Review

Spinal Cord Stimulation for Chronic Intractable Angina Pectoris: A Unified Theory on Its Mechanism

OSMAN A. LATIF, M.D., SRDIJAN S. NEDELJKOVIC, M.D., LYNNE WARNER STEVENSON, M.D.

Department of Medicine, Cardiovascular Division and Department of Anesthesia, Perioperative, and Pain Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts, USA

Summary: The use of spinal cord stimulation (SCS) for chronic intractable anginal pain was first described in 1987. Numerous studies have demonstrated its efficacy in improving exercise tolerance, decreasing frequency of anginal episodes, and prolonging time to electrocardiographic signs of ischemia. This review will examine the potential mechanisms of this antianginal effect and propose a unified hypothesis explaining it. The effect of SCS involves a mutual interaction of decreased pain, decreased sympathetic tone, and a likely redistribution of myocardial blood flow to ischemic regions. Spinal cord stimulation reduces the transmission of nociceptive impulse via the spinothalamic tract due to an enhanced release of gamma aminobutyric acid (GABA) from dorsal horn interneurons. Improvement of myocardial blood flow at the microvascular level has been demonstrated by positron emission tomography (PET). A decreased sympathetic tone has been shown by norepinephrine kinetics, tests of sympathetic reflexes, and the use of ganglionic blockers. We hypothesize that SCS exerts its beneficial effects by decreasing pain and decreasing sympathetic tone, the result of which is decreased myocardial oxygen consumption along with an improved myocardial microcirculatory blood flow.

Key words: angina, syndrome X, spinal cord stimulation, ischemia, autonomic nervous system, myocardial blood flow, gamma aminobutyric acid, spinothalamic tract

Spinal Cord Stimulation: Introduction and Clinical Experience

Recently, spinal cord stimulation (SCS) has emerged as a treatment option for patients with refractory angina pectoris, defined as persistent angina pectoris class III and IV despite maximally tolerated conventional medical treatment.¹ These patients often suffer a dismal quality of life due to constant anginal pain and loss of function. Many of the patients suffer from poor ejection fractions and concurrent peripheral vascular disease. In addition, they require frequent hospitalizations for anginal pain, further taxing today's cost-conscious health care system.^{2,3}

The use of spinal cord stimulation (SCS) was first described in 1967.^{4,5} It has since been used for the treatment of diverse conditions such as neuropathic pain, peripheral vascular disease, spasticity, and Buerger's disease, among others. In 1987, Murphy and Giles published the first report of SCS in the treatment of chronic intractable angina pectoris.⁶ Since then there have been numerous studies examining the effects of SCS on myocardial physiology. The mechanism of action of SCS is complex and involves a unique interplay of pain relief, changes in myocardial blood flow, and modulation of sympathetic activity. Based on a review of the literature, we hypothesize that SCS exerts its beneficial effects by decreasing pain and sympathetic tone, the result of which is an improvement of coronary microcirculatory blood flow.

Spinal cord stimulation is a reversible procedure in which electrodes are placed in the epidural space to stimulate the dorsal columns of the spinal cord. It is intended for patients with chronic intractable anginal pain who have failed maximal medical therapy and are no longer candidates for conventional therapies such as coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA). Randomized, controlled trials have demonstrated that SCS increases exercise duration, increases time to angina, decreases number of angina attacks, decreases sublingual nitrate consumption, and decreases number of ischemic episodes.⁷ A 2-year prospective analysis of patients after SCS implantation showed a significant increase in average exercise time on a treadmill test and a decrease in the number of weekly anginal

Address for reprints:

Osman A. Latif, M.D.
Department of Anesthesiology
Perioperative and Pain Medicine
Brigham and Women's Hospital
75 Francis Street
Boston, MA 02115, USA

Received: June 2, 2000

Accepted: June 26, 2000

episodes.⁸ Also, SCS therapy has proven to be both safe and cost effective, resulting in a reduced number of hospital admissions in this group of patients.^{2, 3} It does not mask new anginal pain or signs of myocardial ischemia, and there is no increase in the incidence of arrhythmia.⁹⁻¹¹ The safe use of SCS systems with the concurrent use of cardiac pacemakers has been reported.^{12, 13} The most common complications are electrode lead migration (23%), infection (5%), and electrode fracture (3%).^{14, 15}

Four potential mechanisms are responsible for the beneficial effects of SCS in angina: reduction of pain perception, decreased sympathetic tone, reduced myocardial oxygen demand, and improved coronary microcirculatory blood flow. The following review proposes that the primary mechanism behind SCS is a reduction in pain and sympathetic tone, which ultimately improves the myocardial oxygen supply-demand ratio.

Inhibition of Pain Perception

There is substantial evidence that SCS can reduce cardiac pain perception by its direct effects on the spinal cord and brain, by reducing release of spinal neuroexcitatory transmitters, and by increasing endorphin levels.

