

Neurological mechanisms of chest pain and cardiac disease

Electrical stimulation of dorsal segments of the spinal cord has been used to treat patients with severe angina pectoris that is refractory to conventional therapies. The concept is based on the “gate control theory” first proposed by Melzack and Wall,¹ in which a neuronal “gate” in the dorsal horn of the spinal cord controls the flow of noxious stimuli to the brain. Thus, spinal cord stimulation (SCS) can be thought of as “closing the gate” on pain. In the most often-used technique, an electrode is inserted over the dorsal columns and placed in the segments where electrical stimulation elicits paresthesias in the painful dermatomes. SCS activates large afferent fibers that have the ability to suppress stimuli from small fibers transmitting nociceptive information, and thereby “closes the pain gate.”

This article will briefly review the efficacy of SCS in relieving angina pectoris, provide an overview of the spinal processing of cardiac nociceptive information and the neural mechanisms of referred pain in the thoracic and cervical spinal cord, and examine the effects of SCS on the heart.

■ SUCCESS RATES WITH SCS

Success rates achieved with SCS for angina pectoris are in excess of 80%.²⁻⁴ In patients with angina undergoing SCS, the severity and frequency of anginal episodes are reduced, and in some cases episodes are eliminated.⁵⁻⁸ The intake of nitrates to relieve angina pain is also markedly decreased.⁹ In addition to pain relief, clinical studies using SCS for the treatment of chronic refractory angina demonstrate increases in exercise tolerance, improvements in ischemia-related electrocardiographic changes (ST segment), and improvements in the quality of life.^{3,6,8,10} Animal studies also indicate that SCS reduces the nociceptive signal and improves the function of the heart.¹¹⁻¹⁶

* Dr. Foreman reported that he has no financial relationships that pose a potential conflict of interest with this article.

■ SPINAL PROCESSING OF CARDIAC NOCICEPTIVE INFORMATION

The challenge is to determine the neural mechanisms underlying angina pectoris that contribute to the success of SCS. Fifteen years of research at the University of Oklahoma, focusing on spinal processing of cardiac nociceptive impulses, have identified the C1-C2 and the T2-T4 segments of the spinal cord as critical for processing information in the neural hierarchy regulating cardiac and respiratory control.

Neural mechanisms of referred pain in the thoracic spinal cord

The responses of individual spinothalamic tract (STT) cells, the cells of origin in the gray matter of the thoracic spinal cord, to nociceptive input from the heart have been assessed by transient coronary artery occlusion or injection of algescic chemicals into the heart, followed by examination of somatic fields.¹⁷ A distribution of STT cells with convergence of somatic and cardiac input was found at the T1-T5 segments. Neurons in the C5 and C6, but not the C7 and C8, segments also responded to cardiac or somatic input, primarily in the proximal region. The receptive fields were located primarily in deep muscle rather than cutaneous tissue.

These findings provide insight into the characteristics of referred pain:

- Pain of visceral origin is referred to somatic regions that are innervated from the same spinal segments as the heart.
- The pain is generally referred to proximal, but not distal, somatic structures.
- The referred pain is experienced as deep pain.

Neural mechanisms of referred pain in the cervical spinal cord

Neck and jaw pain in some patients with angina pectoris served as a basis for exploring neural mechanisms of referred pain in the cervical spinal cord. Early clinical observations of neck pain being unmasked after sympathectomy to reduce angina pectoris led to the

hypothesis that STT cells in the C1-C2 region receive cardiac input.^{18,19} To address this hypothesis, recordings were made from STT cells located in the C1-C2 spinal segments.^{20,21} Coronary occlusion or injection of algescic chemicals into the heart before and after bilateral vagotomy, or electrical stimulation of cardiopulmonary afferent fibers and thoracic vagal afferents, was used to activate the neurons.

