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

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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 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. 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.

The use of spinal cord stimulation (SCS) was first described in 1967. 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. 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. 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 episodes.
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 lead electrode 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 parathesias 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 GABAb 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-ergic 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. 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. 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.

**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. 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). 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.

In another TENS study, an inhibitory action on sympathetic reflexes was found. 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. 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. Application of SCS to dogs can reduce intracardiac neuronal activity, which is otherwise increased with ischemia. 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. 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. In a study by Mannheimer et al., 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, in which brief episodes of ischemia render the myocardium more resistant to later ischemic events. 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

<table>
<thead>
<tr>
<th>First author/year</th>
<th>Patient selection</th>
<th>Methods</th>
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<tbody>
<tr>
<td>DeLandsheere, 1992</td>
<td>8 patients CCS III or IV SCS stopped 48 h prior Antianginal medications stopped 24 prior Unipolar stimulation—Frequency: 33 to 130 Hz Width: 210–450 microseconds Amplitude: 3.5 to 8.25 V</td>
<td>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</td>
</tr>
<tr>
<td>Mannheimer, 1993</td>
<td>20 patients in NYHA III or IV SCS stopped 48 h prior Antianginal medications stopped 12 h prior Stimulator settings not described</td>
<td>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</td>
</tr>
<tr>
<td>Chauhan, 1994</td>
<td>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</td>
<td>TENS / angiogram Coronary blood flow at rest-TENS for 5 min—repeat measurements Judkins-Doppler 8F in normal left coronary ostium</td>
</tr>
<tr>
<td>Hautvast, 1996</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Sanderson, 1996</td>
<td>11 patients with syndrome X Antianginal medications withheld 24 h TENS settings: frequency 70 Hz width 200 ms, 35–50 milliamps</td>
<td>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</td>
</tr>
<tr>
<td>Jessurum, 1998</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Norrsell, 1998</td>
<td>8 patients—CAD 4 patients—syndrome X Beta blockers stopped 48 h prior SCS stopped 48 h prior Stimulation parameters not mentioned</td>
<td>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)</td>
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*Abbreviations: CCS = Canadian Cardiovascular Society Functional Classification, SCS = spinal cord stimulation, PET = positron emission LAD = left anterior descending artery, LCx = left circumflex artery.*
<table>
<thead>
<tr>
<th>Findings</th>
<th>Authors’ conclusions</th>
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<tr>
<td>Resting heart rate and blood pressure elevated during SCS</td>
<td>SCS does not improve regional blood flow</td>
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<tr>
<td>Slightly increased resting myocardial clearance of K-38 after SCS</td>
<td></td>
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<tr>
<td>but not significant</td>
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<tr>
<td>Increased regional myocardial clearance in nonaffected segments before</td>
<td></td>
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<tr>
<td>and after SCS in response to exercise</td>
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<tr>
<td>No significant changes in myocardial clearance both without SCS and</td>
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<td>with SCS from rest to exercise</td>
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<tr>
<td>Decreased magnitude and duration of ST depression with SCS</td>
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<tr>
<td>Increased tolerance to pacing</td>
<td>Anti-ischemic effects secondary to decreased</td>
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<tr>
<td>Lactate production changed to extraction with stimulation at</td>
<td>myocardial oxygen consumption</td>
</tr>
<tr>
<td>comparable pacing rates</td>
<td>Myocardial ischemia does still give rise to</td>
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<tr>
<td>ST depression decreased</td>
<td>pain</td>
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<tr>
<td>Time to ST depression increased</td>
<td>Was this ischemic preconditioning?</td>
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<tr>
<td>Time to ST recovery decreased</td>
<td></td>
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<tr>
<td>Decreased coronary sinus blood flow and oxygen consumption at pacing</td>
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<tr>
<td>producing angina with stimulation, lactate extraction reverted to production</td>
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<tr>
<td>Increased coronary blood flow velocity in syndrome X and CAD but</td>
<td>TENS has a neural mechanism for increasing</td>
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<td>not heart transplant group</td>
<td>coronary blood flow since it had no effect in</td>
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<tr>
<td>No significant changes in coronary arterial diameter of LAD and LCx</td>
<td>the deinnervated heart transplant patients</td>
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<tr>
<td>by electronic digital calipers (Sandhill Scientific)</td>
<td>Site of action is at microcirculatory level</td>
</tr>
<tr>
<td>Significant decrease in epinephrine levels in syndrome X and CAD patients</td>
<td>Suggests decreased sympathetic activity of heart</td>
</tr>
<tr>
<td>No change in rate $\times$ pressure product</td>
<td></td>
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<tr>
<td>No significant changes in coronary blood</td>
<td>SCS work due to homogenization of myocardial</td>
</tr>
<tr>
<td>Total resting blood flow unchanged</td>
<td>blood flow</td>
</tr>
<tr>
<td>Flow reserve decreased</td>
<td>Dipyridamole effect may be blunted by SCS</td>
</tr>
<tr>
<td>Coefficient of variation of flow decreased after stimulation both at rest and with dipyridamole</td>
<td>Short-term effect may increase myocardial blood flow, long-term may provide more homogenization of blood flow</td>
</tr>
<tr>
<td>Decreased mean coronary blood flow velocity</td>
<td>Unlikely to have a direct effect on coronary artery</td>
</tr>
<tr>
<td>Decreased coronary blood flow index</td>
<td>vasomotion or hemodynamics but reduces rate $\times$</td>
</tr>
<tr>
<td>Decreased rate $\times$ pressure product</td>
<td>pressure product and therefore oxygen</td>
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<tr>
<td>Increased coronary vascular resistance</td>
<td>consumption, probably via sympathetic inhibition</td>
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<tr>
<td>No changes in epicardial coronary diameter</td>
<td>rather than a direct effect</td>
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<tr>
<td>No significant difference in abnormal response to cold pressor test</td>
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<tr>
<td>Diameter of stenotic artery decreased in study group</td>
<td>Suggests TENS modulates regional coronary</td>
</tr>
<tr>
<td>Diameter of nonstenotic artery increased in study group</td>
<td>vasomotion in patients with CAD: (1) coronary</td>
</tr>
<tr>
<td>No effect on average peak velocity</td>
<td>branch steal secondary decreased microvascular</td>
</tr>
<tr>
<td>Coronary volumetric flow decreased in stenotic artery and increased in nonstenotic artery</td>
<td>resistance, (2) collateral steal during afferent</td>
</tr>
<tr>
<td>Average peak velocity increased in all CAD patients with pacing,</td>
<td>electrical stimulation</td>
</tr>
<tr>
<td>but no changes when SCS started</td>
<td>Improved regional flow at microcirculatory level</td>
</tr>
<tr>
<td>6 / 8 patients became angina free when SCS started</td>
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</table>