Anatomic Pathways

Spinal cord stimulation inhibits the spinothalamic tract response to stimulation of both somatic and sympathetic pathways.¹⁶ High stimulus threshold nociceptive neurons normally activated by electrical stimulation of cardiopulmonary sympathetic afferent fibers are inhibited by SCS. Experiments show that SCS can also reduce the excitability of spinothalamic tract cells, which is produced by noxious stimuli such as intracardiac bradykinin injections. In addition to this suppressive effect, SCS activates wide dynamic range (WDR) neurons (responsible for paresthesias and innocuous stimuli), which explains why a "tingling" sensation occurs in the somatic fields corresponding to chest pain when SCS is activated.^{16, 17}

Stimulation of A-alpha and A-beta fibers has an inhibitory effect on the response from nociceptive A-delta and C fibers, which is consistent with the gate-control theory of pain.¹⁸ Chandler *et al.* hypothesized that SCS activates the large afferent fibers in the dorsal column which then antidromically transmit impulses via collateral branches to the spinothalamic tract cells and possibly other pathways for nociceptive impulses.¹⁶ Transsection of the ipsilateral dorsal column between the SCS electrode and the spinothalamic tract cell abolishes the pain inhibitory effect of SCS.¹⁶

Role of Gamma-Aminobutyric Acid and Adenosine

Spinal cord stimulation has been shown to decrease the release of excitatory amino acids (glutamate and aspartate) via an increase in the release of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the dorsal horn.¹⁹

Adenosine, which can function as a neurotransmitter and is known to reduce experimentally induced pain, can potentiate the effect of SCS on the spinal cord.²⁰ In addition, a combination of subtherapeutic intrathecal doses of baclofen (a GABA_B receptor agonist) and R-PIA (an adenosine A₁ agonist) has been found to potentiate the effects of SCS in rats which were not initially responsive to SCS.²¹ This results from a normalization of the response of hypersensitized wide dynamic range (WDR) neurons to innocuous stimuli.²² The effects of SCS are suppressed if GABA_B antagonists and adenosine A₁ antagonists are given. Studies confirm that inhibition of excitatory amino acid release via GABA-nergic or adenosine A₁-dependent mechanisms plays a role in the effect of SCS on pain suppression.

Beta-Endorphin Release

In experimental pacing studies, SCS has been found to enhance the release of beta-endorphin.²³ Studies have shown that beta-endorphin (endogenous mu agonist) release occurs as a probable protective mechanism after myocardial ischemia.²⁴ In addition to decreasing the sensation of pain, beta-endorphin is thought to play a role in decreasing myocardial contractility and subsequent oxygen consumption. There is speculation that opioid receptors exist in the presynaptic terminals of sympathetic neurons innervating the heart. Activation of these by beta-endorphin may then cause a decreased release of norepinephrine.²⁵ Patients with silent ischemia have higher levels of beta-endorphin than do patients with painful ischemic symptoms, suggesting that those higher levels of beta-endorphin may suppress pain perception.²⁶

Effect on Cerebral Blood Flow

Evidence that SCS has direct analgesic effects is confirmed by techniques of brain imaging the pain response. Changes in regional cerebral blood flow (rCBF) in areas involved with nociception and cardiovascular control as measured by positron emission tomography (PET) have been documented in patients treated with SCS.²⁷ Of note, the dorsomedial part of the thalamus showed a relative increase in cerebral blood flow with SCS. Since the thalamus is thought to have a function in the mediation of cardiac ischemic pain, Hautvast *et al.*²⁷ speculate that changes seen in rCBF in the thalamus during SCS imply an effect that stimulation has on ischemic pain. Also of note, SCS resulted in a bilateral decrease in rCBF in the posterior inferior insular cortex, an area that modulates sympathetic effects. Increases in rCBF in the right insular cortex correlated with severe chest pain in patients with syndrome X when compared with controls and patients with coronary artery disease (CAD).²⁸ In addition to modulating sympathetic effects, this area of the brain may be involved with abnormal visceral pain perception.²⁸

It is postulated that the beneficial effects of SCS on angina primarily originate from the well-supported effects SCS has on pain perception. Certainly, the literature confirms that SCS has direct analgesic effects on angina and on many other

painful conditions such as low back pain and neuropathic pain. The pain-relieving effects of SCS can then induce other beneficial physiologic changes for the heart as outlined next.

Effects on Sympathetic Tone

Spinal cord stimulation has been shown to result in a decreased sympathetic tone, as shown by norepinephrine kinetics, tests of sympathetic reflexes, and the use of ganglionic blockers. We hypothesize that by attenuating pain, sympathetic tone is reduced.

Norepinephrine Kinetics

The effects of SCS on reducing sympathetic tone can be shown by measuring norepinephrine spillover, which is a measure of how much norepinephrine is released into the body.²⁹ A study of pacing-induced ischemia in patients with severe stable angina using a radioisotope dilution technique demonstrated that SCS attenuated the elevation of total body norepinephrine spillover, with no increase in cardiac norepinephrine spillover.²⁹ In addition, patients showed a decreased rate–pressure product when SCS was introduced during pacing, which supports the relationship between decreased sympathetic tone and resultant decreased myocardial oxygen consumption.³⁰

Heart Rate Variability

Although SCS has not been shown to affect heart rate variability, which is another marker for studying the autonomic nervous system, the clinical results of these studies support an overall beneficial effect on sympathetic tone.^{11, 31} Problems with current studies on heart rate variability include lack of uniformity in the use of SCS and the concurrent use of other vasoactive drugs (beta blockers, calcium-channel blockers, nitroglycerin).^{32, 11} Future better-controlled studies will be necessary to resolve this issue.

Other Studies of Sympathetic Tone

Several other studies support our hypothesis that SCS reduces sympathetic tone. In a study of patients with syndrome X, electrical stimulation by transcutaneous electrical nerve stimulation (TENS) was found to produce peripheral sympathetic inhibition and decrease rate–pressure product. This benefit was concurrent with decreased oxygen consumption as marked by decreased mean coronary blood flow velocity and decreased coronary blood flow index.³⁰

In another TENS study, an inhibitory action on sympathetic reflexes was found.³³ This attenuation was more pronounced in states of increased sympathetic activity, suggesting that stimulation has a mild effect at rest and a more significant action during times of increased sympathetic tone (i.e., pain or ischemia). The effects of SCS on autonomic tone are evidenced by patients' clinical report of warm sensations caudal to the level of electrode placement.^{17, 34} Also, it has been shown that

by attenuating efferent sympathetic activity, SCS can induce vasodilatation of the peripheral microcirculation, an effect that can be blocked by administration of the ganglionic blocker hexamethonium.³⁵ Application of SCS to dogs can reduce intracardiac neuronal activity, which is otherwise increased with ischemia.³⁶ The implications of these and other studies are still not certain; therefore, further studies are needed to clarify the relevance of such findings.

