Effects of cervical spinal cord stimulation on cerebral blood flow in the rat

OREN SAGHER, M.D., AND DAH-LUEN HUANG, M.S.

Section of Neurosurgery, University of Michigan Health System, Ann Arbor, Michigan

Object. Spinal cord stimulation (SCS) is frequently used for the treatment of chronic pain. Although the mechanisms by which SCS alleviates pain are unclear, they are believed to involve changes within the dorsal horn of the spinal cord. Spinal cord stimulation has also been found to cause significant vasodilation in the peripheral vasculature. The mechanisms underlying this effect are thought to involve sympathetic blockade. A rostral vasodilatory effect has also been described, but changes in cerebral blood flow (CBF) have been poorly delineated. Using laser Doppler flowmetry (LDF), the authors examined the effects of cervical SCS on CBF in rats.

Methods. Cervical SCS was found to result in a significant increase in cortical LDF values (83 ± 11% [mean ± standard error of the mean]). The increase in cortical LDF values was not accompanied by a significant increase in systemic blood pressure. Stimulation of the upper cervical spinal cord was more effective in inducing LDF changes than was that of the lower cervical cord. Changes in SDS-induced LDF values were significantly attenuated after spinal cord transection at the cervicomedullary junction and by the administration of the sympathetic blocker hexamethonium.

Conclusions. These results indicate that cervical SCS may induce cerebral vasodilation and that this effect may involve indirect effects on vasomotor centers in the brainstem as well as an alteration in sympathetic tone.

Key Words • spinal cord stimulation • electrical stimulation • cerebral blood flow • sympathetic nervous system • rat

Since its introduction in 1967, SCS has been widely used for the treatment of patients with chronic pain.20,24,31–33 Although the mechanisms underlying its analgesic effects remain a subject of considerable controversy, SCS has become a mainstay of therapy for neuropathic pain. A serendipitous discovery involving the treatment of ischemic pain led to a postulated direct effect on peripheral vascular tone.2 Since then, the effects of SCS on vascular tone have been extensively studied in the laboratory,17–19,28 and it is now generally believed that SCS reduces peripheral sympathetic tone, thereby augmenting blood flow in the limbs.18,19

Because peripheral vasodilation has been shown to occur with SCS, it was only natural to inquire whether the same effect occurs centrally. Changes in SCS-related CBF were the subject of anecdotal reports involving a small number of patients.20 Hosobuchi10 and others1,14,22,27 have found that high cervical SCS increased CBF, although the extent of this augmentation and the underlying mechanisms have not been clearly defined. Few studies have been conducted to examine the role of CBF in the SCS of rats,1,14,36 although in general the results do support a role for alterations in sympathetic tone.

The normal regulation of CBF, which may be altered by SCS, has been the subject of a separate line of investigation. Several important medullary centers have been described that, when electrically stimulated, cause profound augmentation in CBF.13 The fastigial nucleus in the cerebellum also has this effect, and there is evidence that the medullary and cerebellar centers are part of the same autoregulatory circuit.5,30

That cervical SCS may increase CBF is an intriguing, but as yet poorly documented, possibility. The use of cervical SCS to augment CBF and avert cerebral ischemia has been suggested,11,35 but precisely how effective such an intervention would be, or for which causes of ischemia it would be best suited, is not known. Nonetheless, the use of electrical stimulation to alter CBF remains an interesting possibility. In the present paper, we describe the effects of cervical SCS on CBF in rats. The time course and magnitude of SCS-induced changes in CBF are described, and a potential role for sympathetic tone is investigated.

The use of SCS has been found to have a variety of applications in the treatment of intractable pain, spasticity, peripheral vascular disease, and angina. If SCS were shown to exert a clinically significant effect on CBF the repertoire of this already versatile therapeutic modality would be broadened. There is clearly much to be delineated prior to applying SCS to cerebral ischemia. The studies described in this paper represent a first step in this process.