Electrical stimulation of vagal and cardiac sympathetic nerves showed that STT cells in C1-C2 were more responsive to stimuli from vagal afferents than from cardiac sympathetic afferents, and that the somatic fields for these cells were located primarily in the jaw and neck regions.²⁰ In addition, bilateral vagotomy markedly reduced the nociceptive input produced by injecting algescic chemicals in the heart, as evidenced by reduced activity of these STT cells in the cervical region.²¹ Since only 6% of the vagal afferents project directly to the C1-C2 spinal neurons, the rest most likely ascend into the nucleus tractus solitarius and then synapse on cells with axons projecting to the C1-C2 segments.²² This finding suggests that the vagus plays an important role in relaying this information from the heart to the C1-C2 region. These results also support the clinical observations that information transmitted in the vagus contributes to the referral of pain to the neck and jaw.

Effects of SCS on thoracic STT cells receiving cardiac nociceptive information

Spinal cord stimulation of the T1-T2 area in anesthetized primates at an intensity of approximately 90% of motor threshold was performed to record STT cell responses to noxious cardiac input.¹⁴ An increase in cell activity was observed following injection of bradykinin in the heart via the left atrium, which was suppressed with SCS (**Figure 1**). The limiting factor of this study was using animals with normal hearts; study of hearts with previous infarction or ischemic hearts would be more relevant clinically. Nevertheless, this study shows a significant decrease in the processing of impulses in STT cells when the spinal cord stimulator was turned on. This effect is attributed to inhibitory mechanisms impinging on the STT cells and potentially a reduction in nociceptive input from the heart to the spinal cord.

EFFECTS OF SCS ON THE HEART

The intrathoracic intrinsic cardiac nervous system and SCS

Evidence supports the notion that SCS may alter the function of the intrinsic cardiac nervous system to pro-

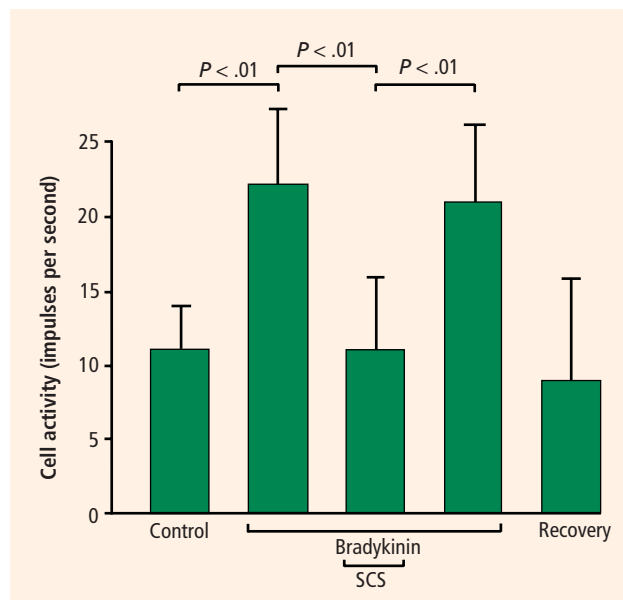


FIGURE 1. Effects of spinal cord stimulation (SCS) on cardiac-evoked activity of thoracic spinothalamic tract (STT) cells. Control: spontaneous activity; bradykinin: intra-atrial injections of bradykinin; SCS: electrical stimulation of the T1-T2 dorsal columns (~80 Hz; 0.25 ms) at an intensity of ~90% motor threshold; recovery: spontaneous activity following the bradykinin response. The line above "bradykinin" indicates that three bars represent responses to bradykinin, and the line above "SCS" represents bradykinin plus SCS (which applies to the second of these three bars). The activity of STT cells in response to bradykinin injection was significantly diminished with SCS to levels observed in controls. Adapted from Chandler et al, *Eur Heart J* 1993; 14:96–105, by permission of the European Society of Cardiology.

tect the heart. We first looked at the effects of stimulation at the T1-T4 region where processing of several different types of neurons is abundant.^{11,15} Recent canine studies have shown that SCS of the T1-T2 dorsal columns using "clinical parameters" (50 Hz, 0.2 ms duration) and an intensity of 90% of motor threshold significantly reduces activity generated by the intrinsic cardiac neurons in their basal conditions and in the presence of regional ventricular ischemia.¹⁵ Another interesting observation is that SCS stabilized these neurons for long periods, even after the stimulus was terminated.¹¹ Clinical studies support this observation, indicating that a cardioprotective benefit may persist even after discontinuing SCS therapy for long periods.²³