It is our belief that the current evidence suggests that SCS reduces sympathetic response and that future controlled studies are needed to confirm this hypothesis. By reducing pain and diminishing sympathetic response, microcirculatory supply–demand relationships are favorably affected.

Influence on Myocardial Blood Flow

Based on the positive clinical outcomes of SCS in end-stage angina pectoris, it is natural to assume that improvement in myocardial oxygenation occurs. Spinal cord stimulation has previously been shown to improve microcirculatory blood flow in patients with nonreconstructable peripheral arterial occlusive disease.^{37–40} For positive influence of SCS on the imbalance between myocardial oxygen supply and demand, it would need to cause one or more of the following: (1) decrease myocardial oxygen consumption, (2) increase myocardial blood flow, or (3) induce a redistribution of blood flow favoring ischemic regions (sometimes referred to as “homogenization” of blood flow). In analyzing the literature, it is our belief that reductions of pain and sympathetic tone that result from SCS lead to decreased oxygen demand, with an improvement in the myocardial demand–supply balance (see Table I).

Evidence Supporting Decreased Myocardial Oxygen Consumption—Decreased Demand

There is good evidence that the anti-ischemic effect of SCS is related to a decrease in myocardial oxygen consumption.^{30, 41} In a study by Mannheimer *et al.*,^{20, 41} patients with New York Heart Association (NYHA) III or IV angina were paced to moderate angina, at which point coronary sinus blood flow measurements and lactic acid samples were taken. Patients with SCS had reduced myocardial oxygen consumption and a proportionally reduced myocardial blood flow as measured via a coronary sinus catheter. When SCS was utilized, myocardial lactate production and anginal symptoms occurred only at the highest rates of atrial pacing. Of note, angina occurred when myocardial lactate production was detected, indicating that the anginal warning system was not deactivated. Unfortunately, the atrial pacing protocol utilized in this study has been questioned since it may result in an anti-ischemic effect as caused by ischemic preconditioning,⁴² in which brief episodes of ischemia render the myocardium more resistant to later ischemic events.^{43–45} Therefore, the relative contributions of SCS to reduction of oxygen consumption and the effects of ischemic preconditioning cannot be distinguished from this early experience.

TABLE I A comparison of studies evaluating the effects of dorsal column stimulation on myocardial blood flow

First author/year	Patient selection	Methods
DeLandsheere, 1992	8 patients CCS III or IV SCS stopped 48 h prior Antianginal medications stopped 24 h prior Unipolar stimulation- Frequency: 33 to 130 Hz Width: 210–450 microseconds Amplitude: 3.5 to 8.25 V	SCS/PET scan Control: K-38 at rest—bicycle test—K-38 injection— K-38 to document recovery after 40 to 60 min Test: SCS for 20 min—K-38—continued SCS exercise test for 30 min up to previous workload—K-38 injection
Mannheimer, 1993	20 patients in NYHA III or IV SCS stopped 48 h prior Antianginal medications stopped 12 h prior Stimulator settings not described	Atrial pacing study Paced to angina—30 min rest—20 rest with stimulation— paced with stimulation to new anginal threshold Coronary blood flow measurements made with continuous infusion thermodilution (Wilton-Webster cath) placed in coronary sinus
Chauhan, 1994	34 patients with syndrome X 15 patients with CAD of right coronary artery (left coronary artery clear) 16 patients with heart transplantations All vasoactive medications stopped 48 h prior TENS settings: frequency 150 Hz, width 300 ms, amplitude 10 to 60 milliamps	TENS / angiogram Coronary blood flow at rest—TENS for 5 min— repeat measurements Judkins-Doppler 8F in normal left coronary ostium
Hautvast, 1996	9 patients in NYHA III or IV Antianginal medication unchanged prior Stimulation 1 h prior to second PET session Bipolar electrode frequency 85 Hz, width 210 microseconds amplitude 1.1 to 7.0 V	SCS / PET scan Baseline study prior to stimulator activation—repeat study after 6 weeks of stimulation for 1 h three times/day plus when anginal pain occurred Stimulation for 1 h prior to second test PET scan using N ¹³ and dipyridamole
Sanderson, 1996	11 patients with syndrome X Antianginal medications withheld 24 h TENS settings: frequency 70 Hz width 200 ms, 35–50 milliamps	TENS / angiogram catheterization—rest (5 min)—cold pressor test (90 s)—catheterization—rest—TENS at rest (5– 10 min)—catheterization—rest with TENS—cold pressor test with TENS—catheterization 3F monorail-Doppler catheter in LAD quantitative coronary angiography with automatic contour detection
Jessurum, 1998	18 patients in NYHA III with significant single-vessel disease of LAD or LCx 10 patients—TENS 5 patients—precordial stimulated treatment 3 patients—TENS to back Vasoactive medications stopped 5 half-lives prior, except for short-term nitrates TENS settings: frequency 80 Hz, width 200 ms, amplitude 30–40 V	TENS / angiogram: angiogram—TENS (6 min)—angiogram measurements made of stenotic and nonstenotic artery 2 Doppler flow velocity wires (0.018 in) in proximal part of LAD and LCx
Norrzell, 1998	8 patients—CAD 4 patients—syndrome X Beta blockers stopped 48 h prior SCS stopped 48 h prior Stimulation parameters not mentioned	Atrial pacing study / angiogram control paced 80 beats/min Rate increased 10 beats/min 2 min until angina— rate locked—angiogram—SCS treatment at rate locked rate (5 min)—angiogram Attempted to place 0.46 mm Doppler guidewire prestenotically in artery shown to correspond to ischemic area (heterogeneous placement of guidewire due to safety issues)

Abbreviations: CCS = Canadian Cardiovascular Society Functional Classification, SCS = spinal cord stimulation, PET = positron emission
LAD = left anterior descending artery, LCx = left circumflex artery.

