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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]

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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 algesic 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 algesic 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 algesic 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.

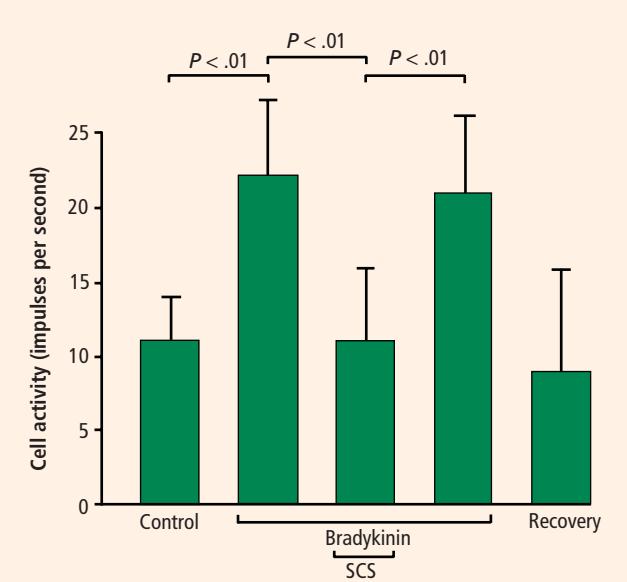

FIGURE 1. Effects of spinal cord stimulation (SCS) on cardiac-evoked activity of thoracic spinothalamic tract (STT) cells. Control: spontaneous activity; bradykinin: intra-atrial injections of bradykinin; SCS: electrical stimulation of the T1-T2 dorsal columns (~80 Hz; 0.25 ms) at an intensity of ~90% 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.

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 protect 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

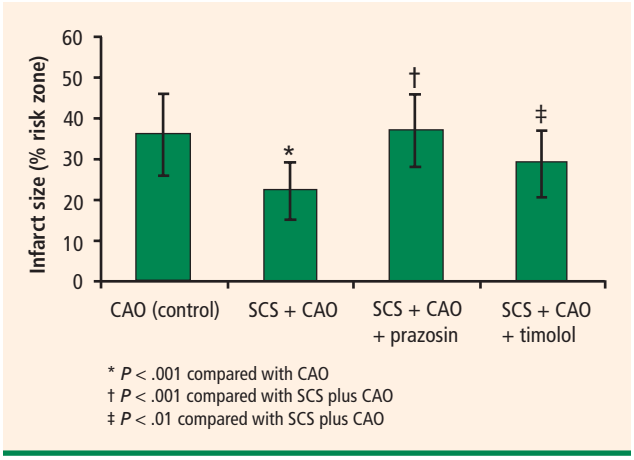

FIGURE 2. Effects of spinal cord stimulation (SCS) on infarct size. The infarct size is plotted as a percentage of risk zone for animals with coronary artery occlusion alone (CAO) compared to animals with preemptive SCS and CAO. Preemptive SCS began 15 minutes before the onset of the CAO, and then both 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 adrenoreceptors.

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 adrenoreceptors.

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