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. 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.50 In summary, increased 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.49 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-Gene-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 leukotrienes.51 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. Similarly, SCS has been shown to improve microcirculatory flow in patients with peripheral vascular disease and in patients with critically ischemic skin flaps. 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. 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. Recent evidence from pig studies implicates bradykinin as essential for preconditioning of short duration and adenosine for preconditioning of longer duration. 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, Mannheimer et al. sampled the great cardiac vein of the coronary sinus, NorrSELL et al. attempted to place the Doppler guidewire prestenotically in areas corresponding to ischemia, and Sanderson et al. placed the catheter into the left anterior descending artery, and Jessurun et al. placed two Doppler flow velocity wires into bilateral coronary arteries. 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. 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. A standardization of protocol is necessary before randomized controlled trials of SCS can be undertaken.

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 parasthesias associated with a functioning unit and the clinician is able to see an artifact of stimulation on the electrocardiogram tracing. 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. 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 spinthalamic tract. 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. Confirmation of these analgesic mechanisms is seen in PET studies of regional cerebral blood flow in areas of the brain involved with ischemia.
nociception. There is good evidence that SCS acts to decrease sympathetic tone, as seen in studies of noradrenaline 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.

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


44. Cohen MV, Downey JM: Ischemic preconditioning: Can the protection be bottled? Lancet 1993;342:6