Findings	Authors' conclusions
Resting heart rate and blood pressure elevated during SCS Slightly increased resting myocardial clearance of K-38 after SCS but not significant Increased regional myocardial clearance in nonaffected segments before and after SCS in response to exercise No significant changes in myocardial clearance both without SCS and with SCS from rest to exercise Decreased magnitude and duration of ST depression with SCS	SCS does not improve regional blood flow
Increased tolerance to pacing Lactate production changed to extraction with stimulation at comparable pacing rates ST depression decreased Time to ST depression increased Time to ST recovery decreased Decreased coronary sinus blood flow and oxygen consumption at pacing producing angina with stimulation, lactate extraction reverted to production	Anti-ischemic effects secondary to decreased myocardial oxygen consumption Myocardial ischemia does still give rise to pain Was this ischemic preconditioning?
Increased coronary blood flow velocity in syndrome X and CAD but not heart transplant group No significant changes in coronary arterial diameter of LAD and LCx by electronic digital calipers (Sandhill Scientific) Significant decrease in epinephrine levels in syndrome X and CAD patients No change in rate $\times$ pressure product	TENS has a neural mechanism for increasing coronary blood flow since it had no effect in the deinnervated heart transplant patients Site of action is at microcirculatory level Suggests decreased sympathetic activity of heart
No significant changes in coronary blood Total resting blood flow unchanged Flow reserve decreased Coefficient of variation of flow decreased after stimulation both at rest and with dipyridamole	SCS work due to homogenization of myocardial blood flow Dipyridamole effect may be blunted by SCS Short-term effect may increase myocardial blood flow, long-term may provide more homogenization of blood flow
Decreased mean coronary blood flow velocity Decreased coronary blood flow index Decreased rate $\times$ pressure product Increased coronary vascular resistance No changes in epicardial coronary diameter No significant difference in abnormal response to cold pressor test	Unlikely to have a direct effect on coronary artery vasomotion or hemodynamics but reduces rate $\times$ pressure product and therefore oxygen consumption, probably via sympathetic inhibition rather than a direct effect
Diameter of stenotic artery decreased in study group Diameter of nonstenotic artery increased in study group No effect on average peak velocity Coronary volumetric flow decreased in stenotic artery and increased in nonstenotic artery	Suggests TENS modulates regional coronary vasomotion in patients with CAD: (1) coronary branch steal secondary decreased microvascular resistance, (2) collateral steal during afferent electrical stimulation Improved regional flow at microcirculatory level
Average peak velocity increased in all CAD patients with pacing, but no changes when SCS started 6 / 8 patients became angina free when SCS started	Results do not support theory that anti-ischemic effects of SCS are dependent on coronary blood flow velocity Current data favor anti-ischemic effect is secondary to decreased myocardial oxygen demand

tomography, NYHA = New York Heart Association, CAD = coronary artery disease, TENS = transcutaneous electrical nerve stimulation,

A study that attempts to resolve the issue of ischemic preconditioning is another pacing study by Norrsell *et al.*⁴⁶ Eight patients with CAD and four with syndrome X (anginal pain in the presence of angiographically normal coronary arteries) were atrial paced to moderate angina. Pacing frequency was maintained (rate-locked) for 2 min, at which point SCS commenced while maintaining the same pacing rate. Because a reperfusion interval was not allowed, their protocol may have potentially compensated for any effects of ischemic preconditioning. Although this study found no significant change in coronary blood flow velocity, the authors concluded that it is likely that SCS exerts beneficial effects by decreasing myocardial oxygen consumption. In addition, it was noted that six of eight patients with CAD became angina free when SCS was started.

Although it is difficult to determine what role ischemic preconditioning may have had in confounding the results of the studies by Mannheimer *et al.* and Norrsell *et al.*, these studies suggest a mechanism involving a decreased myocardial oxygen consumption and demand which we postulate is due to decreased overall sympathetic tone. Both studies directly stressed the heart and made real-time measurements of coronary blood flow compared with other studies done at rest. Mannheimer *et al.* indeed confirmed changes in myocardial blood flow, supporting decreased oxygen consumption and demand. We believe Norrsell *et al.* failed to find changes because they administered SCS for only 5 min; nonetheless, the clinical results were good. Further studies using a standardized protocol of stimulation, stressors, and blood flow measurements are needed.

Lack of Evidence Supporting Increased Myocardial Blood Flow—Increased Supply

There are no studies that support the hypothesis that SCS results in increased myocardial blood flow in diseased vessels at the macrovascular level. The literature supports SCS inducing an increased coronary blood flow in normal segments and having no effect or even decreasing coronary blood flow in diseased segments. Perhaps microcirculatory changes are reflected proximally in normal large (measurable by angiography) vessels that are able to accommodate an increased blood flow, whereas diseased large vessels are already at their maximal blood flow capacity and therefore unable to accommodate any further increases in blood flow. Therefore, although there is likely an improvement in the overall oxygen supply-demand ratio as induced by SCS, it is likely due to decreased myocardial demand and not increased total myocardial blood supply.