Abbreviations used in this paper: CBF = cerebral blood flow; LDF = laser Doppler flow; SCS = spinal cord stimulation; SEM = standard error of the mean.
Materials and Methods

All experimental protocols were approved by the University of Michigan Committee on the Use and Care of Animals. Cervical SCS was undertaken in a series of experiments in which we used adult male Sprague–Dawley rats, each weighing between 300 and 350 g. The technique for SCS is described in detail in the following section. The rats received an anesthetic of isoflurane (Aerrane) 0.5 to 2%, titrated to maintain a mean arterial pressure between 80 and 120 mm Hg. The rats also received gallamine (10 mg/kg), following intubation and initiation of mechanical ventilation, a two-level cervical laminectomy was performed, and a platinum-ball electrode was placed onto the dorsal surface of the spinal cord. Electrical stimulation was performed while cortical blood flow was measured with LDF. Studies to determine the influence of sympathectomy outflow in CBF changes were performed by intravenously administering the ganglion nerve blocker hexamethonium (10 mg/kg, diluted in normal saline to a concentration of 10 mg/ml) 15 minutes prior to the onset of SCS. Systemic blood pressure and arterial blood gas levels were monitored during the entire experiment.

Spinal Cord Stimulation

After the induction of general anesthesia and placement of a femoral arterial line, the rat was placed in a stereotactic frame. A midline incision was made from the occiput to the thoracic spine. For stimulation at C-3, the first cervical lamina was identified and spared. The second and third laminae were cleared of paraspinal muscles, and complete laminectomies were performed, sparing the dura. Meticulous hemostasis was maintained to keep the dorsal surface of the spinal dura dry for the duration of the experiment. A platinum-ball (1-mm) electrode mounted on a stereotactic electrode holder was then lowered onto the exposed dural surface. Electrical stimulation was performed following the initiation of cortical blood flow measurement.

A standard stimulation set up was used, consisting of a stimulator, a constant current unit, and an oscilloscope. Unipolar stimulation (frequency of 50 Hz, pulse width of 100 μsec with a current of 0.6 mA) was used for our experiments. These parameters were chosen based on previously described protocols of SCS in rats. Results of our own experiments have indicated that the current levels used are approximately 50% of the motor threshold, when tested on nonparalyzed rats (unpublished data).

Spinal Cord Transection in Rats

Transection of the spinal cord at the cervicomedullary junction was performed in several experiments to assess the influence of descending pathways. In these experiments, the cervical incision was extended cephalad, exposing the occiput. The interspace between the occiput and C-1 was exposed and the dura was opened. Surface spinal cord vessels were coagulated and the pia was incised. We then used a small dissector to sever the spinal cord completely in the axial plane.

Cerebral Blood Flow Measurement

Cortical blood flow was measured in rats by using an LDF. By using this technique, we were able to obtain real-time data, although spatial characterization and quantitative measurement of blood flow are necessarily sacrificed. We chose a point 4 mm lateral and 2 mm posterior to the bregma. Although we have previously measured CBF on either side of the midline, this series of experiments involved only measurements to the right of the midline to simplify the set up. After establishing a stable baseline of measurements (15–20 minutes), electrical stimulation was performed for 1 minute, and this was followed by 5 minutes of recording without stimulation. Blood pressure data and CBF measurements were recorded.

Statistical Analysis

Cerebral blood flow measurements are expressed as percentage of baseline measurements and are presented as the mean ± SEM. Comparison of values was performed using Student’s t-test. In cases in which multiple groups were compared, an analysis of variance was performed, with a post-hoc Bonferroni’s test.

Sources of Supplies and Equipment

We obtained the gallamine from Sigma Chemical Co. (St. Louis, MO). The Grass stimulator (model S48) and constant current unit (model CCUI-A) were acquired from Grass (Telefactors, West Warwick, RI). Tektronix Inc. (Beaverton, OR) manufactures the oscilloscope (model 5111-A). We obtained the LDF (Laserflo BMP2) from Vasamedics Inc. (Little Canada, MN). The hexamethonium was purchased from ICN Biomedicals (Aurora, OH).