Infarct size and SCS

The effect of SCS on infarct size was explored in a rabbit model using a transient coronary artery occlusion.²⁴ The rabbit was chosen as the model because it does not have collateral blood vessels in the heart.²⁵ It is known that exogenous catecholamines can protect

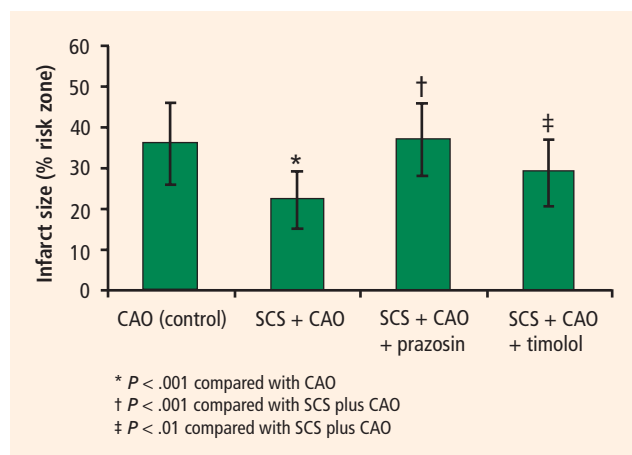


FIGURE 2. Effects of spinal cord stimulation (SCS) on infarct size. The infarct size is plotted as a percentage of risk zone for animals with coronary artery occlusion alone (CAO) compared to animals with preemptive SCS and CAO. Preemptive SCS began 15 minutes before the onset of the CAO, and then both were continued for 30 minutes followed by reperfusion for 3 hours. Vehicle or selective adrenergic blockade (prazosin or timolol) was administered 15 minutes before the onset of SCS. Adapted from reference 24.

the rabbit heart from transient myocardial infarction, an effect that is prevented by alpha-receptor blockade, but endogenous myocardial catecholamines are not essential for protection from ischemic preconditioning in the rabbit.^{26–30} It is also known that adrenoceptors are found on subpopulations of neurons within the intrathoracic cardiac neuronal hierarchy.^{31,32} Modulation of these receptors can influence the progress of cardiac pathology.^{33,34} Our hypothesis, therefore, was that preemptive SCS could reduce myocardial apoptosis, and could reduce infarct size as a result of activation of adrenergic receptors.

Stimulation of the dorsal surface of the T1-T2 segments using “clinical parameters” (50 Hz; 0.2 ms; 90% of motor threshold) was applied approximately 15 minutes before the left coronary artery was occluded and then both the occlusion and SCS continued for 30 minutes (**Figure 2**). This was followed by a 3-hour reperfusion period. The infarct was measured by using tetrazolium, and the risk zone was determined by using fluorescent microspheres. The infarct size was expressed as a percentage of the risk zone. Infarct size was 36% of the risk zone with only left coronary artery occlusion (control). SCS reduced the infarct size to approximately 22%, which was significantly smaller than the control infarct size. Preconditioning by administering a 5-minute occlusion, waiting 10 minutes, and then occluding the artery for 30 minutes also reduced the infarct size to 22% of the risk zone.

Infarct size increased to that observed in the controls following treatment with the alpha-blocker prazosin; beta-blocker treatment with timolol also increased infarct size compared with SCS during coronary artery occlusion without the blockers. From these data, we conclude that SCS has the ability to decrease the infarct size by changing the environment of the heart with respect to the adrenoceptors.

SUMMARY

SCS is an efficacious, reversible, and safe therapy that improves quality of life, increases exercise tolerance, and relieves angina pectoris, but clinical trials in North America are needed to confirm the data coming from Europe.