An often quoted study by Chauhan *et al.* that is purported to support the mechanism by which SCS increases myocardial blood flow at the macrovascular level is actually a study using TENS.⁴⁷ We know of no studies directly comparing the effects of TENS and SCS. Also, this study was done with patients at rest, measurements were taken only from normal coronary arteries, and the changes found in blood flow velocity may have been due to a redistribution phenomenon.³⁰ In summary, in-

creased total myocardial blood supply is not a likely consequence of SCS.

Evidence Supporting Homogenization of Myocardial Blood Flow

While SCS may not cause an increase in total myocardial blood flow, it does induce a homogenization of regional myocardial blood flow, with improvement in regional blood flow to ischemic areas.^{48,49} Using PET, Hautvast *et al.* demonstrated homogenization by showing a decreased coefficient of variation of myocardial flow from ischemic to nonischemic regions in patients with CAD during both rest and dipyridamole stress testing during SCS.⁴⁸ Jessurun *et al.*, in a controlled study of patients undergoing elective angioplasty for single-vessel disease of the proximal left anterior descending coronary artery or left circumflex artery, showed similar results with TENS when measuring coronary volumetric flow in both diseased and normal arteries, indicating a redistribution of coronary blood flow.⁴⁹ Decreased microvascular resistance occurs, allowing collateral filling of ischemic regions by either branch or collateral steal. Homogenization of blood flow will benefit patients by improving the ratio of epicardial to subendocardial blood flow, perhaps by increased collateral flow to ischemic regions.

It is speculated that SCS may improve homogenization of myocardial blood flow by attenuating the effects of dipyridamole or adenosine on coronary arteries, thereby preventing a deleterious redistribution of blood flow from the subendocardium to the epicardium secondary to increased adenosine levels.⁴⁸ Dipyridamole blocks the reuptake of adenosine which, through its action on the adenosine A₂ receptor, is a potent vasodilator responsible for inducing coronary steal.⁴⁸ A study examining the effects of SCS on left ventricular function after adenosine provocation demonstrated a less pronounced decrease in left ventricular ejection fraction, measured by echocardiography, in patients during SCS.⁵⁰ A prolonged time to signs of ventricular dysfunction (regional wall motion abnormalities), decreased anginal pain, and a shorter recovery time were also noted during SCS. However, whether this is due to a blocking of the adenosine effect, improved microvascular blood flow, or other mechanisms is unclear.

Calcitonin-Gen-Related Peptide and Other Mediators

Spinal cord stimulation may have direct local neurohumoral effects which improve coronary circulation. It is speculated that SCS results in a local myocardial turnover of leu-enkephalin and calcitonin-gene-related peptide (CGRP).²³ Croom *et al.* demonstrated that a CGRP antagonist prevents SCS-induced cutaneous vasodilation in rat studies.⁵¹ A subsequent study also suggests a role for CGRP as a mediator in the effect of SCS in increasing the survival rate of skin flaps with critical ischemia.⁵²

Summary

In summary, the effects of SCS on coronary vasculature are likely to occur at the microcirculatory level, without an in-

crease in total coronary blood flow. There is evidence to suggest that these changes in microcirculatory redistribution are secondary to decreased sympathetic outflow.³⁴ Similarly, SCS has been shown to improve microcirculatory flow in patients with peripheral vascular disease and in patients with critically ischemic skin flaps.^{37–40, 52} In the heart, the improved flow at the microcirculatory level combined with a potentially decreased myocardial oxygen demand due to decreased sympathetic tone will reduce the myocardial oxygen supply–demand imbalance in patients with CAD. Further controlled studies with a standardized protocol of SCS and coronary flow measurements are necessary to confirm this hypothesis.

Issues in Designing Studies on Spinal Cord Stimulation

There are multiple issues that need to be resolved in designing further studies on the mechanism of SCS in angina (Table II). First, protocols for pacing studies must recognize the factor of ischemic preconditioning. Evidence from rabbit and dog models shows as little as 1.5 to 2.5 min of ischemia and short periods of myocardial oxygen supply–demand imbalance (without complete occlusion) have been sufficient to “precondition” the heart.⁴⁵ The atrial pacing studies for SCS paced the patients to angina, then made measurements at that pacing rate, followed by a 50-min period of rest, and then paced the patients again. In humans, when two subsequent exercise tests were separated by 15 min, the second test showed an increased duration of exercise and attenuation of ST depression compared with the first test.^{45, 53} Recent evidence from pig studies implicates bradykinin as essential for preconditioning of short duration and adenosine for preconditioning of longer duration.⁵⁴ The cellular mechanisms of ischemic preconditioning are beyond the scope of this discussion, but much needs to be learned before a final verdict on ischemic preconditioning can be made.

A second issue in myocardial oxygen supply–demand is lack of standardization of coronary blood flow measurement, which has been done in multiple locations. Chauhan *et al.* sampled healthy left coronary arteries,⁴⁷ Mannheimer *et al.* sampled the great cardiac vein of the coronary sinus,⁴¹ Norrsell *et al.* attempted to place the Doppler guidewire prestenotically in areas corresponding to ischemia,⁴⁶ Sanderson *et al.*

placed the catheter into the left anterior descending artery,³⁰ and Jessurun *et al.* placed two Doppler flow velocity wires into bilateral coronary arteries.⁴⁹ Differences in the effects of SCS on coronary blood flow may be affected by the site of coronary blood flow measurements. It is known that diseased coronary arteries will behave differently from normal coronary arteries in response to autonomic stimulation.⁵⁵ In addition, the studies differed in the level of cardiac stress applied during their respective measurements. Some studies made their measurements at rest while others used stressors such as dipyridamole, atrial pacing, and the cold pressor test.

