first 2 months after implantation, and infections requiring explantation and antibiotic therapy were rare.

A similar retrospective analysis of 95 cases of SCS for PVD reported a 15.7% complication rate that included 14 cases of spontaneously resolving seroma; 1 cerebrospinal fluid fistula; 22 electrode displacements confirmed by radiograph findings, many of which required re-operation; and 8 generator site infections, none of which required explantation [2]. It is reasonable to treat a potential site infection with oral or intravenous antibiotics and then, if this is unsuccessful, to explant the system. This study also reported that eight patients experienced decubiti at the site of pulse generator implantation, which was subcostal. Many clinicians implant the pulse generator below the belt line in the upper outer quadrant vicinity of the buttocks.

Summary

SCS is a viable option for treating angina pectoris and inoperable PVD. Its mechanism of action remains controversial, but successful pain relief has been consistently reported in various studies. Many clinicians are foregoing a formal trial, choosing instead to obtain an adequate area of paresthesia and implant in one session.

Long-term follow-up of SCS patients treated for angina pectoris shows continued pain relief, increase in activities, and decreased use of medications. Emerging literature supports the finding that SCS is cost-effective in this patient population relative to CABG. SCS does not mask the ischemic pain that signals impending further damage of the myocardium.

In patients with inoperable PVD, SCS relieves pain and improves microcirculatory blood flow. Quality of life and mobility can be improved with SCS. The beneficial effects of SCS on ulcer healing are controversial, and evidence suggests that the best candidates for the procedure are those with ischemic rest pain without

tissue loss. Patients with diabetes mellitus and hypertension may have the least favorable outcomes with regard to limb salvage. No convincing data have been published on the cost-effectiveness of SCS in this patient population.

SCS is a safe procedure that is minimally invasive, reversible, and associated with only infrequent side effects, the most common of which include lead migration and infection. SCS is clearly an option for the improvement of pain and the quality of life in this carefully selected subset of patients.

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