Neuronal convergence onto STT cells underlies the referred pain associated with angina pectoris. With pain referred to the chest and upper arm, cardiac nociceptive information is transmitted via sympathetic afferent fibers to thoracic cells. With pain referred to the jaw and neck, cardiac nociceptive information is transmitted via vagal afferent fibers onto cervical cells. SCS can modulate the responses of thoracic STT cells to nociceptive input originating from the heart.

SCS modulates cardiac function. It stabilizes neurons in the intrinsic cardiac nervous system, and can reduce infarct size via adrenoceptors.

REFERENCES

- Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965; 150:971–979.
- DeJongste MJ. Spinal cord stimulation for ischemic heart disease. *Neurol Res* 2000; 22:293–298.
- Eliasson T, Augustinsson LE, Mannheimer C. Spinal cord stimulation in severe angina pectoris—presentation of current studies, indications and clinical experience. *Pain* 1996; 65:169–179.
- Jessurun GA, DeJongste MJ, Blanksma PK. Current views on neurostimulation in the treatment of cardiac ischemic syndromes. *Pain* 1996; 66:109–116.
- 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.
- De Jongste MJ, Haaksma J, Hautvast RW, et al. Effects of spinal cord stimulation on myocardial ischaemia during daily life in patients with severe coronary artery disease. A prospective ambulatory electrocardiographic study. *Br Heart J* 1994; 71:413–418.
- Eliasson T, Jern S, Augustinsson LE, Mannheimer C. Safety aspects of spinal cord stimulation in severe angina pectoris. *Coron Artery Dis* 1994; 5:845–850.
- Mannheimer C, Eliasson T, Andersson B, et al. Effects of spinal cord stimulation in angina pectoris induced by pacing and possible mechanisms of action. *BMJ* 1993; 307:477–480.
- Linderöth B. Spinal cord stimulation in ischaemia and ischaemic pain: possible mechanisms of action. In: Horsch S, Bläy L, eds. *Spinal Cord Stimulation. An Innovative Method in the Treatment of PVD and Angina*. Darmstadt, Germany: Steinkopff Verlag; 1995:19–35.
- De Jongste MJ, Nagelkerke D, Hooyschuur CM, et al.