In addition, another factor that can affect the outcome of SCS studies relates to differences in pulse width, frequency and amplitude parameters, as well as intervals between last stimulation and cardiac testing. These factors can affect results and were not consistent among study groups. Animal models suggest that low-frequency, high-intensity stimulation may act via a different mechanism than the commonly used submotor threshold intensities.³⁵ A standardization of protocol is necessary before randomized controlled trials of SCS can be undertaken.^{56, 57}

It is important to realize that studies using SCS suffer from inherent drawbacks. It is impossible to do a double-blinded study using SCS since patients feel a sensation of paresthesias associated with a functioning unit and the clinician is able to see an artifact of stimulation on the electrocardiogram tracing.^{17, 56, 58} Another issue is the use of TENS providing external stimulation, which may have some similarities to SCS implanted in the epidural space, but which also shows some differences. Both modalities stimulate large myelinated afferent fibers, but TENS stimulates these fibers in the periphery, in contrast to SCS which stimulates these fibers and other pathways at the level of the spinal cord.¹⁶ Finally, the number of patients studied in trials is small since patients with syndrome X and chronic stable angina do not have indications for invasive procedures such as cardiac catheterization. Therefore, multicenter trials are necessary. We are in the process of initiating such a trial at this time.

Conclusions

Spinal cord stimulation likely produces its beneficial effects in patients with chronic intractable angina by the mutual interaction of (1) pain reduction, (2) a reduction of sympathetic tone, (3) reduced myocardial oxygen demand, and (4) improved coronary microcirculatory blood flow—all resulting in a lessening of myocardial ischemia. We believe that the primary initiating mechanism is due to an attenuation of pain, which is accomplished by stimulation of the dorsal columns and an accompanying decrease in the transmission of nociceptive impulses via the spinothalamic tract.¹⁶ This may occur via increased GABA release from dorsal horn interneurons and also by release of beta-endorphins, which is associated with decreased myocardial oxygen consumption.^{46, 19} Confirmation of these analgesic mechanisms is seen in PET studies of regional cerebral blood flow in areas of the brain involved with

TABLE II Issues in designing studies of spinal cord stimulation for angina

Ischemic preconditioning
Differing location of coronary blood flow measurements
Parameters, duration, and time interval since last stimulation
Impossibility of conducting double-blinded studies
Ethics of invasive procedures in patients not deemed candidates for further surgical / invasive interventions
Use of spinal cord stimulation versus TENS

Abbreviations: TENS = transcutaneous electrical nerve stimulation.

nociception. There is good evidence that SCS acts to decrease sympathetic tone,^{29,33,34} as seen in studies of norepinephrine spillover and in several animal models with a consequent decrease in myocardial oxygen demand. Along with decreased pain, reduced sympathetic tone, and decreased oxygen demand, improvement of myocardial ischemia occurs due to improved blood flow at the coronary microvascular level, which is supported by studies showing increased homogenization of myocardial blood flow.^{48,49}

We hypothesize that the sequence of these interactions is decreased anginal pain, which leads to decreased sympathetic tone, which in turn results in decreased myocardial oxygen consumption and a decreased tone in the basal coronary microvasculature. The final result is a favorable shift away from the point at which an imbalance between myocardial oxygen supply and demand occurs (i.e., ischemia), thereby producing a reduction in pain.