Results

Enhanced CBF After Cervical SCS

In a series of experiments involving five rats, we examined the effects on CBF of electrical stimulation at C2–3. Spinal cord stimulation was found to result in a significant increase in LDF measurements (83 ± 11% over baseline, p < 0.0001). Laser Doppler flow measurements increased 15 seconds following the initiation of stimulation, peaking approximately 30 to 45 seconds later (Fig. 1). Following cessation of stimulation, LDF values gradually returned to baseline values over the next 5 minutes. Because alterations in blood gas levels—especially PaCO2—may have an impact on CBF, we monitored arterial blood gas levels before, during, and after stimulation and found that PaCO2 decreased slightly during stimulation but that pH and PaO2 were unaltered (Table 1).

Stimulation-Induced Changes in CBF are Level Dependent

Clinical evidence suggesting that cervical stimulation, but not thoracic stimulation, results in changes in CBF supports the role of brainstem vasomotor centers. We investigated the possibility that changes in cerebrovascular tone induced by cervical SCS are related to the proximity of stimulation to brainstem vasomotor centers in a separate series of experiments. The stimulation/monitoring paradigm was repeated with stimulation at high (C-1), mid (C-3), or low cervical (C-6) spine regions. We found that stimulation at either C-1 or C-3 resulted in significant increases in cerebral LDF values, whereas stimulation at C-6 resulted in only a modest increase (C-1 compared with C-3, p = 0.02; C-1 compared with C-6, p < 0.0001; and C-3 compared with C-6, p < 0.0001). Figure 2 illustrates the level dependency of the LDF response.

Spinal Transection Attenuates Stimulation-Induced Increases in CBF

We performed a second series of experiments to assess the influence of modulatory circuits in the brain and brainstem on the observed changes in CBF. In this series, we performed stimulation before and after spinal transection at the cervicomedullary junction. Not unexpectedly, transection of the spinal cord reduced systemic mean blood pressure from 115 ± 10 mm Hg to 67 ± 3 mm Hg. We observed a significant reduction in the effects of stimulation on LDF values. In this series of experiments, the increase in LDF values was reduced from 42 ± 3% to 5 ± 6% (five rats, p < 0.05). A time course of this response is represented in Fig. 3.

Sympathetic Blockade Attenuates Stimulation-Induced Changes in CBF

In this series of experiments, we intravenously adminis-
tered hexamethonium (10 mg/kg) 15 minutes prior to the initiation of SCS. Hexamethonium significantly reduced systemic blood pressure \((\frac{110 \pm 32}{100} \text{ mm Hg, } p < 0.0001)\), but not LDF \((-9 \pm 21\%, p > 0.05)\). Subsequent stimulation failed to increase cerebral LDF values to any appreciable degree \((8 \pm 3\%, p > 0.05)\). A time course is depicted in Fig. 4.

**Discussion**

Spinal cord stimulation has been shown to alter vascular tone and peripheral tissue blood flow. Although this was initially an empiric observation, it has been well substantiated clinically. More important, the effects of SCS on peripheral blood flow have been investigated experimentally. The underlying mechanisms are thought to involve alterations in peripheral sympathetic tone and the release of vasodilators. The effects of SCS on CBF have also been observed in isolated cases and small clinical series. A scientific basis for these observations and the underlying mechanism(s) has yet to be well delineated. In the present series of experiments we have attempted to demonstrate these effects in an animal model and to assess the roles of sympathetic tone and descending neural pathways in mediating the observed changes in CBF.

Cervical SCS appears to alter CBF significantly in rats. The effect is immediate and long lasting, an observation that has also been made in studies of SCS and peripheral vasculature. Changes in CBF elicited by SCS also appear to be related to alterations in sympathetic tone. This is again similar to observations made in the peripheral vascular bed following SCS. We have also obtained evidence that cervical SCS–induced cerebrovascular changes involve ascending spinal pathways. The results of these experiments suggest that the CBF response involves changes in rostral activity. Because medullary vasomotor centers and the cerebellar fastigial nucleus have been implicated in profound alterations in CBF, it is possible that cervical SCS may alter CBF by influencing activity within these suprasegmental vasomotor centers.