- Stimulation characteristics, complications, and efficacy of spinal cord stimulation systems in patients with refractory angina: a prospective feasibility study. *Pacing Clin Electrophysiol* 1994; 17:1751–1760.
11. Armour JA, Linderorth B, Arora RC, et al. Long-term modulation of the intrinsic cardiac nervous system by spinal cord neurons in normal and ischaemic hearts. *Auton Neurosci* 2002; 95:71–79.
 12. Cardinal R, Ardell JL, Linderorth B, Vermeulen M, Foreman RD, Armour JA. Spinal cord activation differentially modulates ischaemic electrical responses to different stressors in canine ventricles. *Auton Neurosci* 2004; 111:37–47.
 13. Cardinal R, Page P, Vermeulen M, et al. Spinal cord stimulation suppresses bradycardias and atrial tachyarrhythmias induced by mediastinal nerve stimulation in dogs. *Am J Physiol Regul Integr Comp Physiol* 2006; Jun 15 [Epub ahead of print].
 14. 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.
 15. Foreman RD, Linderorth B, Ardell JL, et al. Modulation of intrinsic cardiac neurons by spinal cord stimulation: implications for its therapeutic use in angina pectoris. *Cardiovasc Res* 2000; 47:367–375.
 16. Foreman RD, DeJongste MJL, Linderorth B. Integrative control of cardiac function by cervical and thoracic spinal neurons. In: Armour JA, Ardell JL, eds. *Basic and Clinical Neurocardiology*. New York: Oxford University Press; 2004:53–186.
 17. Foreman RD. Mechanisms of cardiac pain. *Annu Rev Physiol* 1999; 61:143–167.
 18. Lindgren I, Olivecrona H. Surgical treatment of angina pectoris. *J Neurosurg* 1947; 4:19–39.
 19. White JC, Bland EF. The surgical relief of severe angina pectoris. *Medicine (Baltimore)* 1948; 27:1–42.
 20. Chandler MJ, Zhang J, Foreman RD. Vagal, sympathetic and somatic sensory inputs to upper cervical (C1–C3) spinothalamic tract neurons in monkeys. *J Neurophysiol* 1996; 76:2555–2567.
 21. Chandler MJ, Zhang J, Qin C, Yuan Y, Foreman RD. Intrapericardiac injections of algogenic chemicals excite primate C1–C2 spinothalamic tract neurons. *Am J Physiol Regul Integr Comp Physiol* 2000; 279:R560–R568.
 22. McNeill DL, Chandler MJ, Fu QG, Foreman RD. Projection of nodose ganglion cells to the upper cervical spinal cord in the rat. *Brain Res Bull* 1991; 27:151–155.
 23. Jessurun GA, DeJongste MJ, Hautvast RW, et al. Clinical follow-up after cessation of chronic electrical neuromodulation in patients with severe coronary artery disease: a prospective randomized controlled study on putative involvement of sympathetic activity. *Pacing Clin Electrophysiol* 1999; 22:1432–1439.
 24. Southerland EM, Milhorn DM, Foreman RD, et al. Pre-emptive, but not reactive, spinal cord stimulation mitigates transient ischemia induced myocardial infarction via cardiac adrenergic neurons. *Am J Physiol Heart Circ Physiol* 2006; Aug 18 [Epub ahead of print].
 25. Maxwell MP, Hearse DJ, Yellon DM. Species variation in the coronary collateral circulation during regional myocardial ischaemia: a critical determinant of the rate of evolution and extent of myocardial infarction. *Cardiovasc Res* 1987; 21:737–746.
 26. Ardell JL, Yang X-M, Barron BA, Downey JM, Cohen MV. Endogenous myocardial norepinephrine is not essential for ischemic preconditioning in rabbit heart. *Am J Physiol* 1996; 270:H1078–H1084.
 27. Bankwala Z, Hale SL, Kloner RA. Alpha-adrenoceptor stimulation with exogenous norepinephrine or release of endogenous catecholamines mimics ischemic preconditioning. *Circulation* 1994; 90:1023–1028.
 28. Marktanner R, Nacke P, Feindt P, Hohlfeld T, Gams E. Norepinephrine-induced delayed cardioprotection against stunning is at the expense of a higher postischemic arrhythmia rate. *Cardiovasc Surg* 2003; 11:475–482.
 29. Stein AB, Tang X-L, Guo Y, Xuan Y-T, Dawn B, Bolli R. Delayed adaption of the heart to stress: late preconditioning. *Stroke* 2004; 35:2676–2679.
 30. Thornton JD, Daly JE, Cohen MV, Yang X-M, Downey JM. Catecholamines can induce adenosine receptor-mediated protection of the myocardium but do not participate in ischemic preconditioning in the rabbit. *Circ Res* 1993; 73:649–655.
 31. Ardell JL. Intrathoracic neuronal regulation of cardiac function. In: Armour JA, Ardell JL, eds. *Basic and Clinical Neurocardiology*. New York: Oxford University Press; 2004:118–152.
 32. Armour JA. Cardiac neuronal hierarchy in health and disease. *Am J Physiol Regulatory Integrative Comp Physiol* 2004; 287:R262–R271.
 33. Dell'Italia LJ, Ardell JL. Sympathetic nervous system in the evolution of heart failure. In: Armour JA, Ardell JL, eds. *Basic and Clinical Neurocardiology*. New York: Oxford University Press; 2004:340–367.
 34. Tallaj J, Wei CC, Hanks GH, et al. β 1-adrenergic receptor blockade attenuates angiotensin II-mediated catecholamine release into the cardiac interstitium in mitral regurgitation. *Circulation* 2003; 108:225–230.

Address: Robert D. Foreman, PhD, Department of Physiology, University of Oklahoma Health Sciences Center, College of Medicine, 940 SL Young Blvd., Room 653, Oklahoma City, OK 73190; robert-foreman@ouhsc.edu.