References

- Schoebel FC, Frazier H, Jessurun GAJ, De Jongste MJL, Kadipasaoglu KA, Jax TW, Heintzen MP, Cooley DA, Strauer BE, Leschke M: Refractory angina pectoris in end-stage coronary artery disease: Evolving therapeutic concepts. *Am Heart J* 1997; 134:587–602
- Murray S, Carson KG, Ewings PD, Collins PD, James MA: Spinal cord stimulation significantly decreases the need for acute hospital admission for chest pain in patients with refractory angina pectoris. *Heart* 1999;82(1):89–92
- Laffey J, Murphy D, Regan J, O'Keeffe D: Cost-benefit analysis of spinal cord stimulation for intractable angina pectoris: A win-win scenario? *Hosp Med* 1998;59 No.10:820–821
- Shealy CN, Mortimer TJ, Reswick JB: Electrical inhibition of pain by stimulation of the dorsal columns: Preliminary clinical report. *Anesth Analg* 1967;46:489–491
- Wall PD, Sweet WH: Temporary abolition of pain in man. *Science* 1967;155:108–109
- Murphy DF, Giles KE: Intractable angina pectoris: Management with dorsal column stimulation. *Med J Austral* 1987;146:260
- Hautvast RWM, DeJongste MJL, Staal MJ, van Gilst WH, Lie KI: Spinal cord stimulation in chronic intractable angina pectoris: A randomized, controlled efficacy study. *Am Heart J* 1998;136: 1114–1120
- Greco S, Auriti A, Fiume D, Gazzeri G, Gentilucci G, Antonini L, Santini M: Spinal cord stimulation for the treatment of refractory angina pectoris: A two-year follow up. *PACE* 1999;22(Pt. I):26–32
- Eliasson T, Jern S, Augustinsson L, Mannheimer C: Safety aspects of spinal cord stimulation in severe angina pectoris. *Coron Art Dis* 1994;5:845–850
- Andersen C, Hole P, Oxhøj H: Does pain relief with spinal cord stimulation for angina conceal myocardial infarction? *Br Heart J* 1994;71:419–421
- Andersen C: Does heart rate variability change in angina pectoris patients treated with spinal cord stimulation? *Cardiology* 1998;89: 14–18
- Romano M, Brusa S, Grieco A, Zucco F, Spinelli A, Allaria B: Efficacy and safety of permanent cardiac DDD pacing with contemporaneous double spinal cord stimulation. *PACE* 1998;21:465–467
- Iyer R, Gnanadurai TV, Forsey P: Management of cardiac pacemaker in a patient with spinal cord stimulator implant. *Pain* 1998; 74:333–335
- Andersen C: Complications in spinal cord stimulation for treatment of angina pectoris. *Acta Cardiol* 1997;LII No.4:325–333
- Augustinsson LE: Spinal cord electrical stimulation in severe angina pectoris: Surgical technique, intraoperative physiology, complications, and side effects. *PACE* 1989;12(Pt. II):693–694
- Chandler MJ, Brennan TJ, Garrison DW, Kim KS, Schwartz PJ, Foreman RD: A mechanism of cardiac pain suppression by spinal cord stimulation: Implications for patients with angina pectoris. *Eur Heart J* 1993;14:96–105
- Barolat G: Epidural spinal cord stimulation: Anatomical and electrical properties of the intraspinal structures relevant to spinal cord stimulation and clinical correlations. *Neuromodulation* 1998;1 No.2:63–71
- Melzack R, Wall PD: Pain mechanisms: A new theory. *Science* 1965;150 No.3699:971–979
- Cui JG, O'Connor WT, Ungerstedt U, Linderroth B, Meyerson BA: Spinal cord stimulation attenuates augmented dorsal horn release of excitatory amino acids in mononeuropathy via a GABA-ergic mechanism. *Pain* 1997;73:87–95
- Cui JG, Sollevi A, Linderroth B, Meyerson BA: Adenosine receptor activation suppresses tactile hypersensitivity and potentiates spinal cord stimulation in mononeuropathic rats. *Neurosci Lett* 1997;223: 173–176
- Cui JG, Meyerson BA, Sollevi A, Linderroth B: Effect of spinal cord stimulation on tactile hypersensitivity in mononeuropathic rats is potentiated by simultaneous GABAB and adenosine receptor activation. *Neurosci Lett* 1998;247:183–186
- Yakhnitsa V, Linderroth B, Meyerson BA: Spinal cord stimulation attenuates dorsal horn hyperexcitability in a rat model of mononeuropathy. *Pain* 1999;79:223–233
- Eliasson T, Mannheimer C, Waagstein F, Andersson B, Bergh CH, Augustinsson LE, Hedner T, Larson G: Myocardial turnover of endogenous opioids and calcitonin-gene-related peptide in the human heart and the effects of spinal cord stimulation on pacing-induced angina pectoris. *Cardiology* 1998;89:170–177
- Oldroyd KG, Harvey K, Gray CE, Beasall GH, Cobbe SM: Beta-endorphin release in patients after spontaneous and provoked acute myocardial ischaemia. *Br Heart J* 1992;67:230–235
- Caffrey J, Gaugl J, Jones C: Local endogenous opiate activity in dog myocardium. *Am J Physiol* 1985;248:H382–H388
- Miller PF, Light KC, Bragdon EE, Ballenger MN, Herbst MC, Maixner W, Hinderliter AL, Atkinson SS, Koch GG, Sheps DS: Beta-endorphin response to exercise and mental stress in patients with ischemic heart disease. *J Psychosom Res* 1993;37No.5: 455–465
- Hautvast RWM, TerHorst GJ, DeJong BM, DeJongste MJL, Blanksma PK, Paans AMJ, Korf Jakob: Relative changes in cerebral blood flow during spinal cord stimulation in patients with refractory angina pectoris. *Eur J Neurosci* 1997;9 No.6: 1178–1183
- Rosen SD, Paulesu E, Wise RJS, Tousoulis D, Camici PG: Cardiac syndrome X: A model of chronic visceral pain of cortical origin. *Circulation* 1998;98(suppl 1) No.17:1–850
- Norrsell H, Eliasson T, Mannheimer C, Augustinsson LE, Bergh CH, Andersson B, Waagstein F, Friberg P: Effects of pacing-induced myocardial stress and spinal cord stimulation on whole body cardiac norepinephrine spillover. *Eur Heart J* 1997;18:1890–1896
- Sanderson JE, Woo KS, Chung HK, Chan WWM, Tse LKK, White HD: The effect of transcutaneous electrical nerve stimulation on coronary and systemic haemodynamics in syndrome X. *Coron Art Dis* 1996;7:547–552
- Mortara A, LaRovere MT, Signorini MG, Pantaleo P, Pinna G, Martinelli L, Ceconi C, Cerutti S, Tavazzi L: Can power spectral analysis of heart rate variability identify a high risk subgroup of congestive heart failure patients with excessive sympathetic activation? A pilot study before and after heart transplantation. *Br Heart J* 1994;71:422–430
- Hautvast RWM, Brouwer J, DeJongste MJL, Lie KI: Effect of spinal cord stimulation on heart rate variability and myocardial ischemia in patients with chronic intractable angina pectoris: A prospective ambulatory electrocardiographic study. *Clin Cardiol* 1998;21:33–38