One might argue that the effects of SCS on CBF are caused by specific stimulation of the sensorimotor regions of the brain. That SCS causes activation of brain regions corresponding to the pathways stimulated is certainly not a novel concept. In addition, there is also evidence that SCS is associated with increases in regional CBF. Nonetheless, direct coupling between activated cortical regions and regional blood flow is unlikely to explain the phenomenon observed in the present experimental series. Although the use of LDF does not allow one to examine the spatial characteristics of blood flow, the time course of the observed flow changes is not consistent with a direct coupling mechanism. Spinal cord stimulation–induced changes in LDF significantly outlasted stimulation, lasting for at least 5 minutes after the cessation of stimulation.

Changes in arterial pH and PaCO\(_2\) are also known to cause alterations in CBF. When we examined this issue, we found a slight decrease in PaCO\(_2\) during stimulation. Because this change was slight and would not likely cause an augmentation in CBF, it is not likely related to the observed cerebrovascular changes.

In using LDF measurements as a gauge of CBF, we have

| Arterial blood gas values obtained before, during, and after SCS in five rats* |
|---------------------------------|----------|----------|----------|
| Factor | Prestimulation | Stimulation | Poststimulation |
| pH     | 7.47 ± 0.01 | 7.47 ± 0.01 | 7.47 ± 0.01 |
| PaO\(_2\) | 91.2 ± 1.5 | 93.9 ± 1.8 | 92.9 ± 1.7 |
| PaCO\(_2\) | 37.8 ± 0.9 | 34.8 ± 0.8† | 37.0 ± 0.8 |

* Values are expressed as the mean ± SEM and are based on three trials per animal.
†p < 0.05 compared with prestimulation values.
been able to obtain useful information on the relative magnitude and the temporal characteristics of a cervical SCS–induced CBF response. We have also been able to assess the role of sympathetic tone and the possible involvement of brainstem centers in the observed CBF changes. The use of LDF, however, does not provide information on the spatial characteristics or absolute magnitude of the observed changes. To answer these questions, it would therefore be important to extend these findings with the use of other techniques such as autoradiography. It is worthwhile to note, however, that augmentation in CBF in response to SCS has been documented with other CBF measurements. In a study of the effects of SCS on CBF in goats, García-March, et al.,6 have reported a 35% increase in the rate of CBF (when using radiolabeled iodoantipyrine) and a 55% increase in LDF values. There have also been sporadic clinical reports (when using single-photon emission tomography, positron emission tomography, and xenon imaging as well as transcranial Doppler flowmetry) suggesting an increase in CBF in humans.11,27,35

We were able to obtain from the present series of experiments data that support the anecdotal observations of O. Sagher and D. L. Huang.
cerebrovascular alterations in SCS. In addition, analysis of our data suggests the involvement of indirect medullary stimulation and sympathetic tone alteration in producing these effects. Whether such an “upstream” vasomotor effect proves to be protective in the face of cerebral ischemia is not yet known. Certainly, experimental evidence in related models suggests that SCS does provide some benefit in the setting of ischemic challenges. Peripheral-extremity ischemia is improved by SCS, although the extent to which this is beneficial is a matter of some controversy. It has also been shown that myocardial ischemia is reduced by SCS. It would not be surprising if this were true in the case of cerebral ischemia as well. However, the potential of worsening regional cerebral ischemia through a “steal” effect also exists. This important issue will be addressed in a separate series of studies.

Acknowledgment
The authors would like to thank Dr. Richard Keep for his assistance in preparing this manuscript.

References
18. Linderoth B, Gunasekera L, Meyerson BA: Effects of sympa-

Effects of spinal cord stimulation on CBF

Fig. 4. Graph showing the effect of sympathetic blockade on SCS-induced LDF changes. Following the administration of hexamethonium, the LDF changes seen with cervical SCS were abolished. Values are expressed as mean ± SEM.

Manuscript received October 13, 1999. Accepted in final form February 7, 2000. This study was partially supported by a grant from the University of Michigan Department of Surgery. Address reprint requests to: Oren Sagher, M.D., Section of Neurosurgery, University of Michigan Health System, 1500 East Medical Center Drive, Ann Arbor, Michigan 48109. email: osagher@umich.edu.