33. Sanderson JE, Tomlinson B, Lau MSW, So KWH, Cheung AHK, Critchley JAJH, Woo KS: The effect of transcutaneous electrical nerve stimulation (TENS) on autonomic cardiovascular reflexes. *Clin Auton Res* 1995;5:81–84
34. Naver H, Augustinsson LE, Elam M: The vasodilating effect of spinal cord stimulation is mediated by sympathetic nerves. *Clin Auton Res* 1992;2:41–45
35. Linderöth B, Herregodts P, Meyerson BA: Sympathetic mediation of peripheral vasodilation induced by spinal cord stimulation: Animal studies of the role of cholinergic and adrenergic receptor subtypes. *Neurosurgery* 1994;35 No. 4:711–719
36. Foreman RD, Ardell JL, Armour JA, Barron KW, Chandler MJ, DeJongste MJL, Hull SS Jr, Jou CJ, Min WD, TerHorst GJ, Linderöth B: High thoracic spinal cord stimulation attenuates intrinsic cardiac neuronal activity in the dog: Implications for treating refractory angina pectoris (abstr). *Soc Neurosci* 1998;24(Pt. 1):394
37. Jacobs MJHM, Jorning PJG, Beckers RCY, Ubbink DT, van Kleef M, Slaaf DW, Reneman RS: Foot salvage and improvement of microvascular blood flow as a result of epidural spinal cord electrical stimulation. *J Vasc Surg* 1990;12:354–360
38. Horsch S, Claeys L: Epidural spinal cord stimulation in the treatment of severe peripheral arterial occlusive disease. *Ann Vasc Surg* 1994;8:468–474
39. Favre JP, Richard A, Gournier JP, Barral X: Value of spinal cord stimulation for limb salvage in patients with graft failure. In *Spinal Cord Stimulation II: An Innovative Method in the Treatment of PVD and Angina*, p. 137–145 (Eds. Horsch S, Claeys L). Berlin: Darmstadt/Steinkopff, 1995
40. Fiume D, Palombi M, Sciassa V, Tamorri M: Spinal cord stimulation in peripheral ischemic pain. *Pacing Clin Electrophysiol* 1989; 12 Part II:698–704
41. Mannheimer C, Eliasson T, Andersson B, Bergh CH, Augustinsson LE, Emanuelsson H, Waagstein F: Effects of spinal cord stimulation in angina pectoris induced by pacing and possible mechanisms of action. *Br Med J* 1993;307:477–480
42. Marber M, Walker D, Yellon D: Spinal cord stimulation or ischaemic preconditioning? *Br Med J* 1993;307:737
43. Lessar MA, Stoddard M, Ahmed M, Broadbent J, Bolli R: Preconditioning of human myocardium with adenosine during coronary angioplasty. *Circulation* 1997;95:2500–2507
44. Cohen MV, Downey JM: Ischaemic preconditioning: Can the protection be bottled? *Lancet* 1993;342:6
45. Przyklenk K, Kloner RA: Ischemic preconditioning: Exploring the paradox. *Prog Cardiovasc Dis* 1998;40 No.6:517–547
46. NorrSELL H, Eliasson T, Albertsson P, Augustinsson LE, Emanuelsson H, Eriksson P, Mannheimer C: Effects of spinal cord stimulation on coronary blood flow velocity. *Coron Art Dis* 1998;9: 273–278
47. Chauhan A, Mullins PA, Thuraisingham SJ, Taylor G, Petch MC, Schofield PM: Effect of transcutaneous electrical nerve stimulation on coronary blood flow. *Circulation* 1994;89:694–702
48. Hautvast RWM, Blanksma PK, DeJongste MJL, Pruim J, van der Wall EE, Vaalburg W, Lie KI: Effect of spinal cord stimulation on myocardial blood flow assessed by positron emission tomography in patients with refractory angina pectoris. *Am J Cardiol* 1996;77: 462–467
49. Jessurun GAJ, Tio RA, DeJongste MJL, Hautvast RWM, Heijer PD, Crijns HJGM: Coronary blood flow dynamics during transcutaneous electrical nerve stimulation for stable angina pectoris associated with severe narrowing of one major coronary artery. *Am J Cardiol* 1998;82:921–926
50. Kujacic V, Eliasson T, Mannheimer C, Jablonskiene D, Augustinsson LE, Emanuelsson H: Assessment of the influence of spinal cord stimulation on left ventricular function in patients with severe angina pectoris: An echocardiographic study. *Eur Heart J* 1993;14: 1238–1244
51. Croom JE, Foreman RD, Chandler MJ, Barron KW: Cutaneous vasodilation during dorsal column stimulation is mediated by dorsal roots and CGRP. *Am J Physiol* 1997;272:H950–H957
52. Gherardini G, Lundeberg T, Cui JG, Eriksson SV, Trubek S, Linderöth B: Spinal cord stimulation improves survival in ischemic skin flaps: An experimental study of the possible mediation by calcitonin gene-related peptide. *Plastic Reconstruct Surg* 1999;103: 1221–1228
53. Okazaki Y, Kodama K, Sato H: Attenuation of increased regional myocardial oxygen consumption during exercise as a major cause of warm-up phenomenon. *J Am Coll Cardiol* 1993;21:1597–1604
54. Schulz R, Post H, Vahlhaus C, Heusch G: Ischemic preconditioning in pigs: A graded phenomenon its relation to adenosine and bradykinin. *Circulation* 1998;98:1022–1029
55. Ganz P, Braunwald E: Coronary blood flow and myocardial ischemia. In *Heart Disease: A Textbook of Cardiovascular Medicine*, p. 1161–1183 (Ed. Braunwald E). Philadelphia: WB Saunders, 1997
56. Maynard C, Every NR: Evaluating treatment for intractable angina pectoris: A challenging and scientific problem. *Am Heart J* 1998: 136:943–944
57. Sharples LD, Caine N, Schofield PM, Shapiro LM, Dunning J, Wallwork J: Randomised trials of new surgical procedures are necessary. *Heart* 1999;81:100
58. Deyo RA, Walsh NE, Schoenfeld LS, Ramamurthy S: Can trials of physical treatments be blinded? *Am J Phys Med Rehab* 1990;69 No.1:6–10